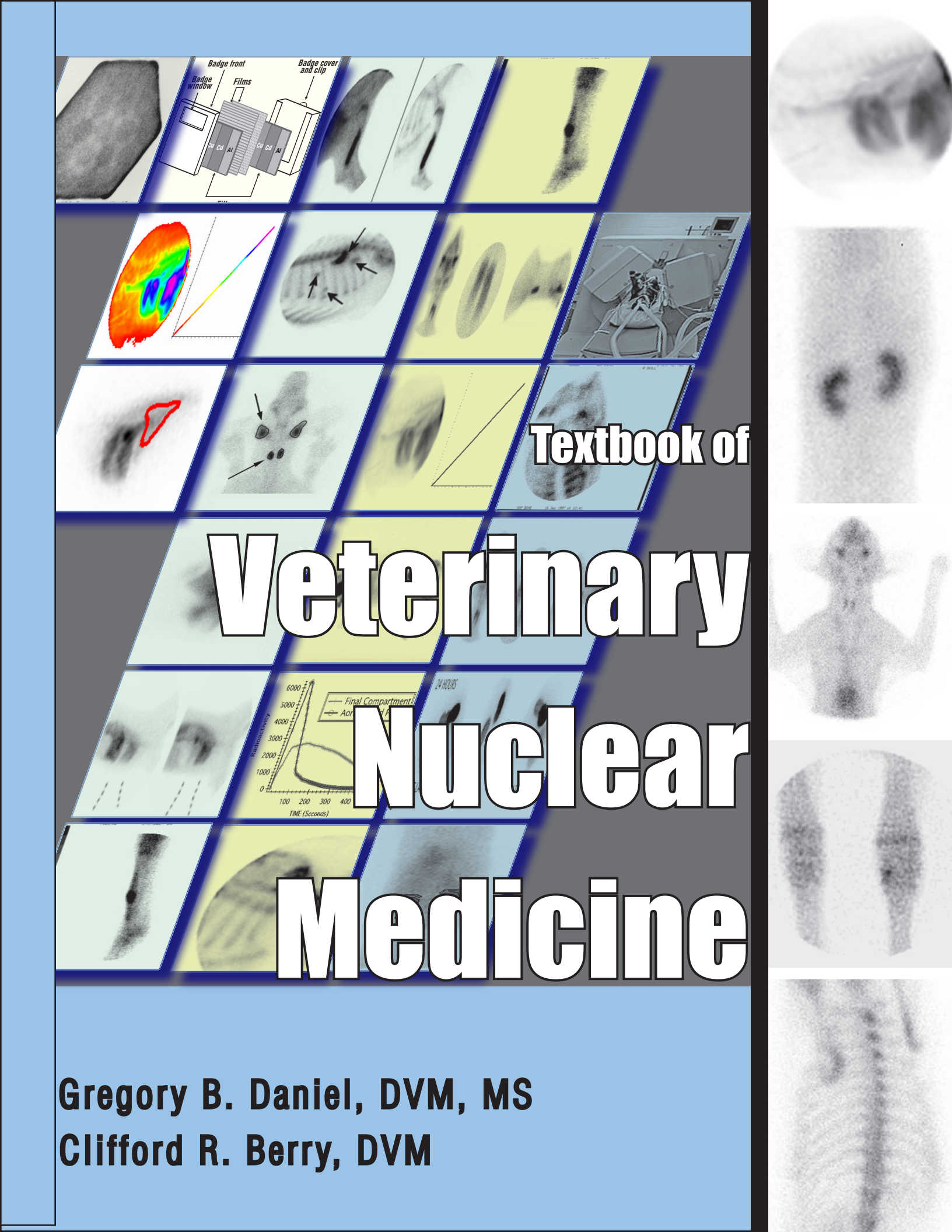




The background of the cover is a collage of various nuclear medicine images. It includes several bone scans (skeletal surveys) showing different views of a skeleton. There are also organ scans, such as a liver scan and a kidney scan. A diagram in the top left shows a 'Badge front' with 'Films' and 'Badges' and a 'Badge cover and clip'. A color-coded image of a kidney is in the middle left. A graph of 'Radioactivity' vs 'TIME (Seconds)' is in the bottom left. A '24 HOURS' scan is in the bottom middle. A 'Final Compartment' graph is in the bottom right. The title 'Textbook of Veterinary Nuclear Medicine' is prominently displayed in the center.

Textbook of Veterinary Nuclear Medicine

Gregory B. Daniel, DVM, MS
Clifford R. Berry, DVM

Published by and in conjunction with the American College of Veterinary Radiology.

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Textbook of Veterinary Nuclear Medicine, second edition

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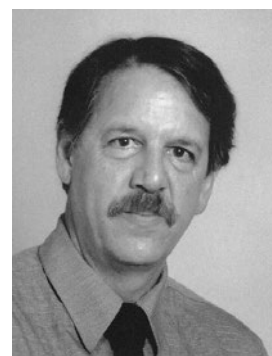
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Dedication



I would like to dedicate my portion of this book to my mentor Dr. Robert Twardock. I must also thank Dr. Steve Kneller and the other radiologist for my training in radiology but I developed my interest in nuclear medicine from Dr Twardock. Over the years I have come to realize that I learned much more from Dr. Twardock than just nuclear medicine. He is the quintessential Professor, always searching for the truth without bias. Today I see people performing research seeking promotion and grant overhead dollars but Dr. Twardock did research for the sake of advancing the body of knowledge in the field. He taught me that in research, you do not seek a desired result but only the true result, positive or negative. He always knew the best way to analyze a problem and ask the right questions. His integrity was beyond dispute therefore others had confidence in his conclusions. My career choice to stay in academia is a direct result of my time spent with Dr. Twardock. Dr. Twardock is popular among the faculty and staff at the University of Illinois and he shows compassion for his fellow man. His devotion to his family and his faith in God was and still is an inspiration to me.

Now I am ready to devote more of my time to my best friend in the world who I also love



I would like to dedicate my portion of this book to my mentor Dr. Philip D. Koblik. Dr. Koblik served as an inspiration and a mentor during my residency training and most importantly he was a close friend. It usually takes a death or tragedy to get our attention in life and with Phil's passing, it definitely shook my world. He is greatly missed by all who had the privilege to work with him at any level when he was Tufts University or University of California, Davis. He inspired me to pursue the unknown and not just take answers that have been passed down from radiologist to radiologist. He helped me to formulate a thought process that drove me into academia for the first part of my career as a veterinary radiologist. Dr. Koblik always was there when I needed help and he was available for research projects, even at two in the morning. Dr. Koblik helped me to see beyond the established norms and to think outside the box. Most importantly, Dr. Koblik taught me how to pursue research goals, and present the data to the scientific community for peer review. I know that Dr. Koblik is greatly missed by his family, fellow colleagues at the University of California, Davis and all of the individuals that he impacted over the years.

I now turn my attentions to the family that God has blessed me with. First and foremost, my wife, Brigitt, whom I love dearly and know that we are connected forever as soul mates. My two children, Jennifer and Hudson, are the pride and joy of my life. My daughter has taught me how to believe in myself, even when there is doubt and despair. She has taught me how to love, the Lord my God and serve others

Preface

The purpose of this book is to advance the field of nuclear medicine by providing an instructional aid to those learning about veterinary nuclear medicine and to be a reference text for those who are performing veterinary nuclear medicine studies. Our first Edition was created as a result of a directive from the Society of Veterinary Nuclear Medicine which operates under the governance of the American College of Veterinary Radiology. At that time, there were no reference texts on the topic of veterinary nuclear medicine. Since that time there have been several textbooks that have devoted chapters to the topic and at least one book that is devoted to Equine Scintigraphy. Still there is not a single text that encompasses the breath of nuclear medicine procedures and applications in both large and small animals. This second edition, called "Textbook of Veterinary Nuclear Medicine," was written to help fill this void. The contributors to this book are leaders in the field of veterinary nuclear medicine. We would like to thank them for their willingness to work on this project. There are many others who would be considered experts in the field of veterinary nuclear medicine but are not contributors to this book directly as authors but their addition of the body of knowledge of veterinary nuclear medicine has served as a foundation for this book and we also recognize them for their contributions. In science, all advancements are based on the knowledge gained from the work of our predecessors. We hope that this text will serve as a stepping-stone for others to continue to move the field of veterinary nuclear medicine forward.

The copyrights to this book belong to the American College of Veterinary Radiology. The copyrights of the images on the enclosed CD reside with the University of Tennessee. Research and the development of new techniques will be necessary for veterinary nuclear medicine to maintain an important role in diagnostic imaging. There is still much to be learned about the application and techniques of nuclear medicine in the veterinary field. We are only limited by the extent of our imagination, time and desire to pursue such interest.

Gregory B Daniel
Clifford R Berry

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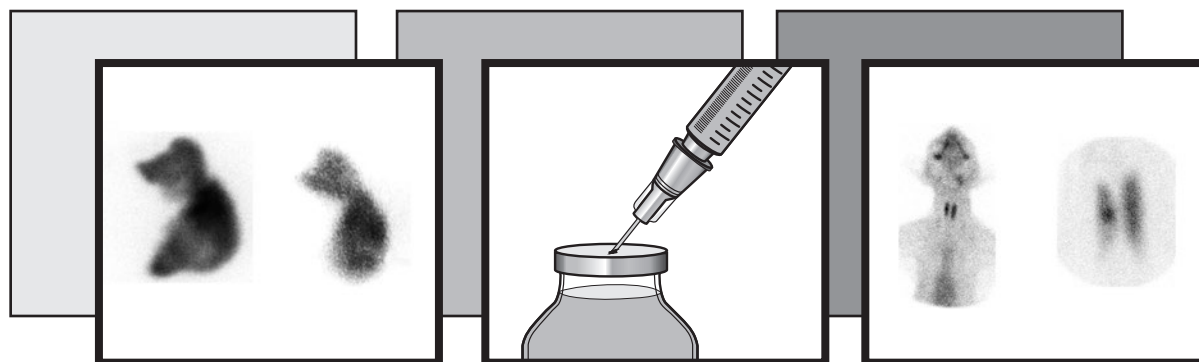
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Radioactive Decay, Radioactivity, Tc-99m Generator, and Radiopharmaceuticals

Richard J. Kowalsky, PharmD



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Introduction

A radiopharmaceutical is a chemical substance that contains a radioactive atom (radionuclide) within its structure and is suitable for *in vivo* use in the diagnosis or treatment of disease.¹⁻⁵ Radiopharmaceuticals are formulated in various physiochemical forms to deliver the radioactive atoms to particular parts of the body. Once localized, the gamma radiation emitted from the radiopharmaceutical escapes from the body permitting external detection and measurement. A scintillation camera detects the gamma radiation creating an image (scan) of the distribution of radioactivity in the organ(s) of interest. This allows evaluation of the functional and morphologic status of the organ(s) in question.

The international unit (IU) of radioactivity is the becquerel (Bq; one disintegration per second).¹ The amount of radioactivity administered to a patient in a nuclear medicine study is termed the dosage that is measured in units of megabecquerels (MBq; 1 Bq = 1 disintegration per second) or millicuries (mCi, or 10^{-3} Ci). The curie (Ci), which is equal to 3.7×10^{10} disintegrations (atoms decaying) per second, is the traditional measure of radioactivity currently used in the United States. The conversion is 1 mCi equals 37 MBq. The amount of radiation absorbed by tissue in the body in which a radioactive substance resides, termed the radiation dose, is traditionally measured in units of rads. One rad (radiation absorbed dose) is equal to 100 ergs of energy absorbed in 1 gram of tissue. The IU of absorbed dose, the gray (Gy), is equal to 1 joule (J) of energy absorbed in 1 kg of tissue (1 Gy = 100 rads). A goal in diagnostic nuclear medicine is to administer the optimum dosage of radioactivity to acquire the desired information with the least amount of radiation dose to the patient. Therefore, the clinical usefulness of a radiopharmaceutical is determined, in part, by the radionuclide's physical properties (radiation, energy, and half-life). In general, the lowest radiation dose and the best diagnostic images are obtained if the radionuclide has a short half-life and emits only gamma radiation of low energy. Technetium-99m, or ^{99m}Tc , is a good example of this, having a 6 hour half-life and gamma emission of 140 KeV which is efficiently detected by the gamma camera.

Radionuclides for therapy will emit particulate radiation (β or α particles), which deposits high amounts of energy per distance traveled (linear energy transfer

or LET) within the target organ or tumor. Phosphorus-32 (^{32}P) emits only β radiation. Some radionuclides emit β and γ radiation simultaneously and, therefore, possess both therapeutic and diagnostic usefulness, such as iodine-131 (^{131}I).

Regardless of its physical properties, a radionuclide is dependent on its chemical form for localization in specific organs. Thus, ^{131}I circulates as the iodide anion and localizes in the thyroid gland but, labeled to an antibody, will bypass the thyroid and seek out the tumor with the antigen that specifically reacts with that antibody. We, therefore, find several different chemical forms labeled with the same radionuclide. Technetium-99m, ^{99m}Tc , is another example. In addition to its desirable physical properties, technetium's unique chemistry is suited to the production of several different radiopharmaceuticals. Another advantage of ^{99m}Tc is ready availability in the hospital from a generator system. On a daily basis, the nuclear technologist elutes ^{99m}Tc in saline from the molybdenum-99 (^{99}Mo) / technetium-99m (^{99m}Tc) generator. The sterile solution of sodium ^{99m}Tc -pertechnetate ($\text{Na}^{99m}\text{TcO}_4$) obtained may be used as is or to prepare other ^{99m}Tc labeled radiopharmaceuticals. Because of these advantages, ^{99m}Tc is the radionuclide used in the majority of nuclear medicine studies. Table 1.1 lists the various radionuclides and their decay characteristics used for routine nuclear medicine studies in both human and veterinary medicine.^{1,5}

Imaging procedures provide diagnostic information about organs or body systems based on the distribution pattern of radioactivity in the body and are either dynamic or static. Dynamic studies provide functional information through measurement of the rates of accumulation and removal of the radiopharmaceutical by the organ. Static studies provide morphologic information regarding organ size, shape, position, the presence of space-occupying lesions and, in some cases, relative function. The pattern of radiopharmaceutical distribution observed in a nuclear medicine scan depends on the particular organ being studied and varies with different diseases. In some studies the normal organ concentrates the radiopharmaceutical and appears "hot," whereas the diseased area excludes radioactivity and appears "cold." The ^{99m}Tc -sulfur colloid liver scan is an example, where a tumor or cyst destroys the phagocytic cells that normally engulf the radioactive colloidal particles. In another type of study, the normal organ excludes

Table 1.1: Useful Radionuclides in Nuclear Medicine

Radionuclide	Decay Mode/ Production	Half-Life	Photon Energy in keV (Photon Abundance %)	Comments
Carbon-11	β^+ ; Cyclotron	20 minutes	394 β^+ (99%); 511 (199%)	Used for metabolic studies; limited use in radiochemistry due to short half-life.
Nitrogen-13	β^+ ; Cyclotron	10 minutes	488 β^+ (100%); 511 (200%)	Used for myocardial perfusion studies.
Oxygen-15	β^+ ; Cyclotron	2 minutes	721 β^+ (100%); 511 (200%)	Used for flow and perfusion studies of any organ or area.
Fluorine-18	β^+ ; Cyclotron	109 minutes	250 β^+ (97%); 511 (194%)	Bound to deoxy glucose and used for metabolic studies.
Phosphorus-32	β^- ; Nuclear Reactor	14.3 days	No Gamma; 695 β^- (100%)	Used for the treatment of polycythemia vera.
Cobalt-57	EC; Cyclotron	271 days	122 (86%)	Used as a flood source for gamma camera quality control.
Chromium-51	EC; Cyclotron	27.7 days	320 (10%)	Used for red blood cell survival studies.
Gallium-67	EC; Cyclotron	78 hours	93 (40%), 185 (20%), 300 (16%)	Used for inflammatory imaging; limited use in tumor imaging.
Gallium-68	β^+ ; Cyclotron	67 minutes	836 β^+ (88%); 511 (200%)	Decay product of ^{68}Ge (decays by EC with a 271 day $T_{1/2}$); used for attenuation correction in PET studies.
Molybdenum-99	β^- ; Nuclear fission (^{235}U)	67 hours	740 (14%), 780 (4%)	Parent in generator for sodium pertechnetate (eluate).
Technetium-99m	IT; Obtained from ^{99}Mo generator	6.02 hours	140 (86%)	Used either as pertechnetate or in combination with a radiopharmaceutical; most common gamma emitter used in nuclear medicine.

(β^+ = positron decay; β^- = negatron decay; EC = electron capture; IT = isomeric transition)

Table 1.1: Useful Radionuclides in Nuclear Medicine (continued)

Radionuclide	Decay Mode/ Production	Half-life	Photon Energy in keV (Photon Abundance %)	Comments
Indium-111	EC; Cyclotron	2.8 days	172 (90%), 247 (92%)	Used as $^{111}\text{InCl}_3$ or ^{111}In -oxime for WBC labeling and inflammatory imaging (delayed imaging of >24 hours possible).
Iodine-123	EC; Cyclotron	13.1 hours	159 (83%), 27 (x-rays)	Used for evaluation of thyroid function; in combination with MIBG or other radiolabeled iodine products for nuclear medicine imaging; radiolabel for antibodies and proteins.
Xenon-127	EC; Cyclotron	36.4 days	172 (25%), 203 (68%), 375 (18%)	Ventilation studies.
Iodine-131	β^- ; Nuclear Fission (^{235}U)	8.04 days	364 (81%), 637	Used for radiotherapy of functional thyroid disorders and radiolabels for treatment of other tumors.
Xenon-133	β^- ; Nuclear Fission (^{235}U)	5.3 days	81 (36%)	Ventilation studies; poor image resolution.
Thallium-201	EC; Cyclotron	73 hours	69 (27%), 71 (47%), 80 (20%; x-rays)	Used for imaging myocardial perfusion.
Samarium-153	β^- ; Neutron Activation	1.93 days	103 (29%)	Used for treating bone metastatic disease; advantage of being able to image distribution within animal as well.

(β^+ = positron decay; β^- = negatron decay; EC = electron capture; IT = isomeric transition)

the radiopharmaceutical and appears “cold;” and the diseased area concentrates activity and appears “hot.” An example is the traditional brain scan with $^{99\text{m}}\text{Tc}$ -gluceptate where a brain tumor, for example, disrupts the blood-brain barrier, allowing radioactivity from the vascular pool to accumulate in the tumor but not in normal brain tissue. In still other studies, the normal organ may concentrate the radiopharmaceutical, but diseased tissue will concentrate it to a greater extent due to increased function or to a lesser extent due to decreased function. An example is thyroid imaging with radioiodide demonstrating the presence

of hyperfunctioning or hypofunctioning nodules. Examples of these scans are illustrated in Figure 1.1.

Basic Physics for Nuclear Medicine

Atomic Structure

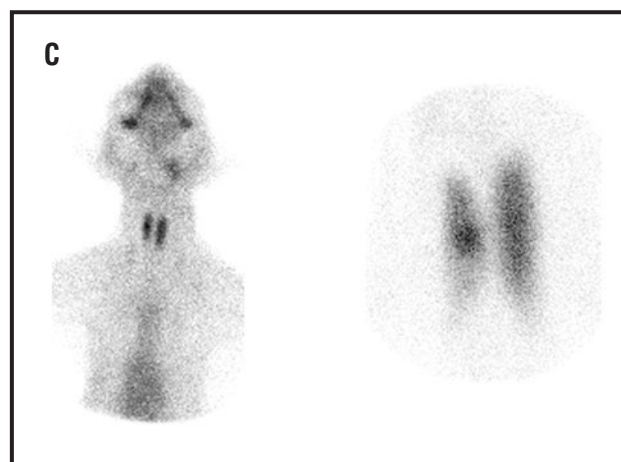
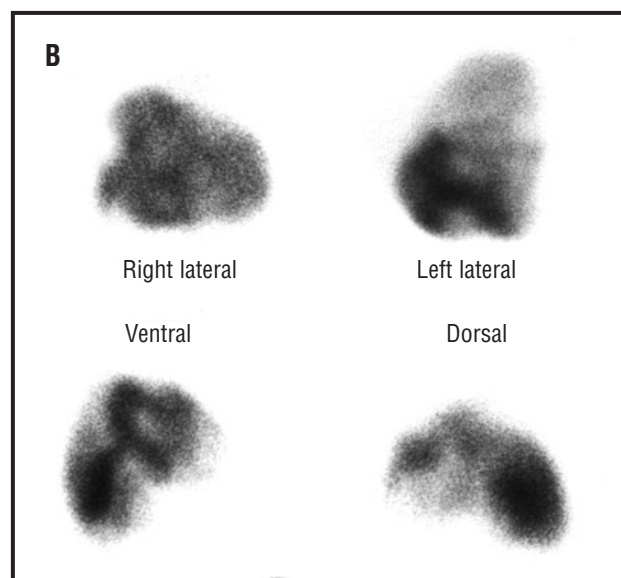
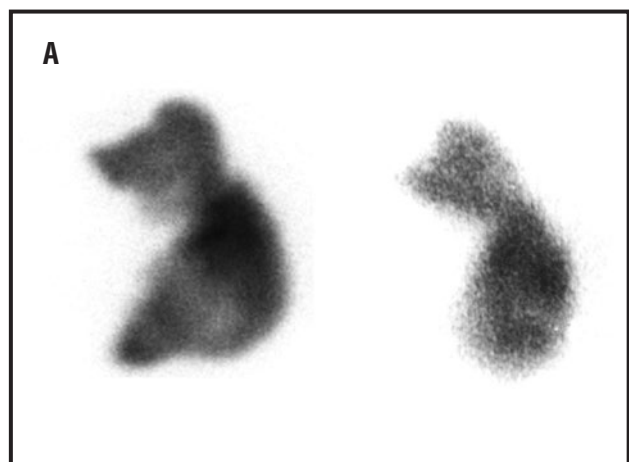
The atom is the building block of all molecules that will define the basic physical and chemical properties of a specific element. Using the older Bohr model

Figure 1.1: Typical normal and abnormal static images obtained with a planar imaging gamma camera

A, Normal uptake of the radiopharmaceutical within the target organ using ^{99m}Tc -DISIDA. A second image has been obtained using ^{99m}Tc -sulfur colloid. The photopenic ventral area in both images is the gallbladder fossa.

B, Abnormal “cold” spots where metastatic tumors have replaced normal hepatic parenchyma resulting in a photopenic void (^{99m}Tc -sulfur colloid study).

C, Ventral images of the thyroid gland using sodium pertechnetate obtained at 20 minutes postinjection. A low-energy, all-purpose collimator was used for the image on the left. A pinhole collimator was used for the image on the right. There is a focal area of increased $^{99m}\text{TcO}_4^-$ in the middle right thyroid lobe seen on the pinhole image.



of the atom, there is a central nucleus (made up of nucleons that include all of the protons and neutrons) and outer electron shells. The atomic number (Z) represents the number of protons within an atom and defines the atom as a particular element (eg, carbon and only carbon has 6 protons, $Z = 6$). The atomic mass (A) equals the number of protons plus the number of neutrons. The atomic weight is the average of the atomic masses of all of the naturally occurring isotopes of a given element. As an example, ^{99m}Tc is defined by a Z value of 43 protons. The atomic mass minus the atomic number equals the number of neutrons ($99 - 43 = 56$).

The neutron-proton ratio defines the atomic stability of a given nuclide or radionuclide (if the atom is unstable or radioactive). As the atomic mass increases, more neutrons are required to achieve atomic sta-

bility. Protons are positively charged and are held in place by certain nuclear forces (called strong forces, such as gluons, bosons). This nuclear “glue” is also impacted and determined by the number of neutrons. A plot of the neutron number versus proton number (atomic number or Z) shows that the line of stability is shifted toward increasing neutrons in a nonlinear, or exponential, fashion when compared with the proton number. A proton number that equals the neutron number defines the line of unity. The line of stability actually defines the stable nuclides for the different elements. Radioactive elements will be found to the right and left of the line of stability. Radioactive elements to the left of the line of stability are considered to be neutron rich or proton poor and will decay by negatron decay (beta minus or β^-). These radionuclides are typically naturally occurring radioactive

elements or elements produced by nuclear reactors (fission by-products). Radioactive elements to the right of the line of stability are considered to be neutron poor or proton rich and will decay by electron capture or positron decay (beta plus or β^+). These radionuclides are typically produced using cyclotrons.

A_x Charge
Z #

Where x is the specific element defined by the atomic number (Z) and A is the atomic mass (protons plus the neutrons); # is the number of molecules within the chemical structure, and charge is the electrical charge of the element. Z or the atomic number is the number of protons present in the element and A represents the total number of neutrons and protons in the element. All elements are usually electrically neutral so that the electron numbers equal the proton numbers.

The electron orbits or shells, according to the Bohr model of the atom, determine the number of electrons that will exist within a given orbit. The number of orbital electrons is equal to the atomic number in a

neutral atom. The inner shell is the K shell. These electrons have the highest binding energy so that these electrons are the hardest to eject from the atom. The end result of ejection of an inner shell electron include: the ionization of the atom, a photoelectron, and inward cascading of the outer shell electrons with the emission of characteristic x-rays. The outer shell electrons (valence electrons) have the weakest binding energies and thereby are easily ejected from their electron orbits. This again results in the ionization of the atom. The halogens or noble gases have an outer shell that is completely filled and thereby are chemically nonreactive. These inert gases include: helium, neon, argon, krypton, xenon and radon.

The Bohr model has, however, been shown to be too simplistic. Quantum physics has shown that the electron clouds are, in fact, probabilities of where electrons are predicted to be over the course of time. At any point in time, any electron can exist anywhere within the atom and can even pass through the nucleus. This passage of the electron through the nucleus explains electron capture as a possible decay scheme. There are many terms that have been used to describe various types of electrons and these are

Table 1.2: Basic Electron Descriptions

Electron	Particle that makes up outer part of atom. Has a negative charge and weighs 1/1860 less than a proton.
Orbital electron	Any electron within any shell that surrounds the nucleus.
Valence electron	Outer shell electron that determines the chemical characteristics and reactivity of a particular atom.
Augér electron	Electron ejected from an atomic orbit by energy released during electron transitions (eg, characteristic radiation).
Photoelectron	Electron ejected from a k shell as a result of interacting with an x-ray or gamma ray photon (photoelectric interaction); there is complete absorption of the photon's energy.
Internal conversion electron	Electron ejected from an atomic orbit because of internal conversion as energy is released from an unstable nucleus. This process competes with the normal emission of a gamma ray from the nucleus as part of the decay process.
Positron	Positively charged electron released from the nucleus of an atom that has undergone beta plus or positron decay.
Negatron	Negatively charged electron released from the nucleus of an atom that has undergone beta minus or negatron decay.

important when we consider different radioactive decay schemes (Table 1.2).

Einstein described the relationship between mass and energy in his famous publication in 1905, $E = mc^2$, where c is the speed of light in a vacuum (3×10^8 m/sec). Based on this relationship, one atomic mass unit (proton or neutron) has 931.5 mega electron volts (or 1×10^6 eV or 1 MeV) mass-energy equivalent and the electron has 0.511 MeV mass-energy equivalent (Table 1.3). There is always a difference between the theoretical sum of the component nucleons (greater) and the actual observed mass of a nucleus. This difference is called the mass deficit and the nuclear binding energy is defined as the energy equivalent of the mass deficit. In a radioactive decay process, the more stable daughter product will have an increased mass deficit.

Radioactive Decay

Nuclides that are unstable are called radionuclides. Because they are unstable, they will undergo radioactive decay where excess energy is given off in the form of particulate and/or electromagnetic radiations. Immutable physical constants for each radionuclide include the type of radiation emitted (form of radioactive decay), the specific energy released by

the radiation, and the physical half-life of the decay process. These parameters predict the usability of a given radionuclide for medical imaging, therapeutic purposes, or both. The daughter product always has a more stable nuclear configuration (may still be radioactive) and less energy with a larger mass deficit. In nuclear medicine, a radioactive atom can either serve as a tracer of a physiologic process (such as sodium pertechnetate being an I^- atom equivalent) or can be chemically bound to some other chemical and is then called a radiopharmaceutical. It is important to realize that the small amounts of a radiopharmaceutical injected (at least 10^6 difference between tracer amounts and normal physiologic chemicals) do not compete with the normal physiological process. These nuclides are mimicking the process so that as the radionuclide decays, one can observe the uptake or clearance patterns using an external radiation detector.

The types of emissions include particulate emissions (alpha particles, electrons, and positrons) and electromagnetic emissions (gamma rays and x-rays). There are five different types of radioactive decay that will be considered. These include: alpha decay, negatron decay (beta minus), positron decay (beta plus), electron capture, and isomeric transitions. There is a

Table 1.3: Basic Properties of Nucleons and Electrons and Their Mass Energy Equivalences

Particle	Charge	Mass (U)	Mass (MeV)
Proton	+1	1.007277	938.211
Neutron	0	1.008665	939.505
Electron	-1	0.000549	0.511

Table 1.4: Definitions Between Isotopes, Isotones, Isobars and Isomers Based on Differences In Their Proton Number, Neutron Number, Atomic Mass or Atomic Energy

Transition Type	Proton Number (Z)	Neutron Number (A-Z)	Atomic Mass (A)	Energy
Isotope	Same number	Different number	Different number	Different number
Isotone	Different number	Same number	Different number	Different number
Isobar	Different number	Different number	Same number	Different number
Isomer	Same number	Same number	Same number	Different number

Table 1.5: Expiration Times for ^{99m}Tc Based on the Amount of ^{99}Mo Present In the Eluate

Initial $\mu\text{Ci } ^{99}\text{Mo}/\text{mCi } ^{99m}\text{Tc}$	Expiration Time (hours)
0.135	1
0.122	2
0.109	3
0.098	4
0.089	5
0.080	6
0.072	7
0.065	8
0.058	9
0.052	10
0.047	11
0.042	12

shifting of nucleons so that there will be a change in atomic number or neutron number, but usually the transition will not impact the atomic mass, except in the case of alpha decay. There are four different types of transitions when one compares the proton number, neutron number, atomic mass, and energy of the parent radionuclide with the daughter product. These transitions include: isotone, isobar, isotope, and isomer transitions (Table 1.4).

Radiation is the emission and propagation of energy through space. Alpha particles are helium nuclei, $^4\text{He}^{2+}$. Beta particles are electrons. Negatively charged beta particles are called negatrons; positively charged beta particles are called positrons. Beta particles have a resting-mass energy equivalent to 0.511 MeV. Gamma rays are a form of high energy, nonparticulate, electromagnetic radiation. They have no mass or charge but will interact with matterlike particles. They are emitted from unstable nuclei secondary to radioactive decay.

To achieve nuclear stability, a radionuclide will eject excess particles from the nucleus so that a nuclear transformation must first take place. In this case, one nucleon is created from another, and “unwanted” particles are then ejected during the actual decay process. Thus, excess energy is released and a new ratio of neutrons to protons is established. In general,

heavy radionuclide nuclei undergo alpha particle decay, as it is easier to release two protons and two neutrons simultaneously. Those radionuclides with too many neutrons for stability undergo negatron decay; those with too many protons for stability undergo positron decay or electron capture.

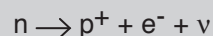
Alpha Decay

Alpha emitters are not used routinely in diagnostic nuclear medicine primarily because they produce dense ionizations (high LET) within tissue accompanied by high radiation dose. The decay of historical interest is that of radium (^{226}Ra), which decays to radon (^{222}Rn) gas according to the following equation:



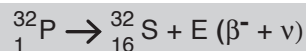
Negatron Decay

Neutron-rich nuclides undergo negatron or beta minus decay. In this process, a neutron is converted into a proton, a negative electron, and an antineutrino ($\bar{\nu}$) in the nucleus of the radioactive atom according to the following transformation:

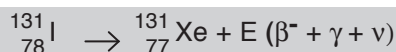


Because the electron and the neutrino do not normally reside in the nucleus, they are released or ejected with a certain amount of nuclear energy. The antineutrino is a massless, chargeless particle that cannot be detected with nuclear medicine instruments and contributes no radiation dose to the patient. Thus, the only important radiation is the beta particle.

There are two types of negatron emitters: pure beta emitters and beta-gamma emitters. A pure beta emitter releases excessive nuclear kinetic energy only with a beta particle and neutrino. Phosphorus-32 is an example of a pure beta emitter in nuclear medicine.



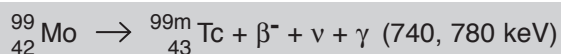
Because pure beta emitters lack gamma ray emissions, they are of no use as diagnostic agents in nuclear medicine but are useful for therapeutic applications. Beta-gamma emitters, however, release excessive kinetic energy as beta particles, neutrinos, and gamma rays. An example of a beta-gamma emitter is iodine-131.



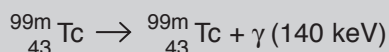
The gamma ray occurs because not all of the excess nuclear energy is released with the beta particle and the neutrino. For example, in the decay of one atom of ${}^{131}\text{I}$, 971 keV of transition energy (E) is released. The most common pattern of release is a beta particle with an energy of 405 keV, a neutrino of 202 keV, and a gamma ray of 364 keV. The maximum energy (E_{max}) the beta particle can obtain is equal to the maximum transitional energy that is released, whereby no gamma ray or neutrino would be released by this particular nucleus undergoing decay. This only happens in a minority of decays, whereas the majority of decay events will result in a beta particle energy equal to 1/3 of E_{max} . There is a spectrum of energies with which the beta particle can be ejected from the nucleus, and the spectrum would look like a filtered polyenergetic x-ray beam where the intensity (x-ray numbers) is plotted against the specific x-ray energy (keV).

Isomeric Transition

Typically in beta decay, the gamma ray is released immediately following the beta particle from the excited daughter nuclide, such as ${}^{131}\text{Xe}$ in the example shown before. However, some excited daughter nuclides hold onto this gamma energy for a measurable period of time before releasing it. So-called metastable radionuclides are designated with a lowercase “m” in the mass number. De-excitation of a metastable species is called isomeric transition. An example of the production of a metastable nuclide is the beta decay of molybdenum ${}^{99}\text{Mo}$ to ${}^{99\text{m}}\text{Tc}$ -technetium and the subsequent isomeric transition of ${}^{99\text{m}}\text{Tc}$ to ${}^{99}\text{Tc}$ shown in the following decay schemes:



and then the ${}^{99\text{m}}\text{Tc}$ will undergo decay,



Following the decay of ${}^{99}\text{Mo}$, some but not all ${}^{99\text{m}}\text{Tc}$ atoms release their gamma ray energy immediately. Others release gamma rays at a later time. Thus, ${}^{99\text{m}}\text{Tc}$ atoms release their energy over a spectrum of time allowing ${}^{99\text{m}}\text{Tc}$ atoms to build up as ${}^{99}\text{Mo}$ atoms

decay. This decay process and the fact that ${}^{99}\text{Mo}$ has a longer half-life than ${}^{99\text{m}}\text{Tc}$ forms the basis for the ${}^{99}\text{Mo}/{}^{99\text{m}}\text{Tc}$ generator. ${}^{99}\text{Mo}$ breakthrough (or leakage) is a concern when using a ${}^{99}\text{Mo}$ generator. Table 1.5 lists the amount of allowable ${}^{99}\text{Mo}$ within an eluate at elution and at various times prior to injection.

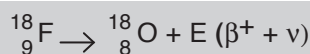
Positron Decay

Positron decay occurs when the neutron-proton ratio is below the line of stability. These proton-rich nuclides decay by converting a proton into a neutron, a positive electron, and a neutrino in the nucleus according to the following transformation:



The positron and neutrino are ejected from the nucleus and a new neutron-proton ratio is established. As with beta minus or negaton decay, there is a spectrum of energies with which the positron can be ejected. The remaining energy associated with the nuclear decay would be distributed to the neutrino. A threshold transitional energy is required by the nucleus prior to the nucleus being able to decay by positron decay. This transitional energy is 1.022 MeV representing the resting mass-energy equivalent of two electrons.

Some positron emitters also emit gamma rays, but all of them produce annihilation radiation. Two 0.511 MeV photons result from the annihilation of a positron with a negative electron as the positron comes to rest outside the nucleus of origin. This results in an annihilation reaction and the production of the two 0.511 MeV photons. The annihilation photons are used to detect and quantitate positron emitting radiopharmaceuticals with positron emission tomography (PET). The decay of fluorine-18, used in ${}^{18}\text{F}$ -fluorodeoxyglucose (${}^{18}\text{FDG}$), is a typical example:



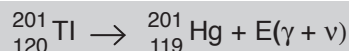
Electron Capture Decay

Positron decay requires that a minimum transition energy (E) of 1.022 MeV be available. Proton-rich nuclides that do not have this transitional energy available decay by electron capture. The end result in the nucleus is the same, but the mechanism is differ-

ent. When the electron capture decay mode occurs, an orbital electron (usually a K shell electron) is captured by the nucleus, whereby it combines with a proton to form a neutron and a neutrino according to the following transformation:



If the ejected neutrino takes all the transition energy, no gamma ray is produced. However, if the neutrino takes only part of the energy, the remainder is released by the excited daughter nucleus as a gamma ray. Many radionuclides in nuclear medicine decay by electron capture. In fact, it is a desirable decay mode because it produces no particulate radiation that would contribute to an increased radiation dose to the patient. As an example, thallium-201, a commonly used radionuclide for cardiac perfusion imaging, decays by electron capture as follows:



In summary, the most desirable radionuclide for diagnostic imaging would have a short half-life, emit only gamma radiation of low energy (100-200 keV via isomeric transition or electron capture decay), and be able to be formulated into several chemical forms. Technetium-99m fits these requirements better than any other radionuclides currently available.

Radioactivity

The radioactivity or rate of radioactive decay of a radionuclide, ie, the number of disintegrations per unit time, is directly proportional to the number of radioactive atoms present and the radionuclide's decay constant, λ . This is described by the following equation:

$$A = \lambda N$$

The decay constant is the fraction of radioactive atoms that decay per unit time. It is mathematically equal to $0.693/(T_{p1/2})$. Thus, the activity of a radionuclide will be large if the number of atoms is large and the half-life is short and vice versa. The decay constant is different for each radionuclide; and, for a given number of atoms, the activities will be differ-

ent also. One can use the above equation to convert activity into weight. For example, one could calculate the actual weight of iodine-131 in a 10 millicurie dose as follows:

$$A = (10 \text{ mCi})(3.6 \times 10^8 \text{ dps/mCi}) = 3.7 \times 10^8 \text{ dps}$$

$$\lambda = (0.693)/[(8.04 \text{ d})(24 \text{ hr/day})(3600 \text{ sec/hr})] = 9.98 \times 10^{-7} \text{ sec}^{-1}$$

$$N = A/\lambda = 3.7 \times 10^8 \text{ dps}/9.98 \times 10^{-7} \text{ sec}^{-1} =$$

$$3.7 \times 10^{14} \text{ disintegrations (atoms)}$$

$$\text{Weight (gm)} = [3.7 \times 10^{14} \text{ atoms}/6.022 \times 10^{23} \text{ atoms/mole}] \times [131 \text{ gm/1 mole I-131}] = 8 \times 10^{-8} \text{ gm}$$

Radioactive decay is an exponential process, which is described by the following equation:

$$A = A_0 e^{-\lambda t}$$

where, A = activity remaining after the original amount, A_0 , decays for a period of time, t . This equation has practical value in calculating the amount of activity present in a radiopharmaceutical vial before or after its calibration date and time.

The following example will illustrate. What is the concentration of ${}^{99m}\text{Tc}$ in a at 11:00 am if it originally contained 100 mCi in 10 mL at 7:00 am? As the concentration at 7:00 am is 10 mCi/mL, the concentration at 11:00 am is:

$$A = A_0 e^{-\lambda t}$$

$$(10 \text{ mCi/ml}) e^{-(0.693/6 \text{ hr}) \times 4 \text{ hr}} = 6.3 \text{ mCi/mL}$$

This equation can also be used to create decay tables for radionuclides. Decay tables are more convenient to use than the exponential equation for making routine calculations. A decay table is a tabulation of specified times and the respective fraction of activity remaining at those times. Thus, the above equation can be rearranged as follows:

$$(A/A_0) = e^{-\lambda t}$$

where A/A_0 is the fraction of radioactivity remaining after various times, t . It results in a postcalibration decay table. The reciprocal of this equation would result in a precalibration decay table. For example, a postcalibration and precalibration decay table for ${}^{99m}\text{Tc}$ per hour is as follows:

Time (hours)	$e^{-\lambda t}$	$e^{+\lambda t}$
0	1.000	1.000
1	0.891	1.122
2	0.794	1.260
3	0.707	1.414
4	0.630	1.587
5	0.561	1.782
6	0.500	2.000

The following example calculations illustrate the use of the decay table.

Example 1:

If a vial of ^{99m}Tc contained 150 mCi at 7:00 am, how much activity is present at 9:00 am?

Answer: 150 mCi (0.794) = 119 mCi

Example 2:

Hospital ABC requires a 20 mCi dose at 11:00 am. How much activity must be put into the syringe if the dose is prepared at 8:00 am? In this case the dose must be precalibrated for 3 hours, decay before use.

One can either multiply the desired activity by the 3-hour precalibration decay factor or divide by the 3-hour postcalibration decay factor.

Answer: 20 mCi (1.414) = 28.28 mCi or

20 mCi / 0.707 = 28.28 mCi

Example 3:

Calculate the activity remaining in a vial of ^{99m}Tc 8 hours later if it originally contained 100 mCi. In this case, because the table does not contain an 8-hour decay factor, one must be created by combining the 6-hour and the 2-hour decay factors.

Answer: 100 mCi (0.5) (0.794) = 39.7 mCi

Molybdenum-99/Technetium-99m Generator

A generator is a system that contains a long-lived parent radionuclide that decays to a short-lived daughter. The most common generator used in human and veterinary nuclear medicine is the $^{99}\text{Mo}/^{99m}\text{Tc}$ generator. The generator consists of a chromatography column containing aluminum oxide to which the ^{99}Mo is adsorbed. The ^{99}Mo decays to ^{99m}Tc where the greatest degree of ^{99m}Tc radioactiv-

Figure 1.2: Decay of ^{99}Mo and ingrowth of ^{99m}Tc activities over time in a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator

A, Time-activity curves show ^{99m}Tc reaches a point of transient equilibrium where it decays at the same rate as the parent, ^{99}Mo ($T_{p1/2} = 67$ hours). This is reached within 23 hours of elution of the generator.

B, Time-activity curves showing daily elutions (drop in amount of ^{99m}Tc) and time period for ingrowth of more ^{99m}Tc ; 50% radioactivity of the ^{99m}Tc is reached by 6 hours after the first elution.

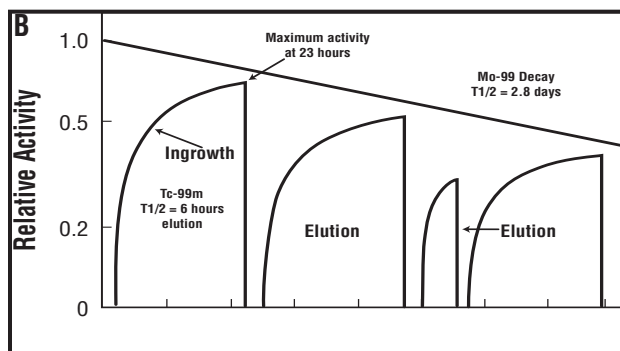
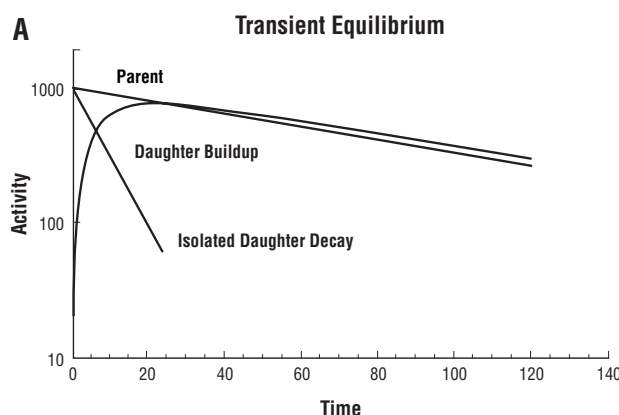


Table 1.6: Tc-99m Radiopharmaceuticals

Tc-99m Agent	Properties/Comments	Mechanism of Localization	Primary Studies
Albumin Aggregated (MAA) [Bracco, CIS-US, Draximage, Mallinckrodt]	Suspension of 10-90 μm particles; preparation: varies with manufacturer, typically add 30-50 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$, incubate 5 min; store at refrigerator temperature; use within 6 hr of preparation; number of particles/vial varies with manufacturer; should dilute number of particles before use in pulmonary hypertension or in case of suspected severe pulmonary thromboembolism (by 50% or from 500,000 particles to less than 250,000 particles).	Capillary blockade.	Perfusion lung imaging. Can also be used for perfusion imaging of a particular organ of interest if injected proximal to the organ's capillary bed. Quantification/confirmation of right to left shunts. Critical organ is the lung; 0.66 rads/3 mCi injected dose.
Albumin Tc-99m Human Serum Albumin [Amersham Health]	True solution; preparation: add 1 mL sterile water and up to 100 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 3 mL, incubate 20 minutes; store at Refrigerator Temperature; use within 6 hr.	Compartmental confinement, distributed in plasma space.	Blood pool imaging. Critical organ is the urinary bladder wall; 0.66 rads/20 mCi.
Apcitide AcuTect [Diatide]	True solution; preparation: add up to 50 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 1-3 mL, heat on boiling water bath 15 min; store at room temperature; use within 6 hr.	Binds to GPIIb/IIIa receptors on activated platelets.	Thrombus localization. Critical organ is the urinary bladder wall; 4.4 rads/20 mCi injected dose.
Arcitumomab (CEA-Scan) [Immunomedics]	True solution; preparation: add 30 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 1 mL, incubate for 5 min, add 1 mL saline; store at room temperature; use within 4 hr.	Reacts with carcinoembryonic antigen expressed on carcinomas.	Localization of metastatic colorectal carcinoma. Critical organ is the kidney; 0.074 rads/20 mCi injected dose.
Bicisate (ECD) NeuroLite [Bristol Meyer Squibb]	True solution; preparation: reconstitute kit with 3 mLs 0.9% NaCl; add 1 mL to 100 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 2 mL phosphate buffer; incubate 30 min. Store at room temperature; use within 6 hr.	Passive diffusion via blood-brain barrier into normal brain; ionization of molecules in brain cells prevents backdiffusion, trapping activity in brain.	Cerebral blood flow imaging. Critical organ is the urinary bladder wall; 2.2 rads/20 mCi injected dose.
Disofenin (DISIDA) Hepatolite [CIS-US]	True solution; preparation: add 12-100 mCi in 4-5 mL; incubate 4 min; store at room temperature; use within 6 hr.	Active transport on hepatocyte membrane (bilirubin anion receptor).	Liver imaging (hepatobiliary). Critical organ is the proximal large intestine; 1.94 rads/5 mCi injected dose.

Table 1.6: Tc-99m Radiopharmaceuticals continued

Tc-99m Agent	Properties/Comments	Mechanism of Localization	Primary Studies
Depreotide NeoTect [Diatide]	True solution; preparation: add 15-50 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 1 mL; heat in boiling water 10 min; store at room temperature; use within 5 hr of preparation.	Binds to somatostatin receptors.	Localization of somatostatin receptor bearing pulmonary masses and neuroendocrine tumors. Critical organ is the kidney; 6.6 rads/20 mCi injected dose.
Glucaptate (GH) TechnoScan [Mallinckrodt]	True solution; preparation: add up to 300 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 2-10 mL; incubate 15 min; store at refrigerator temperature; use within 6 hr.	Glomerular filtration (protein-free fraction) and tubular secretion (protein-bound fraction).	Renal imaging collecting system (early); renal parenchyma (late). Critical organ is the kidney cortex; 4.8 rads/20 mCi injected dose.
Medronate (MDP) [Bracco, CIS-US, DraxImage, Mallinckrodt, Amersham Health]	True solution; preparation: add up to 300 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 2-8 mL; incubate for 2 min; store at room temperature; use within 6 hr.	Chemiadsorption.	Bone imaging. Critical organ is the bladder wall; 4.65 rads/20 mCi injected dose.
Mebrofenin Choletec [Bracco]	True solution; preparation: add up to 100 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 1-5 mL; incubate 15 min; store at room temperature; use within 18 hr.	Active transport at the hepatocyte membrane (bilirubin anion analog).	Liver imaging (hepatobiliary). Critical organ is the upper large intestine; 1.24 rads/5 mCi injected dose.
Mertiatide TechnoScan MAG3 [Mallinckrodt]	True solution; preparation: add 20-100 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$; must add air to vial; boil for 10 min; store at room temperature; use within 6 hr.	Glomerular filtration tubular secretion.	Kidney imaging; renal function. Critical organ is the urinary bladder wall; 2.4 rads/5 mCi injected dose.
Oxidronate (HDP) OSTEOSCAN-HDP [Mallinckrodt]	True solution; preparation: add up to 200 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 3-6 mL to kit; store at room temperature; use within 8 hr of preparation.	Chemiadsorption.	Bone Imaging. Critical organ is the bone surfaces; 6.44 rads/20 mCi injected dose.
Pentetate (DTPA) [Bracco, CIS-US, Mallinckrodt, DraxImage]	True solution; preparation: add up to 160 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 1-8 mL to kit; incubate 2 min; store at room temperature; use within 6 hr (or 1 hr if used for measuring GFR).	Glomerular filtration.	Kidney imaging (collecting system). Critical organ is the urinary bladder wall; 5.4 rads/20 mCi injected dose.
Pyrophosphate (PPI) [Bracco, CIS-US, Mallinckrodt]	True solution; preparation: add up to 75 mCi $\text{Na}^{99\text{m}}\text{TcO}_4^-$ in 2-4 mL to kit; store at refrigerator temperature. Use within 6 hr.	Chemiadsorption (mitochondrial bone crystals and protein and areas of necrosis with excess calcium deposition).	Infarct avid imaging. Critical organ is the urinary bladder wall; 3.45 rads/15 mCi injected dose.

Table 1.6 Tc-99m Radiopharmaceuticals continued

Tc-99m Agent	Properties/Comments	Mechanism of Localization	Primary Studies
Red blood cells (UltraTag RBC [Mallinckrodt])	In vivo labeling: inject Sn-PPi IV (10-15 µg Sn ²⁺ /kg); wait 20 min and inject 20 mCi of Na ^{99m} TcO ₄ ⁻ to label red blood cells (75% label); in vitro labeling kit is available (UltraTag RBC [Mallinckrodt] with ≥ 95% labeling efficiency).	Compartmental confinement within the red blood cells in the vascular space.	Cardiac MUGA (blood pool) and gastrointestinal bleeding studies. Critical organ is the urinary bladder wall; 2.4 rads/20 mCi injected dose.
Red blood cells (heat damaged)	In vitro labeled cells heated at 49-50°C x 15 min.	Splenic sequestration.	Spleen specific imaging.
Sestamibi Cardiolite [Bristol Myers Squibb]	True solution; preparation: add 25-150 mCi Na ^{99m} TcO ₄ ⁻ in 1-3 mL to kit; boil for 10 min; store at room temperature; use within 6 hr.	Passive diffusion (binds to cytosolic substances and mitochondria).	Myocardial perfusion imaging. Critical organ is the upper large intestine; 4.5 rads/30 mCi (stress) and 5.4 rads/30 mCi (rest) injected dose.
Sulfur Colloid [CIS-US]	Colloidal dispersion; 0.1 - 1.0 µm-sized particles; preparation: various manufacturers differ; requires heating in boiling water; store at room temperature; use within 6 hr.	Phagocytosis by mononuclear phagocytic system including the liver [85%], spleen [10%] and bone marrow [5%]. Physical entrapment in the space of Disse.	Liver imaging (morphology). Critical organ is the liver; 1.7 rads/5 mCi injected dose.
Succimer (DMSA) [Amersham Health]	True solution; preparation: mix DMSA reagent: Na ^{99m} TcO ₄ ⁻ 1:1 to 1:2 parts by volume; Incubate for 10 min and use within 30 min of preparation.	Renal cortical binding via peritubular uptake. Tubular reabsorption following glomerular filtration.	Kidney Imaging (differential renal function). Critical organ is the renal cortex; 4.25 rads/5 mCi injected dose.
Tetrofosmin Myoview [Amersham Health]	True solution; preparation: add up to 240 mCi Na ^{99m} TcO ₄ ⁻ in 4-8 mL; incubate for 15 min; store at room temperature; use within 8 hr of preparation.	Passive diffusion.	Myocardial perfusion imaging. Critical organ is the gallbladder wall; 3.69 rads/30 mCi (stress) and 5.4 rads/30 mCi (rest) injected dose.

ity is reached at 23 hours from the previous generator elution (Figure 1.2). The ^{99m}Tc is separated from the ⁹⁹Mo by pulling sterile saline (0.9% NaCl) solution through the generator into an evacuated vial. About 5 mL of saline is all that is required to remove the ^{99m}Tc. What one has in the end is a sterile solution of saline containing the ^{99m}Tc as sodium ^{99m}Tc-pertechnetate (Na^{99m}TcO₄). This process is usually done once each day in the morning and typically provides sufficient ^{99m}Tc activity to perform all of the imaging studies for the day. Occasionally, during the end of the week, one may run out of ^{99m}Tc activity and will be required to re-elute the generator on that particular

day. This is satisfactory because the ^{99m}Tc activity builds up quite rapidly following elution, achieving about 50% of the maximum 23-hour radioactivity by 6-hours following the first elution. A ⁹⁹Mo generator is useful for 2 weeks; however, typically it is replaced at the end of each week.

There are two basic types of generator systems: the wet system and the dry system (Figure 1.3). In the wet system a large reservoir of saline is connected to the generator, which remains bathed in saline continuously. Radioactivity (^{99m}Tc) is eluted by simply connecting a sterile evacuated vial to the elution port. In the dry system, a charge of saline (5 mL)

is attached before attaching the evacuated vial. The 30 mL evacuated vial then draws the 5 mL of saline through the generator to remove the ^{99m}Tc activity followed by 25 mL of air, which “drys” the column. In the early years of generator use, all systems were of the wet variety. As nuclear medicine services grew, the loaded ^{99}Mo activity became increasingly larger, producing radiolysis products in the column, which prevented complete elution of ^{99m}Tc activity early in the week in the wet generator designs. This problem was solved, in part, by creating the dry system approach, which kept ^{99m}Tc in the easily eluted, oxidized form. Today, both systems are used with no apparent elution problems.

There are three tests that should be performed daily on the generator eluate. The first test is a radioactivity calibration using the dose calibrator to determine the activity eluted and the radioactive concentration (mCi/mL). This may be accomplished in two ways: (1) assaying the whole vial to obtain the total activity and from the total volume eluted determining the concentration; (2) drawing up a 1-mL aliquot into a syringe and assaying its contents. This measures the activity in the 1 mL volume plus that in the needle. Next, the 1 mL is expelled back into the eluate vial and the syringe reassayed to determine residual radioactivity. The difference between the two measurements provides the radioactivity per mL. The total activity in the vial can be obtained from the activity per mL and the total volume in the vial. The aliquot method is preferred because the operator is exposed to only a small fraction of the total radioactivity. Also, the concentration measurement using a syringe is more accurate than the whole-vial technique.

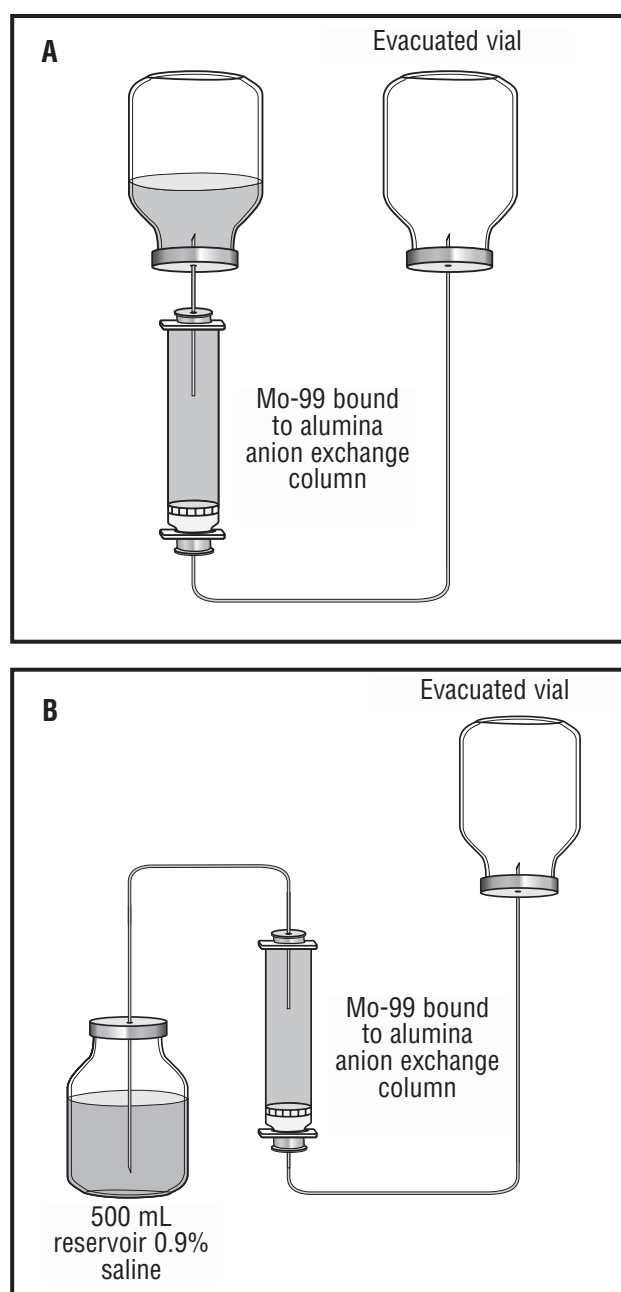
The second test on a generator eluate is a chemical purity test for the concentration of aluminum ion present. This can be done using a simple colorimetric spot test. A small drop of the pertechnetate is placed on a strip of filter paper impregnated with an indicator specific for the aluminum ion, which is the type of column to which the ^{99}Mo is adhered. Similarly, a spot of an aluminum standard solution (10 $\mu\text{g}/\text{mL}$) is made. The aluminum ion present reacts with the indicator to produce a pink color the intensity of which is proportional to the concentration of aluminum ion present. If the color intensity of the pertechnetate spot is less than the aluminum standard spot, the generator eluate passes the test. Thus, the

^{99m}Tc eluate must not contain more than 10 $\mu\text{g}/\text{mL}$ of aluminum ion.

The third test of a generator eluate is the radionuclide purity test for the presence of ^{99}Mo contamination. This is called the moly-99 breakthrough test. This test can be done with a gamma scintillation spec-

Figure 1.3: Diagram illustrating the dry (A) and wet (B) types of $^{99}\text{Mo}/^{99m}\text{Tc}$ generator systems

See text for details.



trometer but usually is done using the lead shield technique in the dose calibrator. With this method the whole vial of generator eluate is placed into a closed lead shield that is then placed into the dose calibrator adjusted to read ^{99}Mo activity. The shield is designed 0.25 inch thick so that all of the 140 KeV ^{99m}Tc photons are absorbed by the lead but only 50% of the more energetic 740- and 780-KeV ^{99}Mo gamma photons penetrate the shield. The photons that penetrate are counted in the ionization chamber and corrected to provide the microcuries of ^{99}Mo . Limits for ^{99}Mo contamination are not more than 0.15 μCi ^{99}Mo per 1 mCi ^{99m}Tc at the time of administration. The expiration time of the generator eluate, based on not exceeding this ratio, can be determined from Table 1.5. By default, generator manufacturers have set an expiration time on ^{99m}Tc generator eluates of 12 hours from the time of elution.

Records must list for each measured elution of ^{99m}Tc from the generator, the ratio of microcuries ^{99}Mo per millicuries ^{99m}Tc , the date and time of measurement, and the name of the person making the measurements. Such records must be kept for 3 years. The Code of Federal Regulations [CFR] details all aspects of nuclear regulations (10 CFR 35.2204). A pdf file copy of the complete 10 CFR part 35 document is available on the CD.

^{99m}Tc Radiopharmaceuticals

Following intravenous injection of pertechnetate, ^{99m}Tc activity localizes primarily in the thyroid gland, salivary glands, choroid plexus, and gastric mucosa. Technetium has a diverse chemistry, however, that allows it to be fabricated into different chemical forms providing a means to target ^{99m}Tc activity to different organs in the body. As pertechnetate, technetium will not bind to other chemical species. Being an oxidizing agent, it can be reduced to a positively charged species that will chelate via coordinate bonding to a variety of ligands. The most common reducing agent used in the preparation of ^{99m}Tc radiopharmaceuticals is stannous ion (Sn^{2+}). ^{99m}Tc agents are typically prepared from a radiopharmaceutical kit. A kit is simply a sterile reaction vial containing the nonradioactive chemicals required to produce a specific ^{99m}Tc radiopharmaceutical after the addition of sodium ^{99m}Tc -pertechnetate. The primary chemical substances present in a kit are the ligand or complexing agent and a reducing

agent, usually stannous chloride. Additional adjuvants, such as stabilizers, antioxidants and dispersing agents may be present also. Kits are available from several manufacturers. An example of the commercial production of the stannous pyrophosphate kit is shown in Figure 1.4. The ligand in the kit dictates the final chemical form of technetium and ultimately its biologic fate in the body. The ^{99m}Tc -radiopharmaceutical is prepared by simply adding sodium ^{99m}Tc -pertechnetate to the kit. This effects dissolution of the lyophilized powder. Subsequently, the stannous ion reduces the pertechnetate to a lower oxidation state, typically Tc (IV), whereby it binds to the ligand, producing the desired radiopharmaceutical. In some instances, heating is required to effect labeling. These preparation parameters are summarized in Table 1.6. Non- ^{99m}Tc -radiopharmaceuticals commonly used in nuclear medicine imaging are listed in Table 1.7.

The newly prepared ^{99m}Tc -radiopharmaceutical should be assigned a control number and the ingredients used to prepare the radiopharmaceutical (eg source and amounts of sodium ^{99m}Tc -pertechnetate, saline, and kit manufacturer data) should be entered into a preparation control log (Table 1.8).

Any radiochemical species present other than the ^{99m}Tc complex are called radiochemical impurities. The principal impurities are free pertechnetate and reduced hydrolyzed technetium (technetium dioxide, $^{99m}\text{TcO}_2$). The impurities will localize in organs other than the target organ, which may interfere with image interpretation and presents an unnecessary radiation burden to the patient. A check for radiochemical impurities can easily be done by performing simple chromatography tests on the prepared radiopharmaceuticals before use. Some of the ^{99m}Tc agents (exametazime, mertiatide, sestamibi, tetrofosmin) provide testing instructions with the package insert. Chromatography tests for other agents can be found in standard radiopharmacy texts.

Radiopharmacy Operations

There are a number of functions that must be carried out in the daily operation of the radiopharmacy lab. Elution of the ^{99m}Tc generator and preparation and quality control of ^{99m}Tc -radiopharmaceuticals were discussed previously. Other functions include receipt, disposition, and waste control of radiophar-

Table 1.8: Tc-99m Radiopharmaceutical Control Log

[illegible]

Table 1.9: Radionuclide Receipt Log

[illegible]

Table 1.10: Radiopharmaceutical Dispensing Log for Patient

[illegible]

RADIOPHARMACEUTICAL:

cine license. Radioactive material for disposal in a sanitary sewer must be soluble and dispersible and not exceed regulatory limits (eg, 1×10^{-5} $\mu\text{Ci/mL}$ for ^{131}I or 1×10^{-2} $\mu\text{Ci/mL}$ for $^{99\text{m}}\text{Tc}$) specified in 10 CFR 20.2001. The amount for each nuclide disposed depends on the volume of the institution's sewage, but the total disposal of all radionuclides must not exceed 1 Ci per year.

Dose Calibrator

A licensee must possess and use a dose calibrator to check each patient dose prior to administration. The dose calibrator is an ionization chamber and associated electronic circuitry that allow readout of radiopharmaceutical dosages directly in the μCi to Ci range. The ion chamber contains an ionizable gas (eg, argon or air) and an electrode to collect the electrons produced by gamma ray ionization of the gas. The range selector is a variable resistor circuit that adjusts the activity range (μCi , mCi , Ci) being measured. The specific radionuclide correction amplifier is a resistance feedback circuit that compensates for detector sensitivity to various photon energies and intensities, providing a readout directly in activity units for any radionuclide.

The dose calibrator is subject to four quality control tests, that include accuracy, precision, linearity, and geometry as specified in 10 CFR Part 35. For all tests the model and serial number of the dose calibrator must be recorded along with other pertinent information described later.

Accuracy is the closeness of a measured value to its true value. Accuracy must be checked at installation

and annually with at least two different radionuclide sources. The sources must be certified at $\pm 5\%$ of the stated radioactivity, must be not less than 50 μCi and one source must have a gamma energy between 100 and 500 keV. Sources used are cobalt-57, barium-133 and cesium-137. After decay correction, the measured radioactivity should not vary by more than $\pm 10\%$ of the calculated (true) radioactivity. The record of the test must include the source identities, activities, and serial numbers, date, results of test, and signature of the radiation safety officer (RSO).

Precision is the ability to measure a source of constant activity repeatedly within a stated degree of reproducibility. Satisfactory performance of this test assures that the dose calibrator is operating consistently from day to day. The precision test must be performed at the beginning of each day of use with a certified source of not less than 50 μCi . A typical source used for this test is cesium-137. After decay corrections, the measured radioactivity should not vary by more than $\pm 10\%$ of the calculated activity. The record of the test must include the radionuclide identity, date, activity measured, and initials of the tester.

Linearity is an assessment of the dose calibrator's ability to measure activity accurately within $\pm 10\%$ error over a wide range of radioactivity. In general, a dose calibrator will demonstrate a linear response below 100 mCi . At high radioactivities, however, a nonlinear response may result, which is observed as an activity reading lower than is present. This falsely

Figure 1.4: Stepwise procedure for production of the stannous pyrophosphate radiopharmaceutical kit

After eluting the generator, some $^{99\text{m}}\text{Tc}$ -laden saline is drawn up and then introduced into the lyophilized kit. After waiting for the specified time, a specific dose can be drawn up for the study to be performed. The lyophilized manufacturer kits contain a reducing agent, several adjuvants, and the specific pharmaceutical that will bind the reduced $^{99\text{m}}\text{TcO}_2$.

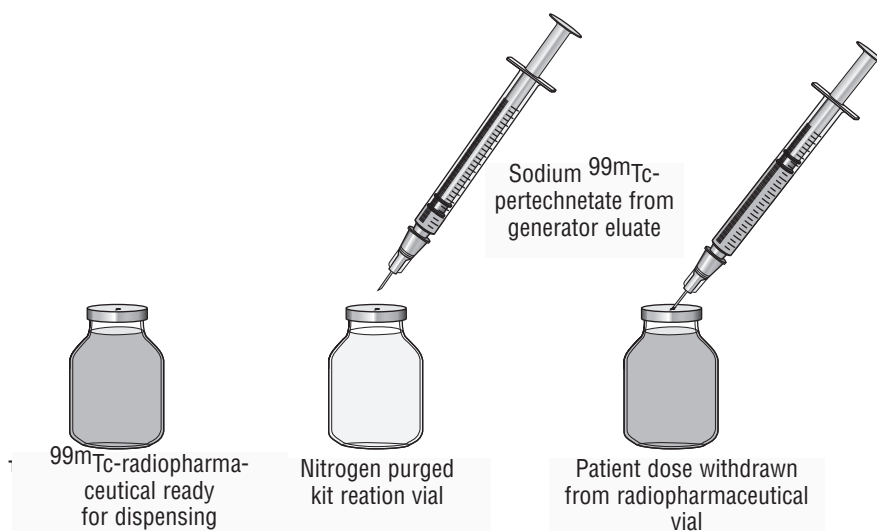


Table 1.7: Other Radiopharmaceuticals Used for Imaging

Radiopharmaceutical	Mechanism of Localization	Use, Administered Radioactivity, Radiation Dose
Ga 67 citrate	Tumors: exact mechanism not known. Studies suggest diffusion into tumor cells as ^{67}Ga -transferrin complex or as neutral ^{67}Ga hydroxide. Intracellular binding is associated with lysosomes or tumor protein. Abscesses: exact mechanism not known. Studies suggest ^{67}Ga bound plasma WBC transport to abscess or abscess binding of ^{67}Ga in WBC lactoferrin or bacterial ferritin and siderophores.	Tumor imaging (Hodgkin's lymphoma): 5-8 mCi IV. Critical organ is the spleen: 3 rads/5 mCi. Abscess imaging: 3 mCi IV.
In 111 capromab pentetide (ProstaScint®) [Cytogen]	Reacts with prostate-specific membrane antigen in prostate carcinoma.	Localization of metastases in patients with biopsy-proven, clinically localized prostate cancer and in post prostatectomy patients for occult or residual metastases: 5 mCi IV. Critical organ is the liver: 18.5 rads/5 mCi.
In 111 oxine	Leukocyte labeling: passive diffusion of ^{111}In oxine complex into WBCs with dissociation and protein binding of the ionic $^{111}\text{In}^{+2}$.	Leukocyte Labeling: 0.5 mCi IV Critical organ is the spleen; 8.5 rads/0.5 mCi.
In 111 pentetate (DTPA)	Cisternography: compartmental confinement.	Cisternography: 0.5 mCi intrathecal. Critical organ is the brain surface: 7 rads/0.5 mCi.
In 111 pentetreotide (OctreoScan®) [Cytogen]	Binding to somatostatin receptors on tumors.	Localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors: 3 mCi (planar), 6 mCi (SPECT). Critical organ is the spleen: 14.77 rads/6 mCi.
In 111 satumomab pentetide OncoScint® [CR/OV]	Reacts with TAG-72 tumor-associated antigen on colorectal and ovarian adenocarcinomas and other tumor types.	Localization of extrahepatic malignancies in patients with known colorectal or ovarian cancer: 5 mCi IV. Critical organ is the spleen: 16 rads/5 mCi.
I-131 Sodium iodide	Active transport.	Thyroid uptake: 5 - 10 μCi per os. Thyroid Scan: 50 - 100 μCi . Critical organ is the thyroid gland: 1.3 rads/ μCi (with 25% uptake).
I 131 metaiodobenzylguanidine sulfate (MIBG); can also be labeled with I 123.	Type I uptake (active transport within sympathetic neurons and cells of neuroendocrine origin) and type II uptake (passive within muscle cells).	Localization of primary or metastatic pheochromocytomas and neuroblastomas: 0.3 mCi/ m^2 up to 1 mCi. Critical organ is the urinary bladder wall: 3 rads/mCi.
I 131 Orthoiodohippurate (OIH)	Active transport: tubular cells. Passive diffusion: glomerulus.	Kidney imaging: 75 - 200 μCi IV. Critical organ is the urinary bladder wall: 3.3 rads/ μCi .
Tl 201 thallous chloride	Active transport (Na^+ - K^+ ATPase myocyte membrane-bound pump) as a K^+ analog.	Cardiac perfusion imaging: 2-3 mCi IV. Critical organ is the kidney medulla: 1.25 rads/mCi.
Xe 133 xenon gas	Passive diffusion used for lung uptake and wash out ventilation studies.	Lung ventilation imaging: 10-20 mCi. Critical organ is the airway mucosa: 0.12 rads/mCi.

maceuticals, dose calibrator and survey meter calibration, surveys, and wipe tests.

Receipt

One must be authorized by a radioactive materials license to receive radioactive material from a vendor. In accordance with 10 CFR 20.1906, arrangements must be made for delivery of radioactive materials into a secured place, preferably the nuclear medicine lab. Any package that is labeled as containing radioactive material (ie, labeled with department of transportation White I, Yellow II or III) or has evidence of potential contamination (ie, wet or damaged packages) must be monitored for surface contamination (ie, by wipe test) and radiation levels (ie, by Geiger-Müller, GM survey meter, or Geiger counter). Surface contamination must not exceed 2,200 disintegrations per minute[DPM]/100 cm² of package surface, and radiation levels must not exceed 200 mR/hour at the package surface nor 10 mR/hour at 1 meter from the package. Monitoring must be completed not later than 3 hours after the package is received during normal working hours and not later than 3 hours from the beginning of the next working day if it is received after working hours. If the preceding limits are exceeded, then the licensee must immediately notify the final delivery carrier and, by telephone and telegram, the administrator of the appropriate Nuclear Regulatory Commission (NRC) regional office. The licensee must establish, maintain, and retain written procedures for safely opening packages of radioactive materials and ensure that the procedures are followed. In addition, it is good practice to radioassay vials of radiopharmaceuticals in the dose calibrator and compare the readings with theoretical activity. Agreement should be within $\pm 10\%$. The previous information should be recorded on a receipt log identifying the radiopharmaceutical name, manufacturer, lot number, and date received (Table 1.9).

Disposition

Radiopharmaceuticals dispensed for routine imaging procedures must be prepared according to the manufacturer's instructions. All dosages must be measured in a properly calibrated dose calibrator. In accordance with 10 CFR 35.63, records must contain the generic or trade name or abbreviation of the radiopharmaceutical, lot number, radionuclide, expiration date, patient's name and identification

number, the prescribed dosage (administered activity) and dosage measured, the date and time of measurement, and initials of the recorder (Table 1.10). Records must be kept for 3 years. All radiopharmaceuticals must be kept in lead vial shields when handling. The vial shield must be labeled with the radionuclide and chemical form, quantity, date, and with the words "**Caution: Radioactive Materials**". Doses prepared for patients must be kept in lead shields labeled with the name or abbreviation of the radiopharmaceutical and the procedure or patient's name. Syringe shields must be used when preparing radiopharmaceutical kits. Shields should be used when administering doses, unless contraindicated.

Volatile or gaseous radionuclides must be stored in the shipper's container and shield. After withdrawing the first dose, multiple-dose containers must be stored in a fume hood. Radioactive gases must be administered in a room with negative pressure so that airborne levels are kept within acceptable concentrations (see 10 CFR 20.1301) by venting to outside or contained in shielded traps. In the event of an accidental spill of radioactive gas, one must have established a predetermined time required to achieve safe levels in the room, based on the largest dose that could be spilled.

Waste Control

The disposal of radioactive material must follow the regulations stated in 10 CFR 20.2001. Accordingly, disposal may occur by (1) transfer to authorized recipient, (2) decay in storage, (3) release into sanitary sewer, or (4) incineration. In general, the first three options are used in nuclear medicine. Because of the expense of transferring to an authorized waste recipient and the fact that most radionuclides have short half-lives, decay in storage is frequently used. Containers can be disposed of in regular trash provided that they have decayed for at least 10 half-lives, that radiation levels are at background levels, and that all radiation signs and labels are obliterated. Records are kept for 3 years and contain the following: date of disposal, date and place of storage, radionuclides disposed, survey instrument used to monitor levels, the background dose rate, the vial surface dose rate, and the name of the person who disposed of the products. All patient excreta is exempt from waste disposal requirements. This is not true in veterinary medicine and measures need to be taken to conform to the original nuclear medi-

low reading is due to recombination of ion pairs in the ion chamber before they can be collected at the electrodes. The linearity test is conducted over the range of radioactivities likely to be measured in practice. Initially, the linearity of the dose calibrator must be established by the “decay method;” and deviations from linearity may be quickly tested, subsequently, by the “shield method.”¹ The linearity test must be performed at installation and quarterly. The records must include the measured and calculated activities, date of test, and signature of the RSO.

The geometry test is designed to assess how the source configuration, volume, and position in the dose calibrator well has any effect on the accuracy of measurement. In general, weak gamma sources, eg ¹²⁵I, demonstrate low readings in higher density materials (eg, glass vials, versus plastic syringes) and appropriate corrections must be made to obtain accurate readings. Variation due to volume can easily be checked by placing 1 mCi of the sample radionuclide into a vial. An initial reading and subsequent reading after 1 mL increments of water are added will indicate whether correction factors are needed for different volumes. Variation of readings with respect to position in the ion chamber well can easily be checked by measuring a 1 mCi source at prescribed distances from the bottom to the top of the well. In general, readings at the bottom and top of the well will be inaccurate due to loss of photon detection in the ion chamber. The position of greatest accuracy should be established and used for measuring radiopharmaceuticals.¹ The geometry test must be done at installation and repeated following dose calibrator repair or adjustment. Records must include configuration of source measured, activity for each volume measured, date of test, and signature of the RSO. All dose calibrator records for accuracy, precision, linearity, and geometry must be maintained for 3 years.

Survey Meter

The GM survey meter must be calibrated annually and following repair. The source used should be certified within $\pm 5\%$ accuracy and be traceable to the US National Bureau of Standards. Calibrate all scales up to 1000 mR/hr. Each scale should be calibrated at least at two points located at approximately one third and two thirds full scale (10 CFR 35.61). The exposure rate measured by the instrument should differ from the true exposure rate by less than 20% at

the two points on each scale. Sources for calibration include cesium 137, radium 226, and cobalt 60. At the time of calibration an apparent exposure reading of a check source must be made and recorded. This check source is to be measured before each use of the instrument to assure proper operation, but no record is required. Records of survey instrument calibration must be maintained for 3 years and must contain the model and serial number of the instrument, date of calibration, results of the calibration, and name of the individual performing the calibration (10 CFR 35.2061).

Surveys of Work Areas

To control contamination and maintain a safe working environment, routine radiation contamination surveys are required. Requirements for area surveys are given in 10 CFR 35.70. It is important to survey all areas where unsealed byproduct material requiring a written directive was prepared for use or administered. A record shall be retained for each survey for 3 years (10 CFR 35.2070). The record must include date of the survey, results of the survey, instrument used, and name of the individual performing the survey.

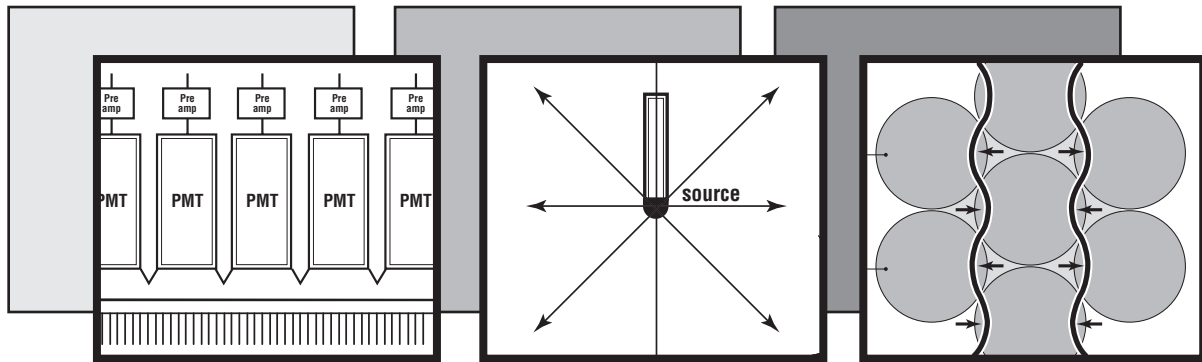
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Radiation Detectors

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Introduction

There are many types of radiation detectors, and their efficiency is highly variable. The type of radiation detector used depends upon the application for which the detector is needed. In this chapter, common radiation detectors that are used in veterinary nuclear medicine are reviewed. The advantages, disadvantages, and applications of each detector type are discussed.

In general, all detectors have the ability to interact with ionizing radiation, whether the radiation is electromagnetic or particulate in nature. The ionizing radiation will deposit energy by Compton or photoelectric interactions resulting in ionization or excitation of atoms within the detector and the creation of ion pairs. Excitation is the elevation of electrons to higher energy states within individual atoms, molecules, or crystals without ionization. These changes within the detector may induce a discharge of visible light that can then be detected; or, if ionization occurs, the ion pair is collected along an anode-cathode axis. The detector must be able to identify the particular radiation in such a manner that the interactions (whether ionization or excitation) are proportional to the amount of radioactivity or the energy of the radiation that is present in the source, environment, or patient. Most of the energy deposited by ionizing radiation is converted to heat and absorbed locally. Because most radiation-induced ionization or excitation may be very small (2.24×10^{-14} J energy deposited if a 140 keV ^{99m}Tc photon is totally absorbed), electronic or chemical amplification is required to register the interaction(s).

Photon Interactions with Matter

Gamma ray and x-ray photons will interact with matter in six basic ways.¹⁻⁵ These include coherent (Thompson or Raleigh) scatter, photoelectric effect, Compton interaction, pair production, nuclear collisions, and no interaction. The probability of a specific type of interaction is dependent upon the energy of the incident photon and the physical and chemical properties of the detecting device. The two most important interactions in nuclear medicine for detection of the gamma or x-ray photon include the photoelectric effect and Compton scatter. In a photoelectric interaction (PE), the energy from the incident photon will be totally absorbed by an inner K-shell electron within the atom. The end result is

the ejection of a photoelectron, an ionized atom, and a cascading of the outer shell electrons to stabilize the inner shell electron vacancy. As the electrons cascade to the inner shell vacancies, the excess energy is given off as characteristic x-rays. Characteristic x-rays have a very low energy and are absorbed locally by other photoelectric interactions or a number of Compton interactions within the tissues. If the characteristic x-ray is absorbed by an outer valence shell electron prior to the x-ray leaving the atom, the ejected outer shell electron is called an Augér electron. The likelihood of a photoelectric interaction is proportional to the atomic number of the absorber³ and inversely related to the energy³ of the incoming photon (gamma or x-ray), $[\text{PE} \approx (Z^3)/(\text{E}^3)]$. The PE interaction will predominate in soft tissues up to 50 keV.

The most common physical interaction for gamma and x-rays between (energy range of 50 keV and 10 MeV) is the Compton effect (CE) or Compton scattering. In this type of interaction, the incident photon will interact with an outer, valence shell electron. Part of the photon's energy will be absorbed by the outer shell electron, while the incident photon continues in a scattered (different) direction where the scattering angle is dependent upon the amount of energy lost to the valence electron. The scattered angle can be calculated by the equation $\Delta\text{E} = 0.0243 \times (1 - \cos\theta)$, where ΔE is the energy lost to the valence shell electron. The higher the photon energy the more forward scattering will occur. This means that the Compton scatter photon tends to retain a forward path in a similar direction of the incident photon had the Compton interaction not taken place.

Radiation Detectors

Radiation detectors can be classified according to their method of detection.^{2,5} The two primary methods used include gas-filled detectors and scintillators. Gas-filled detectors consist of a particular pressurized gas housed within a chamber between two electrodes. Radiation will cause the gas molecules to be ionized resulting in the production of ion pairs. The ion pairs will migrate toward the electrodes (anode and cathode) resulting in an electrical charge difference between the two electrode plates. The net charge or current is proportional to the number of ion pairs formed, which is proportional to the original amount of ionizing radiation detected. In the case of

scintillators, ionizing radiation will interact with inorganic crystals resulting in the release of ultraviolet or visible light. The light is then converted into an electrical signal that is proportional to the energy of the radiation absorbed.

Another form of radiation detector includes semiconductor detectors. These are not currently used in nuclear medicine and are a specialized form of diode that creates a signal by electrons becoming excited by radiation. This raising of the electrons allows a current to pass through the diode. The current is proportional to the radiation that induced the electron excitations.

Detectors can also be classified based on the type of information they provide, including counters (rate counters), spectrometers (energy discriminators), or dosimeters (determine absorbed dose equivalent). Counters are detectors that will individually count a number of radiation events per unit of time. This type of detector, however, gives no information about the radiation itself (particulate versus electromagnetic radiation) or the total amount of energy deposited. An example of a rate counter is a Geiger-Müller (GM) survey meter. An example of a spectrometer is a NaI scintillation crystal with multichannel analyzing capability, where the amount of energy deposited per energy channel or the energy spectrum of the radiation can be detected. NaI scintillators are also counters and the number of counts will correspond to the activity absorbed per unit of time. Detectors that indicate the net amount of energy deposited are called dosimeters. The amount of energy collected over a period of time can be determined, but individual events or counts are not recorded. An example of a dosimeter would be film badges worn by radiation workers.

Detector Modes of Operation

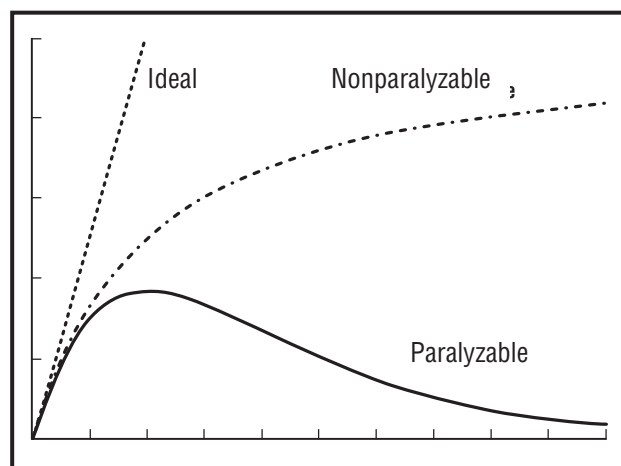
The detector and the associated electronic circuitry are called a detector system. Each system has inherent advantages and disadvantages. Two basic types of detector modes are available: pulse mode and current mode. Pulse mode detectors count individual signals from each ionization interaction. Current mode detectors take all of the electrical signals generated from individual interactions and average them together to form a net current signal. In either mode of operation, there has to be a finite period of time between individual events in order

to detect and produce discrete signals. During this finite period of time, other interactions cannot be recorded. This interval is called the dead time of the system. If a second event occurs during the dead time, the event will not be recorded. If it is close enough to the first signal, then signal distortion could result (called pulse pile-up). Dead time losses increase with increased radioactivity. The component in the system with the longest dead time limits the total count rate of the entire system. In the case of the gamma camera, the analog-to-digital converter is the rate-limiting step and not the sodium iodide crystal.

There are two types of systems that have been used to describe the dead time of detector systems.¹⁻⁵ The first is called a paralyzable system in which an interaction that occurs during the dead time after a previous interaction extends the dead time. In areas of high radioactivity, a GM survey meter (which is a paralyzable system) can actually give up (dead time extended beyond reason) and register zero after a period of time, even though the count rates remain high. In a nonparalyzable system, the count rate will stop increasing with high radioactivities but will not return to zero on the scale. The system is still subject to dead time losses and is not an ideal counting system. Count rates should be linear in their response to increasing radioactivity, no matter how high

Figure 2.1: Dead time implications in paralyzable and nonparalyzable counting systems

Notice how the interaction rates cannot exceed a certain limit in the paralyzable system. The y-axis represents true counts and the x-axis represents the count rate of the system being evaluated.



the interaction rate or the radioactive source being detected (Figure 2.1).

When a detector is operated in the current mode, all the information from individual events, such as their energy, is lost; but the total dose rate can be determined. Detectors that are subject to high interaction rates are operated in current mode in order to avoid dead-time losses, such as the dose calibrator used in nuclear medicine. In this case, the individual events are irrelevant, but the amount of radioactivity is important.

Detectors with spectroscopy capabilities can record and display a range of energies deposited in the detector. Energy distribution and individual events of the incident radiation become the information that is recorded by the detector system. However, all energy deposited from a single ionizing event is not 100% collected depending on the type of interaction.

The detector efficiency or sensitivity is determined by the detector's ability to record radiation events accurately. The overall system efficiency is dependent upon the geometric efficiency (number of events reaching the detector/total number emitted by the radiation source) $\times$ the intrinsic efficiency of the detector (number of events detected/number of events reaching the detector). The geometric efficiency is determined by the relationship between the source of the radiation and the detector (Figure 2.2). As the source is moved toward the detector, the geometric efficiency increases so that it equals 0.5 when flat (if the source is a flat object) against the detector. Well counters that totally surround the

source have the best geometric efficiency, but still do not approach 1.0. The dose calibrator and the sodium iodide (TI) well counters have the best geometric efficiency because of their well design where the radiation source can be placed into the detector. Positron emission tomography (PET) scanners have the best geometric efficiency in nuclear medicine imaging applications, because they have a ring of detectors that surrounds the patient.

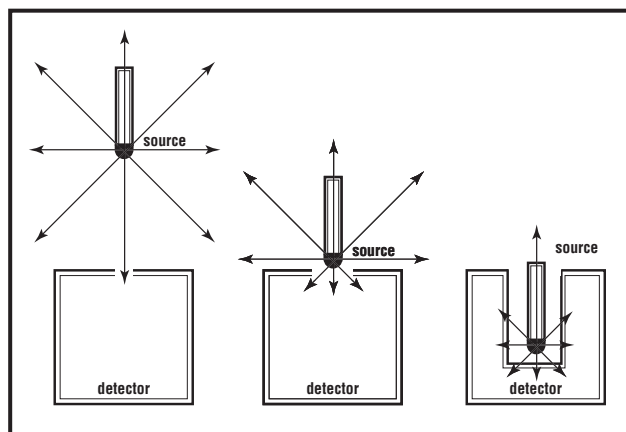
The intrinsic detection efficiency of a detector for gamma or x-rays is also called the quantum detection efficiency (QDE).⁵ The QDE is determined by the energy of the photon and is dependent on the type of detector used (including the atomic number, density, and thickness of the radiation detector). If the photons are mono-energetic and are parallel in nature, then the intrinsic efficiency can be determined: $QDE = 1 - e^{-\mu x}$, where μ = linear attenuation coefficient for the detector and x = the thickness of the detector.^{2,5}

Gas-filled Chambers

A gas-filled detector consists of a chamber that contains a pressurized gas and two electrodes. An electrical potential is placed between the anode and cathode. Ionizing radiation will result in ion pairs being formed within the gas. These ion pairs are collected at the electrodes (positive ions collect at the cathode [-] and electrons collect at the anode [+]). Once the electrons bind to the anode, they travel via a circuit to the cathode where they recombine with the cations. This creates an electrical current that is proportional to the number of ionizations and thereby the energy of the ionizing radiation.

There are three types of gas-filled detectors that are currently in use today in nuclear medicine. They include: ionization chambers (dose calibrators), proportional counters, and GM survey meters. The type of detector is determined by the amount of voltage applied across the electrodes, (Figure 2.3). There are five different regions that are represented within a gas-filled chamber depending upon the voltage applied to the detector. From increasing voltage (starting at 0 volts) these regions include: recombination region, ionization chamber region, proportional region, Geiger-Müller region, and the continuous or spontaneous discharge region. In the recombination region (0 to less than 100 V), there is not enough of a charge to attract the ion pairs that are created and the ion pairs recombine. As the voltage is increased (100 to 400 V), a plateau is reached.

Figure 2.2: Geometric efficiency of three detectors relative to a point source



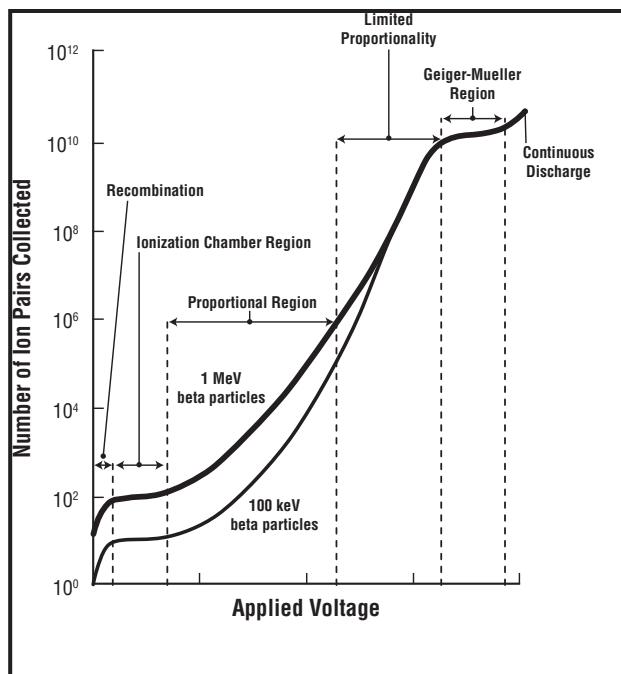


Figure 2.3: Gas-filled detectors related to increasing applied voltages

This region, called the ionization chamber region, represents the area where the electrical charge across the electrodes is strong enough to attract the ion pairs created by the ionizing radiation. Beyond this region is the proportional region (400 to 800 V), where amplification occurs as the electrons formed by ionization approach the anode with enough kinetic energy to result in additional ionizations of other gas molecules. The larger the voltage applied, the greater the electrons' acceleration toward the anode, thereby increasing the kinetic energy of the electron. The energy deposited is proportional to the electrical charge collected from each radiation interaction within the gas.

The GM survey region (1000 to 1500 V) results in electrons from the initial ionization gaining enough energy so that secondary ionizations of other gas molecules occurs. The GM survey meters have been optimized for maximum gas amplification. Electron amplification extends along the entire anode, and a second plateau occurs. As the voltage is increased, saturation threshold has been reached so that a Townsend avalanche effect results. A single ionization can induce near complete ionization of all the gas molecules within the GM chamber. The single

ionizing event will induce the release of secondary electrons. This results in complete ionization so that every event detected will result in the same large pulse. Therefore the size of the pulse is independent of the energy deposited and just specifies that an event has occurred. Spontaneous discharge can occur within the upper voltages of the GM survey region due to electron interactions along the cathode, causing formation of x-rays, which then set off further ionizations. Because of the amplification effect of the high voltage in this gas-filled chamber, very low x-rays will cause an event or pulse to be recorded. This process, called quenching, can result in continuous discharge and thereby a recording of continuous pulses or counts. Quenching is controlled by the addition of a secondary gas to the GM survey probe. Bromine (Br_2) or chlorine (Cl_2) are used as quenching agents. These secondary gases will act as an electron trap and not allow further ionization. Additionally, the quenching gas will absorb the μV radiation responsible for the avalanche effect (promotion of the formation of secondary electrons).

Gas-filled detectors cannot be operated beyond the GM survey region as spontaneous ionization will occur within the gas due to the high voltage across the anode-cathode axis. The voltages for this region are typically above 1500 V.

Portable ionization chambers are characterized by their ability to measure exposure rates from gamma or x-radiation. They are calibrated in mR/hr or R/hr and the exposure range is between 1 mR/hr and 500 R/hr . Their limitations include: accuracy is $\pm 10\%$ of full-scale indication; and energy, pressure, temperature, and saturation will affect performance (the losses are minimal compared to GM survey meters). The response time is relatively slow (3 to 4 seconds to register within a radiation field). These detectors have low energy dependence with a typical minimal energy of 20 keV for x-rays being measured.

Dose calibrators are well-type ionization chambers that are filled with pressurized argon gas in order to maximize intrinsic and geometric detection efficiencies.^{2,5} The dose calibrator does not suffer dead time losses because it operates in the current mode and is linear over a wide range of radioactivities (10 μCi or 0.37 MBq to 2 Ci or 74 GBq). The radioactivity is determined by a simple relationship between the exposure rate recorded by the dose calibrator, the distance between the source and the detector, and the

gamma ray exposure constant for the given radionuclide ($R\text{-cm}^2/\text{mCi-hr}$).⁵

$$\text{Radioactivity (mCi)} = \frac{\text{Exposure Rate} \times \text{Distance}^2}{\text{Gamma ray exposure rate constant}}$$

Proportional chambers are used to measure alpha and beta radiation sources and have a full-scale reading of 500,000 counts per minute.⁵ They are used for alpha emitter contamination and can be used to discriminate quantitatively between beta minus and gamma contamination. Disadvantages include: the proportional chamber has a high directional dependence, requires special probes for alpha detection, and has a slow response time and a fragile window. These are not applicable for diagnostic radiology or nuclear medicine.

Geiger-Müller survey meters are used as survey instruments to detect gamma and beta contamination, exposure rates and release levels from veterinary patients. With specialized probes, they can be used for alpha detection.^{2,5} The typical full-scale reading is 0.1 to 200 mR/hr or 800 to 80,000 counts per minute. GM survey meters have a gas amplification factor as high as 10^{10} . The major advantage is the rapid response that permits detection of small amounts of contamination. The major disadvantages include the limited range for detection, energy dependence (betas must be at least 150 keV) and the possible paralysis of response at high radiation fields or exposure rates (dead times of tens to hundreds of microseconds). In radiation fields of greater than 100,000 counts per minute (30 mR/hr), there will be dead time losses of at least 20%. Ionization chambers should always be used to measure high radiation

fields due to the low energy dependence and accurate measurement of exposure rates.⁵

Scintillation Detectors

Scintillation detectors are made of materials that will absorb various types of radiation and emit visible or ultraviolet light (scintillate) after the interaction.¹⁻⁵ These are used in screens for radiology cassettes, fluoroscopy units (photocathode and image intensifiers), gamma cameras, and computed tomography and positron emission tomography scanners. The light detected is usually amplified and converted to an electrical signal except for film screen interactions. When ionizing radiation interacts with the scintillation material, electrons are energized and carried to a higher excited energy level.^{2,5} When the electrons return to their normal valence state, the excess energy is released as a light emission. For scintillators, a high conversion efficiency is required, which is the fraction of the energy that is deposited in the material that is converted to light. The decay times of scintillators are short, and the material should be transparent to its own light emissions for ready transport of the light information to the photomultiplier (PM) tubes or radiographic film. The frequency spectrum of the light emitted should match the photocathode receptor, and the attenuation coefficient of the scintillation material should be high so that the detection efficiency is high. In all scintillators, the amount of energy deposited will result in a proportional amount of light released. Common scintillation materials are shown in Table 2.1.

The gamma camera is a sensitive radiation detector with a specific ideal energy range (between 100 and 200 keV).

Table 2.1: Inorganic Scintillators Used in Medical Imaging

Material	Atomic No.	Density (g/cm ³)	Emission (nm)	Detection Efficiency (%)	Uses
NaI (TI)	11,53 (81)	3.67	415	70 (140 keV)	Gamma camera (3/8" thick) and PET scanners (2.5 cm thick)
Bi ₄ Ge ₃ O ₁₂	83,32,8	7.13	480	12-14	PET scanners
CsI (Na)	55,53	4.51	420	85	Input phosphor of image intensifier
CdWO ₄	48,74,8	7.90	540	40	CT scanners

Gamma Camera

The Anger scintillation or gamma camera is the radiation detector used in nuclear medicine. The camera detects and counts gamma rays or x-rays emitted from the patient and then creates an image based on the distribution of the radionuclide within the patient.¹⁻⁵ The essential pieces of the gamma camera include the collimator, sodium iodide (thallium) (NaI(Tl)) crystal, coupling grease or light pipe, photo-multiplier tubes, pre-amplifiers, amplifiers, analog to digital converter (ADC), pulse height analyzers (PHA), computer memory, computer acquisition/processing stations, and display screen, (Figure 2.4). The collimator, NaI (Tl) crystal, light pipe, photomultiplier tubes and pre-amplifiers are found within the detector assembly. In older camera systems the final conversion from an analog to a digital signal did not take place until the electrical signal reached the computer hardware where the ADC, pre-amplifier, and amplifiers are found. Newer digital cameras have the analog to digital conversion at the level of the photomultiplier tubes within the camera head so that there will be an improvement in the signal to noise ratio, and the certainty of each signal that is sent to the computer is greater. The function of each component of the gamma camera system will be discussed separately and dealt with in a linear stepwise fashion as the gamma ray is emitted from the patient, detected by the NaI crystal, and the resulting electrical signal created.

Collimators

The first part of the detector assembly is the collimator (Figure 2.5). Collimators are made of lead that is cast with many small holes or created by combining with lead foil them to create many small openings within the collimator sheet. These openings extend from the top to the bottom surface of the collimator. The interspaced lead between the openings of the collimator has a given thickness and height. The shape of the collimator openings when viewed from the top of an uncovered collimator can be triangular, square, circular, or hexagonal. Collimators selectively allow gamma or x-rays emitted from within the patient and traveling in a certain orientation through the collimator openings for interaction with the radiation detector. The collimator limits the overall detection efficiency of the camera system because only 1 in every 10,000 gamma rays emitted from the

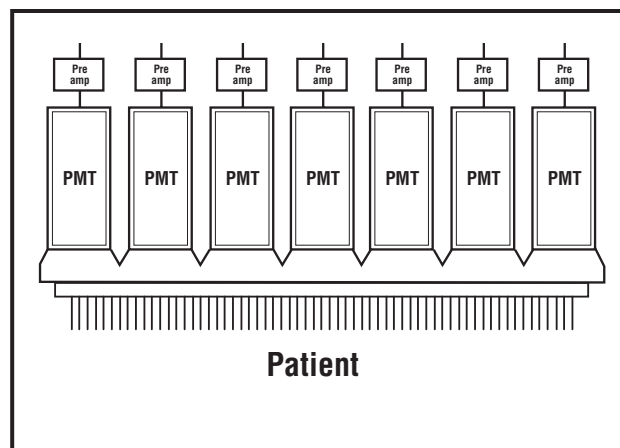


Figure 2.4: Schematic cross section of gamma camera head

The pre-amplifiers (PA) are on the inside of the camera head. The photomultiplier tubes (PMT) collect the light emitted from the sodium (Tl) iodide crystal. The light events emitted from the crystal are secondary to the energy absorbed from the gamma rays that are emitted from the patient and pass through the collimator (depicted as a parallel collimator in the schematic). The patient is placed on top of the collimator for imaging.

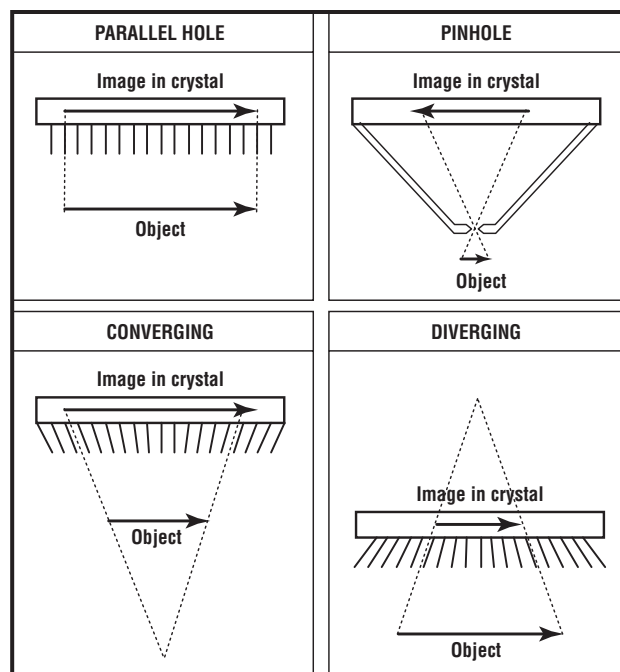


Figure 2.5: Examples of different types of nuclear medicine collimators

patient will ever strike the sodium iodide crystal. The collimator absorbs off-axis gamma rays, preventing the radiation from reaching the gamma camera crystal. The collimator selection will affect the image size, image orientation, and overall image resolution. Collimator type is the single largest determinant of overall camera system resolution (called specifically the extrinsic camera resolution; see chapter 4 for details on determining total system resolution).

Different types of collimators are available in nuclear medicine and are readily interchanged so that a collimator can be matched to the specific type of study and the radionuclide being used. The collimator first needs to be matched to the energy of the photon emitted by the radionuclide being imaged. If high energy photons are imaged with a low energy collimator, septal penetration will result in image degradation to the point of a nondiagnostic quality study. The collimator can also be matched for sensitivity (count rate) or resolution. If one needs counts, then resolution will be sacrificed; and, if resolution is important, count rates will decrease.

The most common collimator design is a parallel hole orientation, where the collimator consists of multiple holes of identical shape and orientation (usually round or hexagonal). These holes are parallel to each other and perpendicular to the NaI (Tl) crystal. The septa between the holes are composed of a high molecular weight material (usually lead) that will attenuate the photons of a specific energy range.

The holes of the parallel hole collimators vary in their diameter and height. These differences will influence the collimators' performance in terms of resolution and sensitivity. The three common types of parallel hole low energy collimators are: low energy all purpose (LEAP), low energy high resolution, and low energy high sensitivity. In general, collimators with small diameter holes and longer height have improved spatial resolution (ability to discriminate two small objects close to each other in the patient) but decreased sensitivity (number of photons reaching the camera is decreased). By increasing the collimator hole diameter or shortening their height, the sensitivity (number of counts reaching the crystal) of the collimator will improve but at a cost of decreased spatial resolution. The low energy, high resolution collimators are used to improve resolution. With these, the dosage of the radiopharmaceutical can be increased or the imaging times increased to compensate for the decrease in sensitivity. The low energy

high resolution collimators are best suited for high count rate, static images, such as a bone scan, where motion is not a problem and the final image may not be statistically count limited. Count rate losses of up to 30% are noted when comparing the low energy high resolution collimator with the low energy all-purpose collimator. High resolution collimators may be used where photon flux is adequate and the acquisition times are not limited by patient motion. High sensitivity collimators are used for studies where photon flux or acquisition times are limited, such as dynamic flow studies. The LEAP collimator is a general-purpose collimator with mid-range resolution and sensitivity.

With any collimator system, spatial resolution decreases with increasing distance from the patient. As a rule of thumb, spatial resolution is degraded approximately 1 mm for each cm the patient is positioned away from the face of a parallel hole collimator (Figure 2.6).^{2,5} Count sensitivity, however, does not decrease as the patient is moved further from the crystal.

The converging and diverging hole collimators are multi-hole collimators that are angled relative to the detector assembly.² These collimators are used to magnify or minify the image. The septa in a converging hole collimator converge toward a point source in space in front of the detector assembly. The object will then be magnified as the image but not inverted. As the distance from the patient to the collimator increases so does the magnitude of magnification. A diverging hole collimator will minify the image by increasing the field of view. In the diverging collimator, the septa are divergent toward the patient so the camera can image a larger object by minifying the image.

The pinhole collimator is a conical-shaped, lead collimator with a small single aperture at the end of the cone.^{2,6} The principles of image formation using a pinhole collimator are similar to that of an optical pinhole camera. Only those gamma rays that pass through the aperture of the collimator are recorded by the gamma camera. The resultant image is upside down, and the two lateral sides of the image are reversed with respect to the original patient or object (totally inverted). The recorded image size, field of view, resolution, and sensitivity of a pinhole collimator depend on the length of the cone, the cone angle, the object to collimator distance, and the diameter of the aperture. Depending on the distance of the

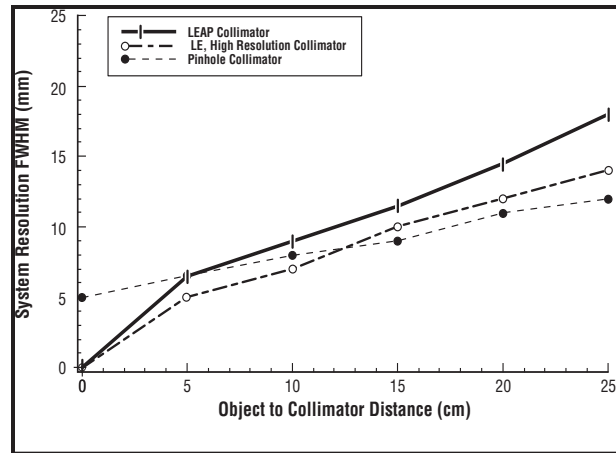


Figure 2.6: Spatial resolution of different collimators as the object to collimator distance

changes FWHM = full width at half maximum; LEAP = low-energy, all-purpose; LEHR = low-energy, high-resolution.

patient from the pinhole aperture the image will be magnified, appear the same, or be minified. The image will be magnified if the patient to collimator distance is less than the length of the collimator cone. The image will be the same size as the patient to collimator distance equal to the length of the collimator cone. The image will be minified if the patient to collimator distance is greater than the collimator cone length (Table 2.2).⁶ Pinhole collimators have typical aperture insert sizes that range from 2 to 6 mm.

Experimentally derived data has shown that sensitivity of the pinhole collimator for a flood source phantom does not change from 0 to 40 cm away from the pinhole aperture. As would be expected, the 3 mm pinhole aperture is the least sensitive due to the small aperture size opening when compared with 5 mm and 6 mm pinhole apertures.⁶ At 0 cm, a 3 mm pinhole aperture has a sensitivity of 0.3 million counts per minute, a 6 mm pinhole aperture has a sensitivity of

1.1 million counts per minute, and a LEAP collimator has a sensitivity of 5.0 million counts per minute. If a point source is used, the greatest sensitivity is seen with a 6 mm pinhole collimator, then a 5 mm, 3 mm, and a LEAP collimator. As the distance is increased for a point source, the pinhole collimator sensitivity exponentially decreases so that at 2.54 cm, the 3 mm pinhole sensitivity is less than that of the LEAP collimator and, by 8.0 cm, the 6 mm pinhole aperture sensitivity is less than the LEAP collimator.⁶ The 3 mm pinhole aperture has the best resolution with a full width half maximum (FWHM) of 2.9 mm when compared with the 6 mm pinhole aperture (FWHM = 6 mm) and a LEAP collimator (FWHM = 4.9 mm). For the spatial resolution to be better than the LEAP collimator, one needs to use a 2 or 3 mm aperture insert for the pinhole collimator.⁶

Detector Assembly

The scintillation detector of the gamma camera is a

Table 2.2: Image Size, Patient Distance Aperture to Camera Distance Influences on Pinhole Images

Patient Distance	Aperture to Camera	Image Size	Image
At aperture	14 inches	Magnified	Inverted
14 inches away from the aperture	14 inches	Equal object to image size	Inverted
Greater than 14 inches away from the aperture	14 inches	Minified	Inverted

thin, large diameter sodium iodine [NaI (Tl)] crystal. The crystal converts the energy from the gamma ray into visible light.

The NaI (Tl) crystal will absorb the incident gamma and x-ray photons by standard photoelectric or Compton interactions. The high atomic number of the iodine ($Z = 53$) increases the likelihood of a photoelectric interaction and absorption of the entire incident photon.

If the photon energy is deposited in an electron and the electron is ejected from the iodine atom, there will be a disruption of the valence band so that the electron will shift into the higher energy conduction band. The valence shell electrons are susceptible to scatter photons as they are loosely held in their outer valence orbits by a lower binding energy. This binding energy is the lowest because the outer valence shell electrons are farthest from the nucleus. Above this energy level of the valence band is a higher energy state called the conduction band. The energy difference between the valence and the conduction bands is called the forbidden gap. The conduction band does not exist in a pure crystal. Because the sodium iodide crystal has a conduction band (because it contains thallium impurities), electrons that absorb energy will move from the valence to the conduction band. Electrons within the conduction band are electronically unstable and thereby return to the valence band with the release of energy in the form of visible light (wavelength of 413 angstroms). The energy deposited by the incident photon is then directly proportional to the number of light photons released as the electrons return from the conduction band to the valence band. As mentioned earlier, a total of 20 to 30 light photons are emitted per keV of energy absorbed.

For the typical gamma camera, the sodium iodide crystal can be made round or square, measures 12" to 20" in diameter and is 0.25" to 0.375" in thickness. If the gamma camera has been specifically suited for PET imaging (eg, C-PET Tomography, Philips Medical Systems) then the NaI (Tl) based crystal will measure 2.5 cm in thickness.

The sodium iodide crystal is coupled to the photocathode of the photomultiplier tubes by a light pipe or coupling grease. The light produced by the sodium iodide crystal is transferred to the photocathode. The photocathode will produce electrons in numbers that are proportional to the intensity

of the light flash. Because the number of electrons produced is not large enough to generate an electrical signal, there is an electron amplification process within the photomultiplier (PM) tube. Each PM tube consists of a series of dynodes that are positively charged. Electrons ejected from the photocathode are accelerated to the positively charged dynodes. As the electrons collide with a dynode, more electrons are ejected. By accelerating the electrons through a series of dynodes, each with greater voltage differences, the number of electrons produced from each light flash is amplified 1×10^6 to 1×10^8 times.⁵

The camera's positioning circuitry will determine the point of absorption of the gamma ray in the crystal. When the photon is absorbed within the NaI (Tl) crystal, a light flash is produced that spreads isotopically from the point of absorption. The light is detected by the array of PM tubes. Those PM tubes closest to the light flash receive the greatest intensity signal. The amount of light received by each PM tube is inversely related to the distance from the PM tube to the point of absorption. The output signal from each PM tube is weighted to determine the point of origin. Four spatial coordinate signals are generated for each gamma ray photon interaction: +X, -X, +Y and -Y.² Increasing the number of PM tubes in a camera will improve the ability of the positioning circuitry to determine the point of absorption in the crystal. Older cameras had 19 PM tubes. A significant improvement in resolution occurred by increasing the number to 37. Some newer cameras have >75 PM tubes. By decreasing the size of individual PM tubes and increasing the PM tube number, gamma camera spatial resolution has significantly improved.

Pre-amplifiers will alter the shape and the magnitude of the signals from the PM tubes. The pre-amplifiers are located close to the PM tubes by a short electrically shielded cable to minimize electrical noise. The amplifier acts on the signal to further change its size and shape. Pulse duration is decreased by clipping the end of the pulse signal. This prevents sequential pulse overlap or pulse pile-up.

The newly shaped and amplified electrical signal is then received by the pulse-height analyzer (PHA). The PHA is an energy discriminator (Z pulse) and limits the recorded signal to only those signals that have the discrete or acceptable energy information. Those signals with energy amplitudes above

or below a specified window will be rejected. As the amplitude of the signal is proportional to the energy of the absorbed photon, the PHA can be selected for a specific energy photon. Centering the window of acceptance over the photopeak of the desired radionuclide eliminates most of the scatter radiation due to a lower energy. The center of the PHA is matched to the photopeak energy of the desired radionuclide. The window width specifies the limits of the upper and lower discriminators. By increasing the width of the window, the acceptance zone around the photopeak is widened thus increasing the number of accepted counts but also including more scatter radiation. Narrow windows 5% to 10% provide the best resolution by excluding more scatter radiation but decrease count rate. Large windows 30% to 40% greatly increase count rate but at the expense of resolution. Most users will set a 20% window centered on the photopeak.

Adjusting the PHA to the center of the photopeak must be done every day. Older camera systems display the Z (energy) pulses on a cathode ray tube (CRT) as bright horizontal bands. The analyzer will blank out a boxlike region on the screen at the location of the window. By adjusting the center of the PHA, the window is moved to the brightest bands corresponding to the photopeak of the radionuclide. Most new cameras have multichannel analyzers in the camera, which will display the entire energy spectrum of the radionuclide. The window is adjusted to the center of the radionuclide's gamma photopeak. An alternative method to peak the camera is to have the rate scaler display the count rate and adjust the PHA center until the maximum count rate is obtained. This will correspond to the center of the photopeak.

The numbers of recorded gamma rays, with an energy pulse accepted by the pulse height analyzer are recorded by the scaler or counter. This count information can be used by the camera to acquire analog images. Image acquisition is either time based or count based. For a count based acquisition, the camera is set to record a specific number of counts. For a time based acquisition, a preset time is selected and all counts are recorded during the specified time interval. During the acquisition, each recorded count will result in a small dot of light on the output phosphor of the cathode

ray tube. By exposing film to the cathode ray tube, each light flash will result in an expose recorded by the film. Analog imagers are a thing of the past and no longer used. Currently, the output of the gamma camera is sent to a dedicated nuclear medicine acquisition computer.

Important corrections for gamma camera inaccuracies are necessary for correct X, Y orientation of the signal coming from the gamma camera (Figure 2.7). Areas of decreased count density between photomultiplier tubes are normalized with correction matrices that are build into the camera or acquired routinely for correction of signal position (linearity correction) as well as differences between the sensitivities of the photomultiplier tubes.

Camera uniformity without the collimator should be assessed daily or, at a minimum, weekly (see chapter 4 on Quality Control) prior to usage to ensure accuracy of gamma camera function. The proper energy settings for the various radionuclides are required prior to acquiring the study so that the camera is properly peaked for the photon energies of the radionuclide being used. In addition, there are dead time losses within the gamma camera system due to the way the information is processed. Count rates in the range of 300,000 counts per second will result in 10% to 30% dead time losses. The NaI (Tl) requires about 0.25 μsec to emit 67% of its light after photon absorption. The typical camera system temporal resolution from the photomultiplier tubes through the amplifier is about 1.5 to 3.0 μsec .

Digital Camera Systems

Various new camera systems are available that are considered digital at the camera head. The scintillation event as recorded by the NaI (Tl) crystal is directly recorded, based on the x and y circuitry and the Z pulse information, into a digital image at the camera. This bypasses a certain amount of the electronics that are necessary in the older camera systems, such as the ADC and any pulse shaping/amplification that is required prior to image display. The newer camera systems include automated tuning modules within the electronics of the head of the camera. The digital camera will have auto correction features to account for imperfections in the crystal-photomultiplier assembly and the position logic circuitry. The energy signal is first corrected as

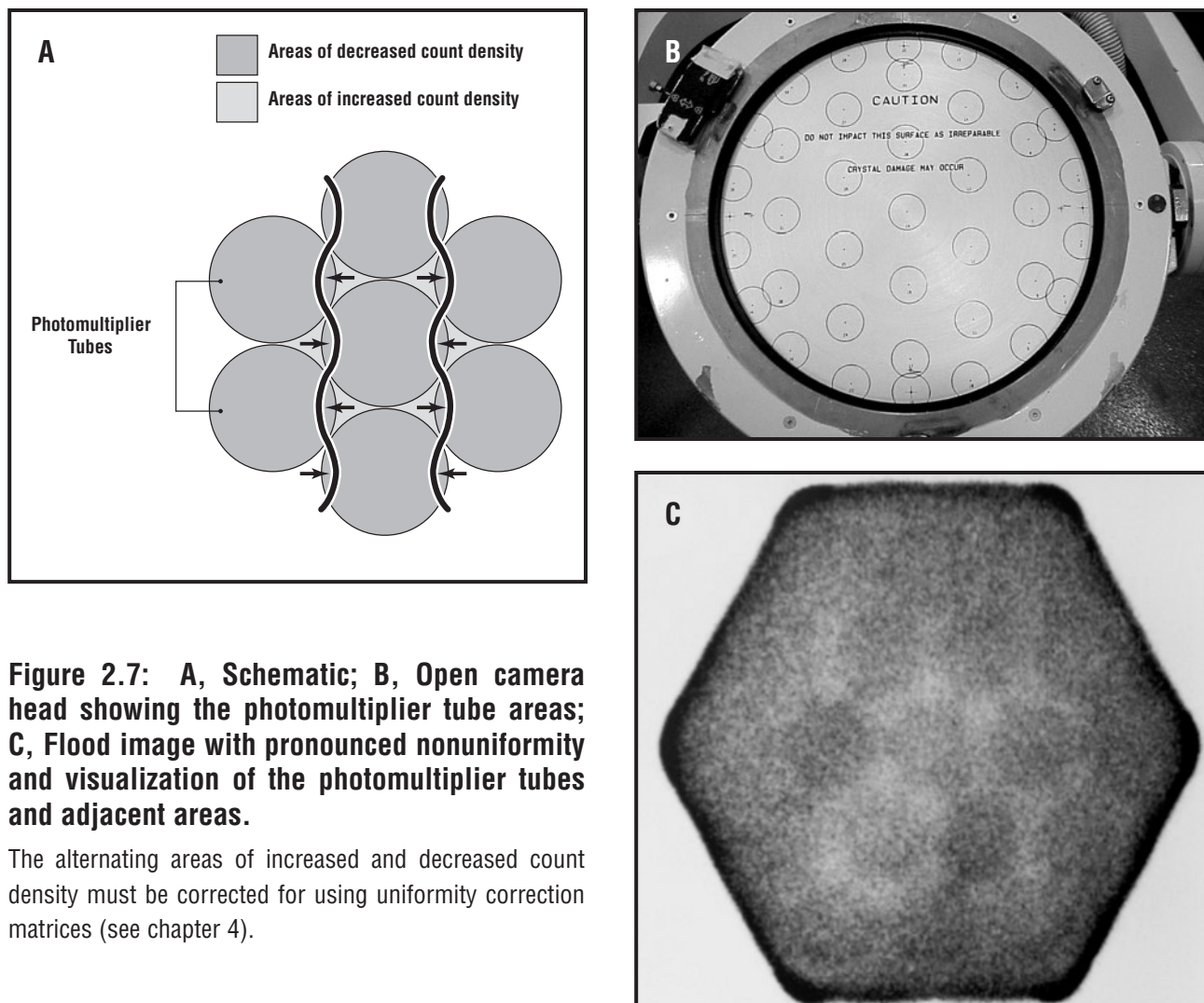


Figure 2.7: A, Schematic; B, Open camera head showing the photomultiplier tube areas; C, Flood image with pronounced nonuniformity and visualization of the photomultiplier tubes and adjacent areas.

The alternating areas of increased and decreased count density must be corrected for using uniformity correction matrices (see chapter 4).

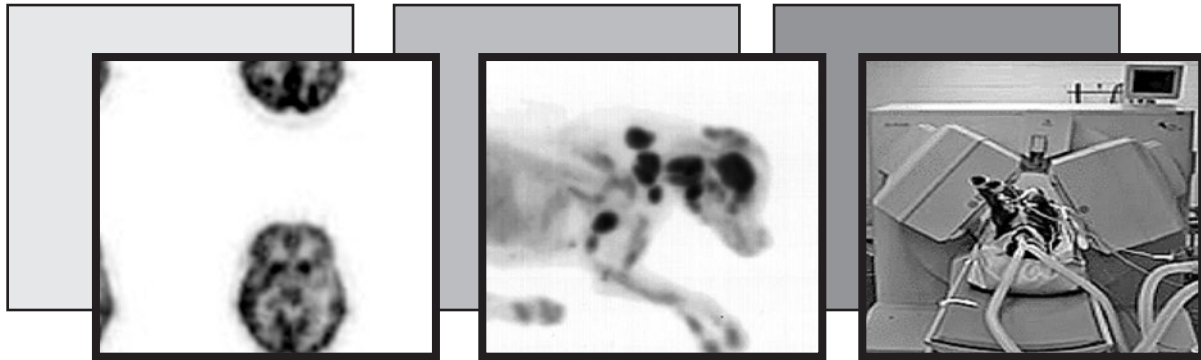
a function of its position and then is energy corrected. Additional automated corrections in the newer camera heads include balancing and tuning of the photomultiplier tubes to minimize the effect of PMT drift or electronic component aging. This automated feature of PMT tuning also enables, energy and the linear correction circuitry to work correctly.

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Single Photon Emission (Computed) Tomography and Positron Emission Tomography

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Introduction

Single photon emission (computed) tomography (SPE[C]T) and positron emission tomography (PET) have gained wide acceptance in human nuclear medicine as a standard of imaging.¹⁻¹⁰ As implied in the name, these techniques are a form of emission computed tomography where the patient is surrounded by either a series of detectors (PET = complete 360°) or a detector(s) that is rotated around the patient (as with single head, dual head, and triple head gamma camera SPE[C]T systems). These techniques allow for better anatomic spatial visualization and localization of radiopharmaceutical accumulation. Because the data is acquired as a volume, multiplanar reformatting is available. Both SPE[C]T and PET offer some form of attenuation correction so that quantification of uptake of the radiopharmaceutical within the field of view can be more accurately calculated.

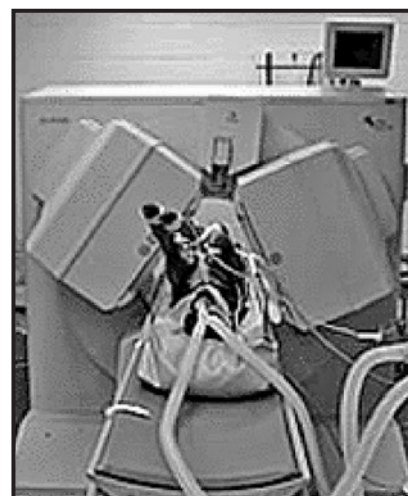
Single Photon Emission (Computed) Tomography (SPE[C]T)

Advances in computer technology and gamma camera detector design have allowed for rotational acquisitions of volumetric data sets that can then be used for the evaluation of the radiopharmaceutical localization within the patient.¹⁻⁹ Recent technological advances have allowed for SPE[C]T imaging of positron emitters as well as attenuation correction algorithms using attenuation maps utilizing other gamma emitting radionuclides with dual energy acquisition.⁶⁻⁸ SPE[C]T studies have become accepted as the standard of care in humans for myocardial perfusion imaging, bone SPE[C]T imaging and brain perfusion imaging. Reconstructed data sets can be reviewed in three dimensions as well as in multiplanar formats for three-dimensional evaluation. As with planar imaging, camera to patient distance is the primary reason for image degradation. Equipment costs, requirement of general anesthesia, and lack of specific demand for myocardial or brain perfusion imaging are considered the major disadvantages to the technique and thereby restrict immediate clinical applications within veterinary medicine.

For SPE[C]T imaging, there are various camera configurations that include a single, dual, and triple head camera system with 360-degree rotational capabilities (Figure 3.1). Dedicated SPE[C]T brain imaging systems are available for perfusion imaging

where an entire ring of detectors or a single large circular crystal is used. The patient's head is placed into the center of the ring of detectors for imaging. The advantage of the dual head system is flexibility for the application of 90-degree and 180-degree camera orientation. In the late 1990s, dual head SPE[C]T systems were equipped with high energy collimators, increased crystal thicknesses, a form of annihilation photon coincidence detection circuitry so that these dual head camera systems could serve as a semiquantitative PET acquisition camera and image ¹⁸F-FDG.^{3,6,8} The disadvantage of this setup when compared with true PET is the inherent poor detection efficiency of the NaI (Tl) crystal for 511 keV annihilation photons. Counting rates are much slower and less reliable in the SPE[C]T systems than in the PET systems. The advantages of the triple head system are that accurate attenuation correction can be done using a radioactive rod where one of the gamma cameras will be used for the collection of the attenuation correction data. In addition, triple head cameras provide the closest patient to detector distance and greater speed for image acquisition, although true temporal (three-dimensional dynamic imaging) scintigraphy is still not possible. The dual head camera systems are better suited for a combination of either SPE[C]T or planar camera acquisitions (including whole body bone scans). Ring detector systems, such as those dedicated to brain imaging, have the highest sensitivity of these SPE[C]T systems.

Figure 3.1: Photograph of a dog that has been placed inside a triple headed SPE[C]T system under general anesthesia



SPE[C]T can be used to evaluate the three-dimensional uptake of any stable radiopharmaceutical within an organ or area of interest. Because SPE[C]T images represent cross-sectional anatomy, overlying background radioactivity can be removed and specific abnormalities within the organ of interest better quantified. SPE[C]T imaging requires stringent quality control so that camera uniformity is even more important than with planar acquisition. A radionuclide that is stable within the organ of interest for the period of time being imaged is necessary for accurate count density information. Most data acquisition sets require between 10 and 25 minutes for completion, depending on the number of cameras used, the stops per camera rotation, and time allowed for data acquisition per stop. Larger dosages can be used so that count statistics are improved. All reconstruction planes will have limited resolution based on count statistics and the inherent overall system resolution.

The timing of specific SPE[C]T studies is dependent upon the radiopharmaceutical, the stage of uptake, and clearance of the radiopharmaceutical. There are five specific parameters that must be defined prior to starting a SPE[C]T acquisition, including: rotational direction (clockwise or counterclockwise), distance or arc angle traveled (usually defined in terms of degrees (120° to 360°), matrix format, number of steps (stops), time per stop. There is a continuous acquisition format but the step and shot format is more commonly used. Also, the specifics regarding the orbit the camera(s) will take during the rotational orbit around the patient is recorded by the computer system prior to acquisition to decrease patient to camera distance. Circular, contoured, or elliptical orbits are used for defining a gamma camera(s) path around the patient. The camera should move around the area of interest to obtain the maximum amount of information with the minimal tissue attenuation and patient to camera distance. Centering the area of interest within the center of rotation of the camera(s) is important for obtaining the most information about the radiopharmaceutical distribution in the area of interest. Typical matrix camera sizes include $128 \times 128 \times 16$ (body studies) and $64 \times 64 \times 16$ for focal regions of interest, such as cardiac studies. The number of stops for a step and shot acquisition is dependent on the number of cameras (single head versus triple head setup). Typically between 16 and 64 stops are used with an acquisition time between 15 and 60 seconds for each stop. A continuous acqui-

sition is also possible, where the gamma cameras rotate in slow sequence around the patient without a step and shot format. In that case the total imaging time is defined.

Within SPE[C]T images the overall subject contrast is greater when compared with planar images because there is no longer the effect of summation of depth information. As mentioned previously, the quality control for the gamma cameras when using SPE[C]T is critical. Intrinsic uniformity flood fields of 30,000,000 counts are acquired for each camera, and a central field of view uniformity of less than 1.5% is required. A center of rotation correctional study is done using the same collimator that is going to be used in the SPE[C]T study. This is obtained by placing 500 μCi of the radionuclide and a 360° tomographic study. This center of rotation study allows the computer to define the true center of rotation of the camera(s) so that the actual physical axis of rotation coincides with the center of rotation of the camera system.

The spatial resolution of current SPE[C]T systems is on the order of 6 to 8 mm FWHM (full width half maximum) at 140 keV. The spatial resolution of SPE[C]T systems is usually best at the periphery of the field of view and decreases in the center of the field of view. The loss of resolution is an inverse function of distance from the patient and directly related to collimator sensitivity. In addition, matrix size will impact the image acquisition parameters and amount of time per camera stop. There is a four-fold reduction in the overall counts recorded in each pixel when the image matrix is changed from $64 \times 64 \times 16$ to $128 \times 128 \times 16$.

The sensitivity in SPE[C]T depends on allowing the maximal detector crystal surface to circle the volume of interest. One way of accomplishing this is to use multi-head detector units. Collimator selection as in conventional planar imaging has the largest effect regarding the trade off between resolution and sensitivity. Special collimator designs (fan beam and cone beam) are capable of improving sensitivity and resolution, as well as, compensating for attenuation losses. These collimator designs require special reconstruction algorithms that may produce truncation artifacts when imaging larger patients.

Nonlinearity artifacts are amplified when using SPE[C]T. A 0.5 mm intrinsic nonlinearity in a gamma camera will barely be noticeable on a planar

image, but with SPE[C]T a noninterpretable image could result.

Reconstruction of the volumetric raw data sets after the acquisition has been completed requires specific input for the type of planes to be reconstructed and the types of filters applied for final image reconstruction. Prior to initial data reconstruction, a sinogram (the image produced where the radioactivity within the patient appears as a sine wave in a vertical direction) of the study is produced to evaluate for motion during the image acquisition. This step is a common reconstruction operation for all computer systems associated with SPE[C]T data. A sinogram enables recognition of patient motion or lack of correct camera motion during the data acquisition phase. The basic reconstruction algorithm that is applied to the raw data is filtered backprojection as used in computed tomography and positron emission tomography. Standard filters used for final image reconstruction include Butterworth, Wiener, or Metz filters with specified cut-off frequencies and orders. These cut-off frequencies and orders are applied to the image data set in the frequency domain after Fourier transformation of the filtered back projection data set. Once the specific filter has been applied and the new frequency data set is obtained, the images are produced by an inverse Fourier transformation (see chapter 5 for further information regarding image processing). Additional surface rendering programs are available that allows one to evaluate for contour abnormalities of radiopharmaceutical uptake.

SPE[C]T quantification of the radionuclide in question is still not fully realized. Dramatic improvements in quantitative capabilities have been accomplished over the past decade; however, the ability for SPE[C]T quantification of radionuclide binding within a given region cannot be truly quantified as it can in PET. One of the problems previously noted is the lack of time of flight acquisition capabilities or evaluating radionuclides/radiopharmaceuticals in a true dynamic fashion as with PET. The principle limitations that still need to be overcome in SPE[C]T include: (1) attenuation correction, (2) scatter correction, (3) image noise, (4) temporal resolution, and (5) finite spatial resolution of the camera/collimator system.

Attenuation correction is available from most commercially available SPE[C]T camera systems using a transmission and either simultaneous or sequential

emission computed tomographic study to be done. Rods containing ^{67}Ga are used either between cameras or opposite a camera so that a body contour attenuation map can be created and then attenuation correction applied to the final emission data set. Scatter correction is made using a subtraction technique (energy data acquired in the window that are below the photopeak are subtracted from the photopeak) or a deconvolution scatter filter called a Metz filter applied to the low spatial frequencies during the reconstruction algorithm.

In summary, equipment expense, lack of specific disease processes that would benefit, and anesthesia requirements have limited the application of SPE[C]T imaging in veterinary medicine. SPE[C]T imaging offers unique three-dimensional radiopharmaceutical distribution information that remains to be explored in veterinary medicine. The ability to identify new abnormalities has yet to be realized also.

Positron Emission Tomography (PET)

Positron emission tomography (PET) is widely used in human medical practice for imaging cancer patients.¹⁰⁻⁶⁵ The high cost and limited availability of PET currently prohibits its routine use in veterinary patients. PET is available on a limited basis for veterinary research, and there is much to be learned about both human and veterinary diseases using animal patients. Traditional imaging methods, such as radiology, ultrasound, computed tomography, and magnetic resonance imaging provide information regarding tissue structure and anatomy.²⁵ In contrast, functional rather than structural factors define the images obtained using PET.²⁵ A radiopharmaceutical tagged with a positron-emitting radionuclide is administered to the patient, and the PET detector maps the distribution of the radioactivity. The resulting image is a 3-dimensional map of radiopharmaceutical distribution (location and intensity) in the patient.²⁵ Because accumulation of the radiopharmaceutical is dependent on cellular function, PET conveys information regarding physiologic and metabolic processes in the body. PET can be used to provide complementary information to anatomic images and vice versa.²⁵ Recently, PET/CT combination scanners have been released in the human market so that image registration between imaging modalities is not an issue.

Radioactive Decay by Positron Emission

A radionuclide that has an unstable nuclear configuration where the nucleus is proton rich or neutron poor must have a minimum energy of 1.022 MeV in order to undergo positron decay.²⁵ Positron-emitting radionuclides are produced using cyclotrons, which bombard stable (nonradioactive) elements with protons.²⁵ As reviewed in chapter 1, the positron is emitted from the nucleus after nuclear reconfiguration where a proton becomes a neutron and a positron. The resulting “daughter” element has a neutron-proton ratio that is more stable than the radioactive “parent” radionuclide. This transition is an isobaric one where the atomic mass is preserved; however, a new element that has one less proton than the parent radionuclide is formed. The positron released from the radioactive nucleus during decay is a positively charged particle with the same mass as an electron.^{31,32} The positron will travel a short distance within the tissues (usually mm) depending on the energy of the positron. When the positron comes to rest, it will combine with an electron and undergo an annihilation reaction where there is a matter/anti-matter conversion and all of the mass of the electron and the positron are converted into electromagnetic radiation. The mass energy equivalent for the electron and the positron is 1.022 MeV. The annihilation reaction results in the formation of two annihilation photons that have an energy of 0.511 MeV and are emitted (180°) from each other in exact opposite directions. Detection of these two annihilation photons traveling in opposite directions is the foundation for PET imaging.

The PET Detector and Camera System

PET cameras are designed to detect gamma rays of 0.511 MeV and are composed of a ring of bismuth germanate (BGO) detectors that encircle the patient. These BGO crystals are coupled to a photocathode and photomultiplier tube.^{25,27} The crystal absorbs the annihilation photon resulting in a light flash, which is subsequently converted into an electrical signal by the photocathode.²⁷ The annihilation photons that are emitted at 180° to each other and are registered by detectors on opposite sides of the

patient.²⁵ These detectors record “true” events based on coincidence detection circuitry so that any 180° photons are counted only if they arrive within a preset coincidence window or time period (within nanoseconds of each other). A typical coincidence window is set at 10 to 15 nanoseconds; gamma rays arriving at opposite detectors within this preset window of each other are considered as a “true” event.^{25,27}

Detection of the gamma rays by opposite detectors means that the annihilation reaction occurred somewhere along the line between the two detectors. This line is called the line of response.^{25,27} By placing detectors 360° around the patient, the location of radioactivity in the body can be mapped by creating multiple lines of response. The emission scan is the image of the positron radiopharmaceutical distribution within the patient generated by reconstruction of recorded events along all of the lines of response during a given time period.²⁵

The patient is composed of various tissues with differing thickness and physical density. Because of this, the tissues of the patient will attenuate some of the annihilation photons as they pass through the body.³¹ Attenuation must be accounted for to accurately quantify the concentration of the distributed radioactivity from the positron within the patient.^{25,27} To achieve this, a transmission scan is acquired prior to the emission scan. The patient remains in the same position for both studies.²⁵ The source of radioactivity for the transmission scan is a ⁶⁸Ge/⁶⁸Ga ring or rod external to the patient, which decays by positron decay.³¹ Attenuation of the annihilation photons from the ⁶⁸Ge/⁶⁸Ga source by the body is then measured and mapped creating an attenuation image, (Figure 3.2). Emission data is corrected for attenuation by dividing the emission data by the transmission data to produce the final PET image.^{25,27} The initial transmission study takes between 3 and 5 minutes depending upon the radioactivity of the attenuation ⁶⁸Ge/⁶⁸Ga source.

Unique Features of PET

PET has unique features that enable the investigator to obtain quantifiable metabolic information not available using any other imaging modality. First, many molecules in the body are composed of organic elements including carbon, nitrogen, oxy-

gen, and hydrogen. These “building blocks” have radionuclides that decay by positron emission. The most common positron emitters include carbon 11, nitrogen 13, oxygen 15, and fluorine 18. The ^{18}F molecule is similar to hydrogen and can be used to replace hydrogen atoms on many organic molecules.^{25,27} Biologic processes can then be measured by replacing stable molecules with positron emitters. Individual steps within metabolic pathways can be measured using positron-emitting radionuclides tagged to normal physiologic organic molecules. Second, the high sensitivity of PET detectors facilitates use of very small amounts of radiotracer, which allows physiologic processes to be observed without competitive inhibition in the patient. Finally, the count density for each pixel of attenuation-corrected PET images is directly proportional to the number of positron emissions occurring, so that the image data reflects the concentration of radionuclide that has accumulated in a specific region.^{25,27} Accurate quantification of the metabolic process under study can be obtained. Because of the short physical half-lives of these positron-emitting radionuclides, com-

parative studies after pharmacological intervention can be done in order to document immediate effect of the pharmacologic agent being tested.

^{18}F -Fluorodeoxyglucose

One of the most commonly used radiopharmaceuticals for PET imaging is ^{18}F -fluorodeoxyglucose (FDG), an analogue of glucose. FDG is an example of a radiopharmaceutical that is designed to permit observation and measurement of a single metabolic step in vivo. The FDG model is an ideal model for quantifying the rate of the hexokinase reaction of glycolysis.

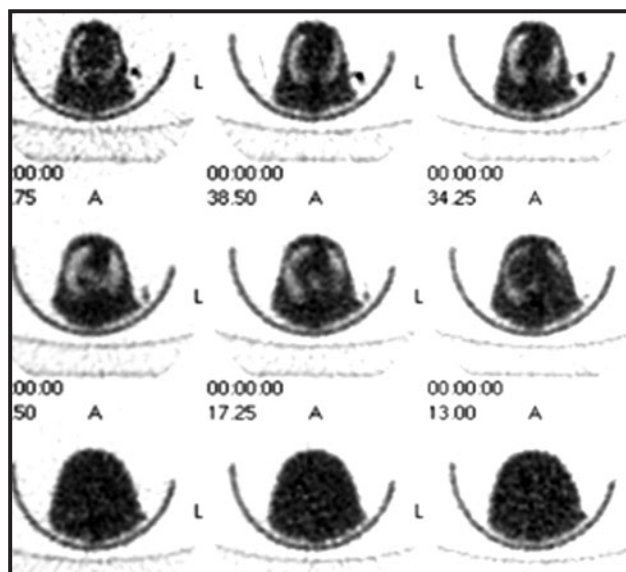
Glucose enters cells via a family of glucose-transporting proteins named GLUT1 to GLUT6.²⁸ Once inside the cell, glucose is converted to pyruvate via a series of enzymatic reactions called glycolysis.³⁴ Glycolysis is a fundamental pathway in the generation of cellular energy and functions both to degrade glucose to generate ATP and to provide synthetic building blocks.²⁸ Phosphorylation of glucose by hexokinase to glucose-6-phosphate (G-6-P) is an irreversible reaction that traps glucose within the cell. Hexokinase has such high affinity for glucose that its activity is saturated in the brain, liver (in the presence of insulin), and fat. Therefore, the rate of glycolysis is essentially equal to the maximum velocity of the hexokinase reaction.

The next step in glycolysis is isomerization of glucose-6-phosphate (G-6-P) to fructose-6-phosphate (F-6-P) by the enzyme glucose phosphate isomerase.²⁸ There are strict structural requirements for the enzyme substrate in order for this reaction to occur.³⁴ An analogue of glucose, 2-deoxyglucose (2-DG) differs from glucose in that the hydroxyl group at carbon 2 (C-2) has been removed. 2-DG competes with glucose for transport into cells via the glucose transporters. Like glucose, 2-DG is a substrate for hexokinase, and is phosphorylated by hexokinase to 2-deoxyglucose-6-phosphate (2-DG-6-P).^{11,12} However, because of the structural difference between glucose and deoxyglucose, 2-DG-6-P is not a substrate for the enzyme glucose phosphate isomerase.¹² Thus, following phosphorylation by hexokinase, 2-DG is trapped within the cell unable to undergo any further metabolism.

Tagging a radioactive compound to 2-DG provides a means to measure the rate of glycolysis by the accumulation of 2-DG within tissues.¹¹ 2-flourine-

Figure 3.2: Reconstructed transverse images of a dog prior to the ^{18}F -parafluorobenzyl-guanidine study

These images were obtained using transmission tomography by rotating a $^{68}\text{Ge}/^{68}\text{Ga}$ (positron emitter) rod around the dog's caudal thorax and cranial abdomen. The attenuation correction values obtained were then applied to the final imaging study.



2-deoxyglucose (FDG) is 2-DG with the hydrogen molecule at the C-2 position replaced by a fluorine-18 molecule (that is, glucose with the hydroxyl group at C-2 replaced by fluorine).¹² The FDG model is an elegant example of a biochemical approach designed to measure a specific metabolic pathway, in this case, glycolysis. FDG retains the chemical character of 2-DG because of its similar geometry. FDG is an appropriate substrate for hexokinase but, like 2-DG, is not a substrate for glucose phosphate isomerase. Therefore, phosphorylated FDG (FDG-6-P) cannot be further metabolized and all radioactivity will be in the form of either the original substrate, FDG, or the product of the hexokinase reaction, FDG-6-P.¹¹ This principal of “biochemical trapping” of FDG-6-P thereby permits biochemical isolation of the hexokinase reaction.¹⁴ The radioactivity accumulating in a tissue over time is proportional to the rate of the hexokinase reaction in that tissue, which, at steady state, reflects the rate of glycolysis.

PET Applications Using Fluorodeoxyglucose in Oncology

Early indications for PET imaging included evaluation of brain and cardiac metabolism.^{4,29} Over the past 10 years, PET has been primarily used for evaluation and management of cancer patients, (Figure 3.3),^{4,10} Recently, the following was said of the role of PET in oncology:

“The impact of PET imaging in cancer will be one of if not the most important development in nuclear medicine in the next decade.”⁴

FDG-PET is a sensitive tool for tumor detection and characterization. Common indications for PET are summarized in Table 3.1. FDG-PET has been shown to be efficient in detecting sites of malignancy and is unique in its ability to differentiate malignant from benign lesions.^{4,10,30-34} FDG-PET is used to assess regional lymph nodes for tumor involvement and detect distant metastatic disease for tumor staging.^{4,10,31-34} It has been reported that higher uptake of FDG-PET in malignancies is a poor prognostic indicator in some tumors, thereby providing a clinical tool for assessing tumor malignancy and predicting outcome.^{4,30,32-39} Because of this, patients with higher uptake of the FDG may be better suited for more aggressive treatment regimens. FDG-PET is also more sensitive than traditional methods, such as computed tomography (CT) or magnetic resonance

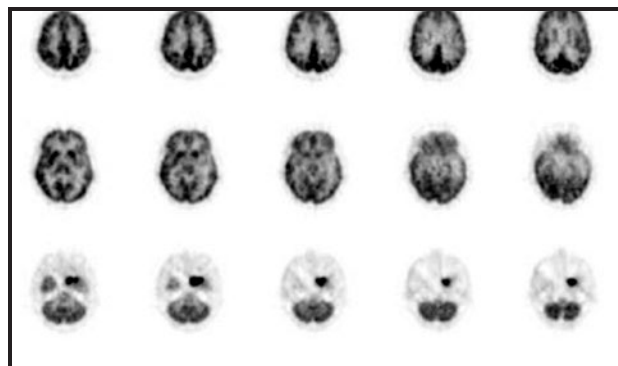


Figure 3.3: ¹⁸F-FDG reconstructed coronal images from a human with cancer recurrence following radiation therapy

The focal area of increased ¹⁸F-FDG at the inferior aspect of the temporal lobe is consistent with hypermetabolism from an actively dividing tumor. (courtesy of Dr. R.E. Coleman, Duke University Medical Center).

imaging (MRI), for detecting residual tumor following chemotherapy because FDG-PET measures response to therapy by evaluating tumor metabolism, an earlier indicator of treatment response than structural or anatomic change as seen on CT or MRI.^{4,30,32-39} FDG-PET can be used to detect recurrent disease and help differentiate recurrent neoplasia from post-treatment scar tissue or radiation-induced necrosis.^{4,30-48}

The rationale for use of FDG-PET in clinical oncology is based on glucose transport and the high metabolic turnover within tumor cells. Malignant cells are known to have aberrant energy metabolism, and an increase in the rate of normal glycolysis is a well-documented characteristic of many malignant cells.⁴⁹ Reprogramming of cancer cell gene expression results in a biochemical shift so that glycolysis is increased secondary to the increased activity of key glycolytic enzymes and increased numbers of glucose transporters at the cell surface. These biochemical changes result in increased uptake and sequestration of FDG by cancer cells due to increased intracellular influx of FDG and a higher rate of phosphorylation of FDG. All of these biochemical abnormalities are exploited by using FDG-PET for the detection of aggressive malignant disease.

Table 3.1: Indications for ^{18}F -FDG-PET Scanning

Indication	Comments
Tumor detection and characterization	FDG-PET is an exceptionally sensitive tool for detecting sites of malignancy and is unique in its ability to differentiate malignant from benign lesions accurately.
Staging malignant disease	FDG-PET is used as a sensitive, noninvasive method to assess regional lymph nodes for tumor involvement and to detect distant metastatic disease.
Determining prognosis	Higher uptake of FDG in malignancies has been reported to be a poor prognostic indicator in some tumors.
Assessing response to therapy	FDG-PET is more sensitive than traditional methods, such as CT, for detecting residual tumor following chemotherapy, because FDG-PET measures response to therapy by evaluating tumor metabolism, an earlier indicator of treatment response than structural change.
Detecting recurrent disease and differentiating recurrent neoplasia from post-treatment scar tissue or necrosis	FDG-PET is effective for detecting recurrent neoplasia and distinguishing recurrent tumor from benign changes, such as fibrosis.

Quantitative ^{18}F -FDG Uptake

Assessment of tissue glucose metabolism can be made from FDG-PET images at varying levels of complexity.^{50,51} Qualitative visual inspection of static images to identify focal areas of increased FDG accumulation is the first initial evaluation. Semiquantitative analysis of images can be done when using standardized uptake values (SUV) or region of interest ratios (for example, lesion-background ratios). Quantitative measurement of the local glucose metabolic rate using a static image with presupposed deductive estimates of the rate constants can also be determined. In the last instance, the specific turnover of FDG can be calculated within a very specific area of interest. Use of this method is limited because these rate constants are not universal. Required population estimates of these constants for a given tumor type are available for only a limited number of tumors of the central nervous system. Quantitative (direct) measurement of the local glucose metabolic rate using dynamic imaging and simultaneous arterial blood sampling can be done in order to determine the rate constants with the use of compartmental modeling.

Direct measurement of the local glucose metabolic rate is the most sophisticated measure of glucose metabolism.⁵¹ The equation for calculating the local glucose metabolic rate is:

$$\text{MR} = \frac{\text{CP} [k_1 \times k_3]}{\text{LC} [k_2 + k_1]}$$

where MR equals the metabolic rate of glucose; Cp equals the plasma glucose concentration; k_1 , k_2 , and k_3 are the rate constants for FDG; and LC is the lumped constant.

While the direct measurement of glucose metabolic rate has the most reasonable theoretical basis for quantifying glucose metabolism, its use for quantifying uptake of FDG by malignancies is limited. This is primarily because the lumped constant is not known for most tumor types and repeated arterial blood sampling is necessary for measuring the absolute glucose metabolic rate. This technique therefore is not practical for routine use in clinical patients.

An alternative method for quantifying (considered semiquantitative) uptake of FDG by tumors is the standardized uptake value (SUV). The SUV is a simple, practical, semiquantitative measure of FDG uptake, and is referred to as semi-quantitative because it is not a measure of the absolute glucose metabolic rate. Use of the SUV is based on the principle that it has been correlated with the absolute metabolic rate of glucose (Figure 3.4).⁵¹

The SUV is a measure of the concentration of radioactivity in a lesion corrected for the dose of FDG

administered and the weight of the patient.^{4,10} The SUV is calculated as follows:

$$\text{SUV} = \frac{\text{Decay Corrected Concentration of Tissue Activity}}{\text{Injected Dose/Body Weight (kg)}}$$

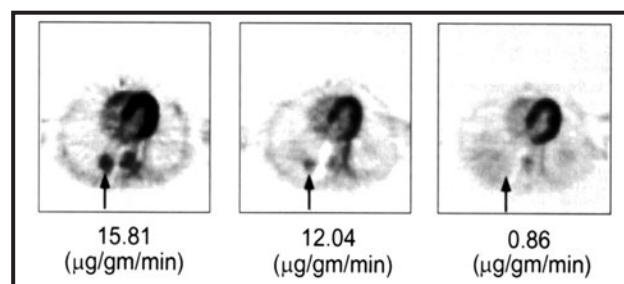
Computer software programs convert attenuation and decay corrected (to the time of injection) count density information for the original PET images into SUV images on a pixel-by-pixel basis. The SUV is then easily determined by drawing a region of interest (ROI) encompassing the desired area and a mean SUV for the area of interest calculated. However, controversy does exist over the usefulness of the SUV.^{51,53,54} The correlation with the absolute glucose metabolic rate is only fair,⁵¹ and there are other factors that can influence the SUV besides just the absolute glucose metabolic rate.^{51,54} Despite the recognized deficiencies of the SUV, however, this measurement is used routinely for determination of glucose uptake and metabolism within areas of interest. The SUV does provide a measure that can also be compared over time within a given patient.

Distinguishing Malignant from Benign Disease

The importance of determining definitively whether a mass is malignant or benign is obvious as both treatment and prognosis differ. Accurately distinguishing patients with malignant disease from patients with

Figure 3.4: Example transverse images from a person with a focal metastatic lesion in the mediastinum and increased ^{18}F -FDG uptake

The calculated standardized uptake values (SUV) are shown in the image. The SUV for the tumor (left image) is close to 12x greater than corresponding SUV in the lung (right image).



benign disease allows patients to receive appropriate therapy as quickly as possible. Malignancies typically have an SUV ranging from 3 to 20 (Figure 3.5).

While FDG-PET has very high sensitivity for detecting malignancies, a limitation of FDG-PET is less than ideal specificity. FDG-PET is not specific for malignant tumors alone because any tissue with increased glucose metabolism will accumulate FDG.^{17-21,60-67} Uptake of FDG by inflammatory cells occurs because inflammatory cells utilize increased amounts of glucose for chemotaxis, phagocytosis, and respiratory burst, (Figure 3.6).²¹⁻²⁴ Accumulation of FDG occurs in infectious and non-infectious inflammatory lesions, including CNS⁵⁷ and abdominal abscesses,⁵⁸ pneumonia,^{58,59} pancreatitis,^{63,64} CNS toxoplasmosis,⁵⁵ mastitis,⁶⁰ rheumatoid arthritis-associated lung disease,⁶¹ osteomyelitis,^{24,62} sarcoidosis,^{63,64} and tuberculosis.^{65,66} In most cases, however, the intensity of uptake of FDG by inflammatory lesions is far less than for malignancies, helping to distinguish malignant from benign lesions.^{14,15} Typical SUVs for most inflammatory lesions range from 1 to 3.

SUVs have been calculated for dogs with osteosarcoma using an F-18 labeled monoclonal antibody to canine osteosarcoma.⁶⁸ In addition, SUVs have been calculated for dogs with pheochromocytoma using the epinephrine analogue, ^{18}F -parafluoro-benzylguanidine (Figure 3.7).⁶⁹

Granulomatous inflammatory lesions will occasionally show high intensity uptake of ^{18}F -FDG and could be misdiagnosed for malignancy. An exception is the ^{18}F -FDG uptake associated with pyogranulomatous disease. Fungal infections produce a pyogranulomatous reaction that can result in SUVs that are higher than some tumors.^{70, 71}

Summary

Positron emission tomography provides information regarding physiologic and metabolic processes in the body. Fluorine-18-fluorodeoxyglucose is used in PET to detect malignancies based on their increased glucose metabolism. The amount of FDG accumulating in a lesion can be quantified using the standardized uptake value (SUV), a semiquantitative measure of glucose metabolism. Malignant lesions are identified by SUVs that are typically higher than the SUVs of benign lesions. FDG-PET is sensitive for identifying malignant tumors, but specificity is

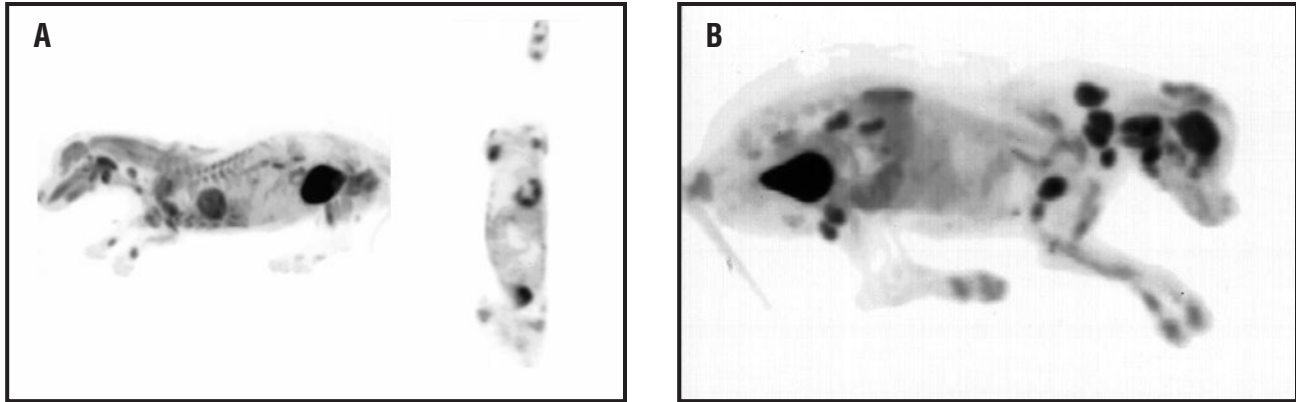


Figure 3.5: Whole-body $[^{18}\text{F}]$ -FDG PET images from 2 dogs with lymphoma

A, Note high-intensity uptake of FDG in mandibular, prescapular, and popliteal lymph nodes. The SUVs of these lesions ranged from 3 to 7. Normal uptake of FDG is seen in the brain, kidneys, and urinary bladder. B, Whole-body FDG-PET images of a second dog with lymphoma. Note high intensity uptake of FDG in mandibular, prescapular, and popliteal lymph nodes. The SUVs of these lesions ranged from 3 to 7. Normal uptake of FDG is seen in the brain, kidneys, and urinary bladder.

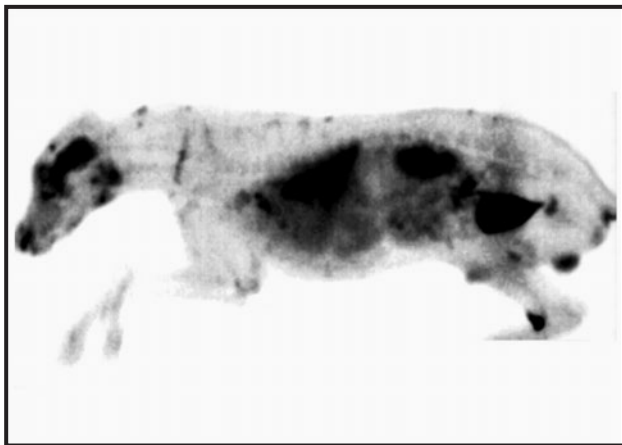


Figure 3.6: Whole-body $[^{18}\text{F}]$ -FDG PET image of a dog with disseminated blastomycosis

Note high-intensity uptake of the FDG. The SUV was 4:1. This is an example of an inflammatory disease with high uptake of FDG contributing to decreased specificity of FDG-PET for detecting malignant neoplasia.

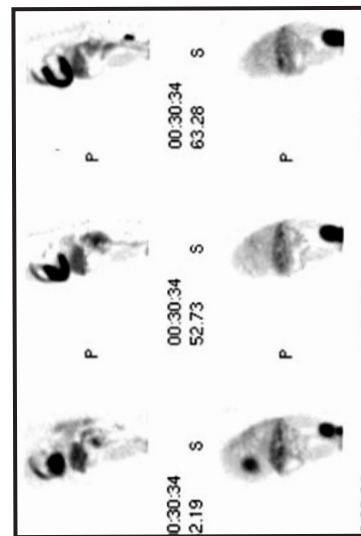


Figure 3.7: Reconstructed sagittal images from a dog 25 minutes after injection with $[^{18}\text{F}]$ -parafluorobenzyl-guanidine [PFBG]

Left lateral sequential sagittal images (reconstructed to 5 mm slice thickness). There is normal cardiac uptake (uptake-1 and 2; see chapter 7). There is an abnormally large area of intense increased PFBG uptake in the right adrenal gland (uptake-1). The histologic diagnosis was pheochromocytoma.

limited due to increased uptake of ^{18}F -FDG by inflammatory lesions.

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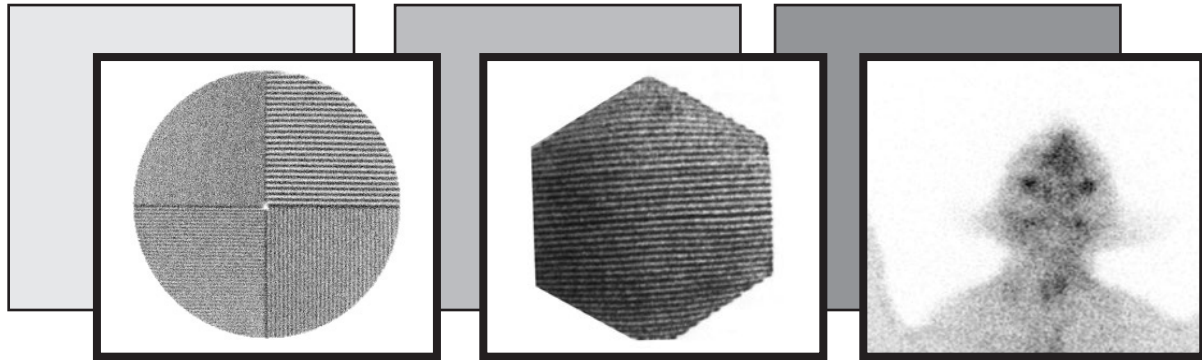
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Quality Control and Image Artifacts

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Introduction

Quality control of the gamma camera is critical to the daily operation of nuclear medicine. The gamma camera is a complex instrument, and malfunction of any part of the gamma camera decreases image quality and produces image artifacts and altered image appearance. Camera malfunction could lead to incorrect interpretation of a study and misdiagnosis. For this reason, routine procedures are employed to ensure adequate camera performance. This chapter, describes procedures needed to assure optimal performance of the gamma camera, dose calibrator, and radiopharmaceuticals. This information will facilitate the identification of defective equipment or radiopharmaceutical impurities. In addition, factors influencing scintigraphic image quality and common artifacts will be discussed.

Quality Control of the Gamma Camera

Routine quality control is necessary to monitor equipment function and assure that images are of highest quality.¹ The need for quality control is important for all nuclear imaging studies but is especially important for studies that include quantitative analysis. Subtle changes in camera performance may not be apparent on static images but could result in

inaccurate quantitative data. The frequency of performing quality control depends on the needs of the individual laboratory. Certain quality control procedures should be performed at regular intervals for all applications, whether clinical or research related. For quantitative studies, daily and weekly quality control should be performed on the gamma camera. Table 4.1 suggests daily, weekly, and biannual quality control studies in order to ensure peak gamma camera performance.

Setting the Pulse Height Analyzer

The pulse height analyzer (PHA) is an energy discriminator that allows the gamma camera to record only photons within a specified energy range.^{2,3} The energy of the absorbed photon determines the amplitude (or height) of the resultant electrical signal. If the gamma ray from the radionuclide is completely absorbed by the crystal, then the resulting electrical pulse will match the specified gamma energy of that radionuclide. Photons that are scattered prior to hitting the crystal or photons not completely absorbed by the crystal will depart less energy in the crystal. Therefore, they will generate an electrical signal of lesser height and the electrical pulse will not be accepted. Most modern gamma cameras have a multichannel analyzer (MCA) that has channels or bins to record the number of photons absorbed at each energy level. The display or graph of the MCA

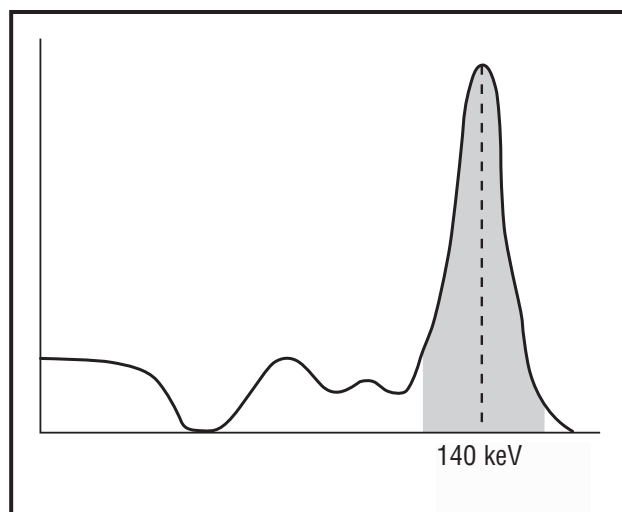
Table 4.1 Quality Control Program for Nuclear Medicine Laboratory, Including Daily, Weekly, and Biannual Calibrations

Test	Daily	Weekly	Periodically (Biannually)
Peaking the PHA	X	X	X
Visual Inspection of Field Uniformity	Optional	X	X
Quantitative Assessment of Uniformity		X	X
Uniformity Correction Factor		X	X
Linearity and Spatial Resolution		X	X
Sensitivity		X	X
Extrinsic Uniformity			X
Off Peaking Flood Field Uniformity			X

is a histogram, with the number of photons recorded (y-axis) for each energy channel (x-axis). The range of energy values is called the energy spectrum. Primary unscattered gamma rays account for the greatest number of photons absorbed by the crystal. An MCA display will have a peak at the energy of the unscattered gamma rays, and this peak is referred to as the photopeak.⁴ The shaded area in Figure 4.1 represents a 20% window centered at the 140 keV photopeak of ^{99m}Tc . The process of centering the window over the photopeak is referred to as peaking the camera. Peaking the camera should be performed at the beginning of each day and before performing quality control.⁵ It is best to use a ^{99m}Tc source and not the patient when peaking the camera. Note the difference in the spectrum generated from ^{99m}Tc within the patient compared with an isolated source, (compare Figure 4.1 with Figure 4.2). Note the scatter in the spectrum when the patient is used to peak the camera. The lower edge of the photopeak is unclear, and the camera cannot accurately distinguish the true photopeak from the larger Compton scatter region. In cameras that have auto peaking functions, the large amount of scatter radiation could result in the window drifting toward the scatter and away from the center of the photopeak. Ideally, a source that produces 10,000 to 20,000 counts per second (cps),

Figure 4.1: Energy spectrum of an isolated source of ^{99m}Tc

The shaded area represents the window centered over the 140 keV photopeak.



such as a 100 to 300 μCi point source, will be sufficient to create the desired photon flux for intrinsic measurements or autopeaking.⁵

Artifacts associated with improper PHA setting include:

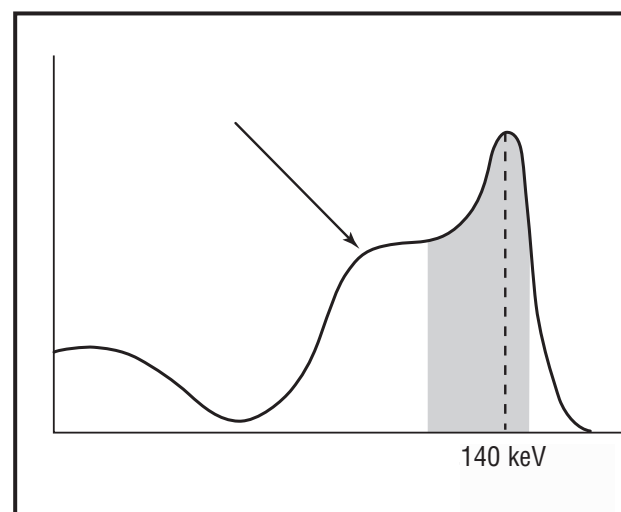
- ❑ *Low count rates.* The maximum count rate is obtained when the window is centered on the photopeak.
- ❑ *Nonuniformity.* The image will have a honeycomb pattern of the photomultiplier tubes (PMTs) if the window is placed above or below the photopeak (Figure 4.3).
- ❑ *Poor resolution.* The image will also have poor resolution if the window is set below the photopeak. The camera is recording scatter radiation that does not accurately represent the radionuclide distribution within the animal.

Field Uniformity

A properly functioning gamma camera should have a uniform response across the entire field of view of the crystal.⁶ That is to say, if the intensity of the pho-

Figure 4.2: Energy spectrum of ^{99m}Tc using the patient as the Radioactive source

Note the lower energy scatter radiation (arrow) that is more prominent than seen in Figure 4.1. If the gamma camera has an autopeak function, it may miscalculate the position of the photopeak (shifted below the true photopeak of 140 keV) due to the contribution of the scatter radiation.



ton bombardment is the same over the entire field of view, then the counts recorded from all portions of the crystal should be equal. To test field uniformity, a uniform photon flux is applied to the camera. Measurements made with the collimator in place are called extrinsic measurements, and measurements made with the collimator removed are called intrinsic measurements.

Intrinsic Uniformity Field

Intrinsic field uniformity measures performance characteristics of the gamma camera. The NaI crystal, light pipe or coupling grease, photomultiplier tubes, preamplifiers, amplifiers, pulse height analyzer, positioning electronics, analog-to-digital converter, and display system all affect the uniformity of flood image.⁶ To measure intrinsic uniformity the collimator is removed, and a uniform flux of radioactivity must bombard the detector. A radiolucent shield should be placed over the camera to protect the NaI crystal. Often the shield will have a lead ring around the periphery to decrease edge-packing artifacts. A point source of radioactivity is placed a distance equal to five useful fields of view (UFOV). For a 15-inch (38.1 cm) diameter crystal, the source

should be 75 inches (190.5 cm) away from the detector surface. A shorter distance would result in a hot focus of activity at the center of the detector. It is also important that the source is centered over the detector. The radioactivity of the source would be sufficient to provide a count rate between 10,000 and 20,000 cps.⁷ The flood image from a properly functioning gamma camera should have a uniform intensity across image field (Figure 4.4). There may be minor alternation in intensity corresponding to the location of the photomultiplier tubes and spacing between them.

Extrinsic Uniformity Field

Extrinsic field uniformity takes into account the performance characteristics of the gamma camera and the collimator. Collimators can be damaged by impact injury resulting in denting or collapsing the collimator holes, which can result in nonuniformity. This is especially true for foil collimators as compared with cast collimators. To measure extrinsic uniformity, a uniform source of radioactivity (usually a flat source) is placed directly on the collimator surface. The size should be sufficient to cover the entire field of view. There are two types of flat sources⁸:

1. A Lucite sheet impregnated with ^{57}Co . ^{57}Co has a physical half-life of 271 days and emits a 122 keV gamma ray.

Figure 4.3: Flood image acquired with the collimator off and a point source of 300 μCi of $^{99\text{m}}\text{Tc}$ suspended five UFOVs (approximately 75 inches) from the crystal surface

The acceptance energy window from the PHA has been placed eccentric (below) the photopeak. Note the honeycomb pattern of the PMTs with the relative photopenic areas between them.

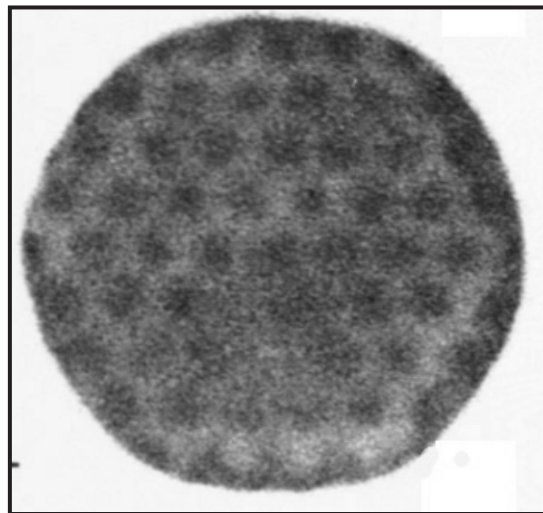
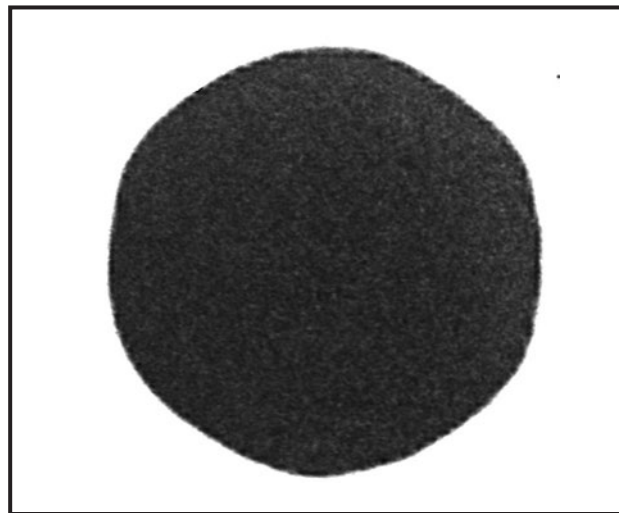


Figure 4.4: Flood image obtained as in Figure 4.3, with the window centered over 140 keV



2. A thin-walled flat Lucite container that can be filled with water. This container can then be filled with a small quantity of $^{99m}\text{TcO}_4^-$. The flood source should be inverted several times to ensure adequate mixing of the ^{99m}Tc in the water and equal radioactivity across the camera.

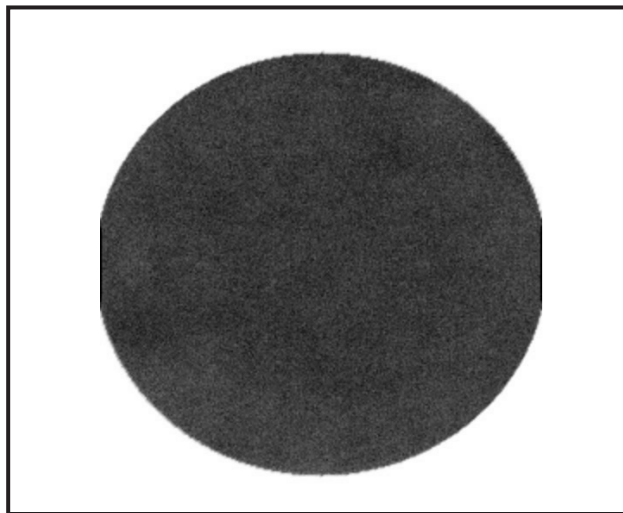
The presence of the collimator will greatly reduce the camera's detection efficiency. A higher quantity of radioactivity is needed in flood sources that are used for extrinsic measurements. A source containing 1 to 5 mCi (37 to 185 MBq) is necessary to provide the desired count rate; a point source cannot be used. This quantity of radioactivity is too high to be placed directly over the camera detector (without a collimator) and, therefore, should not be used for intrinsic measurements. The advantage of a flat ^{57}Co sheet source is the ease of acquiring the flood field images, which will facilitate daily flood uniformity evaluations. The image acquisition parameters are described next. Extrinsic flood images are usually acquired with the flat flood source directly on the camera surface.

Evaluation of the Flood Images

Visual Inspection

The image intensity of all flood images should be uniform across the entire field of view. Minor variation in count density may not be apparent on visual inspection as it takes a 5% to 10% gradient in image intensity before it is visually apparent (Figure 4.5). Five percent variations in field uniformity would not

Figure 4.5: Flood image obtained as in Figure 4.4, with 5% uniformity



influence static image interpretation but will produce errors in quantitative analysis. Focal abnormalities related to a specific part (single PMT) of the camera will be easier to detect.

Semiquantitative Analysis

A dedicated imaging computer can provide a more objective evaluation of the flood field uniformity. A line profile is a plot of pixel intensities in either a vertical or horizontal direction, (Figure 4.6). If the line profile is placed across the flood field image, the peaks and valleys denote the variation in pixel intensities. Ideally, the line profile would be a flat line across the surface of the camera (ie, equal intensity). This is never the case due to the random nature of radioactivity decay. A three-dimensional surface plot of the flood image provides a similar evaluation (Figure 4.7). The surface plot displays hundreds of individual line profiles giving a three-dimensional appearance of the flood field. Again, the surface of the plot should be relatively flat and smooth without large peaks and valleys.

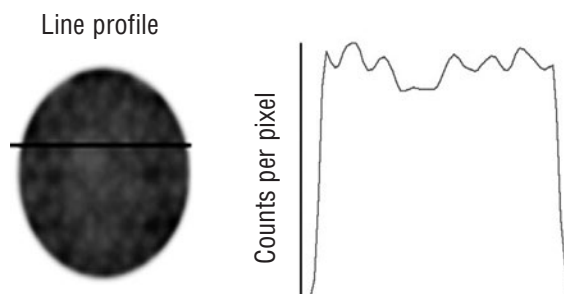
Quantitative Analysis

Intrinsic Camera Uniformity

The methodology for performing intrinsic uniformity quality control tests can vary. The National Electronics Manufacturers Association (NEMA) has established standards to characterize a specific performance parameter, such as field uniformity⁹:

Figure 4.6: Flood image with a line profile plot

Note the nonuniformity of the flood image and the undulating nature of the line profile plot across the surface. A uniform flood field should have a flatter line profile plot.



- ❑ Remove collimator (intrinsic uniformity being tested).
- ❑ Set a 15% window centrally over the ^{99m}Tc photopeak.
- ❑ Place a 3 mm-thick lead ring around the edge of the camera to prevent an edge-packing artifact, a peripheral rim of apparent increased radioactivity, and to identify the UFOV. Lucite shields with an outer lead ring can be purchased from various nuclear medicine supply companies that also sell ^{57}Co flat field sources.
- ❑ The ^{99m}Tc source should be placed five times the UFOV diameter away from the center of the detector. The source can be suspended above the camera using an intravenous fluid pole or a ceiling mount. The gamma camera is then lowered as close to the floor as possible with the NaI(Tl) crystal pointing toward the source. Intrinsic uniformity improves with increased source-to-camera distance.
- ❑ NEMA suggests a matrix size, that produces pixel size with a linear dimension of 6.4 mm. This corresponds to a 64 x 64 x 16 matrix for a large-field-of-view (LFOV) gamma camera. Alternatively, an image could be acquired using a 256 x 256 x 16 matrix and then converted to a 64 x 64 x 16 matrix before quantitative analysis by folding the image twice using the appropriate computer operation.
- ❑ For a small-field-of-view (SFOV) camera (10-inches or 25.4 cm), the total count should be at least 1,000,000. For a LFOV camera (15-inches or 39.1 cm), the total count should be at least 3,000,000. The larger 20 x 15 inch rectangular-field-of-view cameras require at least 5,000,000

counts. NEMA requirements are for the central pixel of the image to have a count density minimum of at least 10,000. This would correspond to an image total of 41,000,000 counts for a 64 x 64 matrix.

- ❑ Perform a nine-point smoothing operation using the smoothing kernel shown:

1	2	1
2	4	2
1	2	1

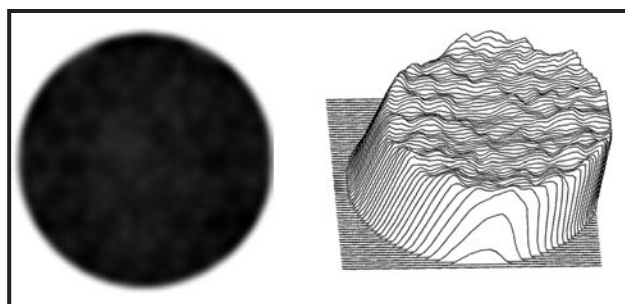
- ❑ Draw a large, region of interest on the inside of the outer portion of the camera flood image so as to exclude the outer rim of radioactivity (particularly if a lead ring was not used to block the edge packing artifact).
- ❑ Determine the maximum and minimum pixel intensities in the useful field of view (area within the region of interest).
- ❑ Determine the maximum and minimum change of counts over a range of any five pixels in any row or column. The highest and lowest integral uniformity values for the five contiguous pixels are then used to calculate the differential uniformity (see following text). The last two steps are typically done as an automated flood-field-processing program performed by most commercial software vendors specific to the dedicated nuclear medicine computer that is being used. The useful field of view represents the 95% center of the camera diameter, and the central field of view represents the 75% center of the camera imaging field.

There are certain limits that are necessary when acquiring the original 64 x 64 x 16 flood matrix. These include:

- ❑ The count rate should not exceed 20,000 cps.
- ❑ Each pixel should have a minimum count density of 10,000 counts per pixel.

The integral uniformity defines the maximum deviation of the maximum and minimum pixels. The differential uniformity, is the maximum integral uniformity measured in 5 x 5 pixel areas, that has been measured at every possible position in the flood image. Calculate the integral and differential uniformity using the following formulas:

Figure 4.7: Flood image from Figure 4.4, with a three-dimensional surface plot



$$\text{Integral uniformity} = \frac{\text{Max cts} - \text{Min cts}}{\text{Max cts} + \text{Min cts}} \times 100$$

$$\text{Differential uniformity} = \left[\frac{\text{Largest slice deviation (max - min)}}{\text{Max} + \text{Min}} \right] \times 100$$

New cameras will have integral uniformities of less than 5%. Acceptable uniformity for SPE[C]T studies range from 2% to 3%. Older refurbished planar cameras will have integral uniformities between 4% and 10%. Above 10% is considered unacceptable non-uniformity even for planar imaging.

Common causes of gamma camera nonuniformity include:

- ☐ PMT drift.
- ☐ Variation in preamplifier or amplifier gain.
- ☐ Malfunctioning positioning circuitry.
- ☐ Off-peak window setting of the PHA.
- ☐ Spatial distortion (nonlinearity).
- ☐ Hydroxylation of the NaI crystal.
- ☐ Defects and/or cracks in the NaI crystal.
- ☐ Defects in optical coupling of the NaI crystal to the photocathode for each PMT. One should never position the gamma camera with the crystal vertical to the horizon for long periods of time. Always place the gamma camera in a horizontal position with the camera face pointing up or down. This ensures that the optical grease will not slide downward because of gravity, resulting in nonuniform optical coupling of the crystal and the PMTs.
- ☐ Malfunctioning cathode ray tube (display).
- ☐ Damaged collimator that has bent or distorted septa (extrinsic resolution).
- ☐ High count rate, resulting in dead time count losses.

Uniformity Correction Factor

Field uniformity is one of the most important limitations of gamma camera performance. With the introduction of SPE[C]T, subtle nonuniformities (5% integral uniformity) in detector response became intolerable.⁸ Nonuniformities in the detector response are magnified when data from many angles

are back-projected to compute multiplanar images.

Most gamma cameras have incorporated electronics to improve field uniformity. The integration of the digital computer with the gamma camera affords a means to correct for nonuniform detector response. One of the first methods used was matrix multiplication.¹⁰ A “flood” image is stored in the computer from which a matrix of correction factors can be calculated. The stored flood image is typically a very high-count-density image, and the process of acquiring and storing this flood image is often referred to as calibration of the gamma camera. In this process, a flood image is acquired for 30 to 60 million counts and used to correct later images. For some cameras the nuclear medicine technician performs this operation, but others require service engineers. A matrix of correction factors is calculated for each pixel by dividing the value of each pixel in the correction matrix by the average of all pixels in the matrix. The matrix of correction factors for the entire image is then used to multiply each value of the pixel in the planar image to be normalized.

One of the first on-line methods for correction of field nonuniformities was called count skimming.¹¹ In this application, a high-count flood image is stored in a 64 x 64 matrix in the microprocessor memory. The minimum-count pixel of this matrix is determined. A correction factor is generated for all other pixels in the matrix based on the low-count-density pixel. The correction factor for each pixel is the ratio of the minimum pixel count divided by the individual pixel count. During subsequent acquisitions, counts are eliminated in a random fashion across the image field but proportional to each pixel's ratio. In this method, counts are eliminated and the detector sensitivity is lowered to that of the lowest-count-density region of the detector. The disadvantage of this technique is the loss of counts, thereby decreasing the overall camera efficiency. The trade-off for decreased camera efficiency is better field uniformity. The magnitude of count loss is determined by the uniformity correction factor, which can be seen in images from gamma cameras that allow the operator to turn off or on the uniformity correction circuitry. A flood image is acquired with the uniformity correction circuitry on and then repeated with the uniformity correction circuitry off. Images are acquired for a specific time or number of counts. If the corrected image acquisition is count-limited, the time of acquisition must be recorded and the uncorrected image obtained for the

same period of time.

The uniformity correction factor (UCF) is determined by the following formula. For count-limited acquisitions, the UCF is calculated by subtracting the time required to acquire the uncorrected flood from the time required to acquire the corrected flood divided by the time required to acquire the corrected flood times 100. For time-limited acquisitions, the UCF is calculated by subtracting the total counts acquired within the uncorrected flood image from the total counts acquired in the corrected flood image divided by the counts acquired in the uncorrected flood times 100 (formula below).

$$\text{UCF} = \frac{\text{Uncorrected image} - \text{Corrected image}}{\text{Uncorrected image}} \times 100$$

The UCF determines the percentage of counts that will not be counted as a trade-off for a more uniform field. The uniformity correction circuitry can hide many camera imperfections associated with a poorly tuned camera. This results in the progressively higher UCF that is needed to maintain an acceptable integral uniformity. If the UCF becomes high, then a service engineer may be needed to evaluate and possibly tune the entire gamma camera. This is true even if the field uniformity remains acceptable.

Another form of correction is based on energy correction.^{4,10-12} The energy spectra (Z pulse) should be the same from all locations across the scintillation detector, but this is not the case. Count density variation is partly due to the differences in energy spectra from each tube. Energy correction algorithms correct uniformity by adjusting the position of the photopeak of the energy spectrum. A microprocessor is programmed to record the pulse height spectrum for each area within a 64 x 64 or 128 x 128 matrix of the detector. A correction factor is then generated and applied to each Z pulse prior to the signal arrival at the PHA. The position of the photopeak is electronically adjusted so the photopeak falls within the center of the window. Alternatively, an energy window can be adjusted to the position of the photopeak. Some manufacturers store this correction map at the factory in a ROM chip that is placed in the electronic circuitry within the camera head. The user cannot update this correction map. Other manufacturers allow service personnel to update this information on-site.

Spatial Resolution

The spatial resolution of a gamma camera is the ability to distinguish two objects as separate on the final image. The better the resolution of the camera, the closer the objects can be and still be separately seen. The spatial resolution of a gamma camera can be quantified using the full width at half maximum (FWHM) of a line spread function. A line spread function can be determined by imaging a narrow line of radioactivity on the collimator (extrinsic) or on the crystal face (intrinsic). A piece of 2-0 silk suture material soaked in a solution of ^{99m}Tc works well as a discrete line source. An image of the line source is acquired using a large matrix 256 x 256 or 512 x 512. In an ideal system the image would be a discrete line, but in reality the margins are blurred. Using the analysis functions of the computer, a count density profile is generated perpendicular to the line source. A count density profile through the line source will represent the blurring inherent in the gamma camera. A count density profile with a narrow base indicates better resolution than a count density profile with a broad base. The count density profile is shown as a graph (Figure 4.8). The x-axis is the distance (number of pixels), and the y-axis is the counts recorded in each pixel. Based on the size of the field of view and the number of pixels in the line profile, a distance measure for each pixel can be determined as follows.

If one assumes the field of view is 15-inches or 381 mm and the image is acquired in a 512 x 512 matrix,

$$\begin{aligned} \text{Pixel size} &= \frac{\text{Diameter of the image field}}{\text{Number of pixels}} \\ &= \frac{381 \text{ mm}}{512} \\ &= 0.76 \text{ mm} \end{aligned}$$

The resolution is defined as the width (mm) of the count density profile (line spread function) at 50% of its maximum value (FWHM). The spatial resolution of the scintillation camera is a combination of the influence of the collimator and the intrinsic resolution characterizing the crystal and the camera electronics. The total resolution of the gamma camera can be approximated by the following formula:

$$\text{FWHM}_T = \sqrt{\text{FWHM}_E^2 + \text{FWHM}_I^2}$$

Where $FWHM_T$ is the total system resolution, $FWHM_E$ is the extrinsic resolution and $FWHM_I$ is the intrinsic resolution.

Most gamma cameras have an FWHM resolution between 3 and 7 mm. The FWHM technique will provide a precise measurement of resolution but is very laborious for routine assessment. A resolution phantom can be used as a quick and easy method for weekly evaluation of resolution and linearity.

A resolution phantom is composed of lead bars or small holes in a lead sheet. The distances between the openings test the resolution limits of the camera. This device is used for routine assessment of resolution. Intrinsic resolution is measured by removing the collimator, and placing the resolution phantom directly on the detector surface, positioning the point source five UFOV diameters away from the center of the camera face to generate uniform photon flux. Extrinsic resolution is determined by placing the resolution phantom directly on the collimator. A flat, uniform source is then placed on top of the resolution phantom. The distance between the openings of the resolution phantom should be at the resolution limit of the camera. Failure to differentiate the bars or holes indicates a decrease in resolution of the camera. Resolution phantoms do not measure the

specific resolution but rather the limits of resolution. As a rule, the FWHM is usually 1.7 times the small bars discerned on the phantom.² There are a variety of resolution phantoms available commercially, and the phantom must be matched to the resolution of the gamma camera.⁸

Four-Quadrant Bar Phantom

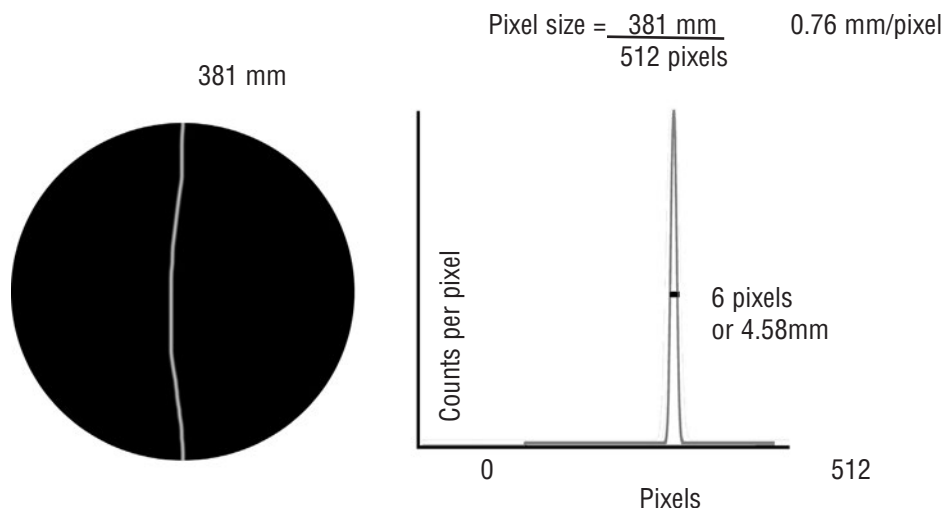
The bar phantom is composed of alternating strips of lead and plastic spaced at four different distances forming four distinct quadrants. The bar sizes are chosen to match the intrinsic performance of the gamma camera so that the smallest bar is at the resolution limit of the gamma camera. This is usually 2 mm for newer cameras. A 256 x 256 matrix image is acquired with the bar phantom on the crystal surface (collimator removed) and a 300 μCi $^{99\text{m}}\text{Tc}$ source placed five UFOV distance away from the gamma camera (Figure 4.9). The image is reviewed for linearity of the bars. Ideally the four-quadrant bar phantom is rotated at 90° intervals, and four total images are acquired so that the smallest bars are used to assess each quadrant of the image field.

Parallel-Line Equal-Spaced (PLES) Phantom

This phantom consists of lead bars that have the

Figure 4.8: Image of a line source of radioactivity acquired in a 512 x 512 matrix

A line profile is created perpendicular to the line of radioactivity. The resolution of the gamma camera is measured by the width of the curve at half of the maximum value (FWHM). Because the field of view is 15-inches or 381 mm, each pixel represents 0.76 mm. There are six pixels at FWHM, so the resolution is measured as $6 \times 0.76 = 4.58$ mm.



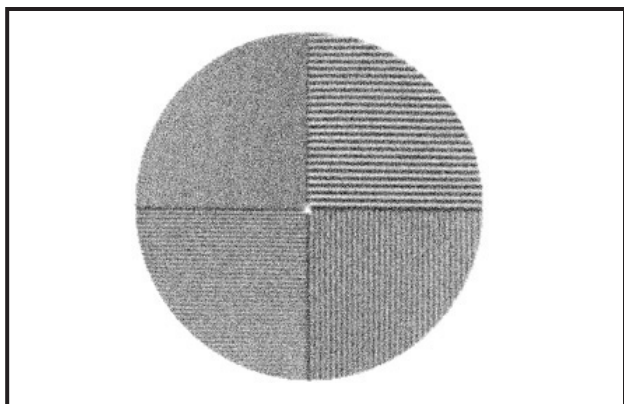


Figure 4.9: Image acquired without a collimator and with a point source placed 5 x UFOV with a four-quadrant bar phantom over the crystal surface

The camera resolution can be determined by finding the smallest bars that can be resolved. Linearity can also be assessed by the degree of distortion of the bars.

same width and spacing, embedded in Lucite (Figure 4.10). The bar sizes are selected to match the lower limits of spatial resolution for the particular gamma camera. As already described, an image is acquired. This image is used to assess the spatial resolution, linearity, and spatial distortion for the entire detector area. The PLES phantom is rotated 90° and a second image acquired so that linearity in the horizontal and vertical direction can be assessed.

Orthogonal-Hole (OH) Phantom

This phantom consists of a sheet of lead in which rows and columns of equal-diameter holes are arranged at right angles to one another (Figure 4.11). OH phantoms are available with a variety of hole diameters that include 6.4 mm, 4.8 mm, 3.2 mm holes that are spaced correspondingly at intervals of every 10 mm, 9.6 mm, and 6.4 mm. Again, the hole diameter size should be matched to the lower limits of spatial resolution of the gamma camera. A single image can be used to assess spatial resolution, linearity, and spatial distortion for the entire image field.

Linearity

Linearity is the ability of the gamma camera to precisely reproduce the distribution of radioactivity without geometric distortion. A straight line of radioactivity should be recorded as a straight line by the gamma camera. Linearity is assessed by the



Figure 4.10: Image of a parallel-line equal-spaced (PLES) phantom acquired in the same fashion as described for Figure 4.9

Resolving the bars provides an assessment of resolution. The space between bars should be at the resolution limit of the camera. Linearity can also be assessed by the degree of distortion of the bars.

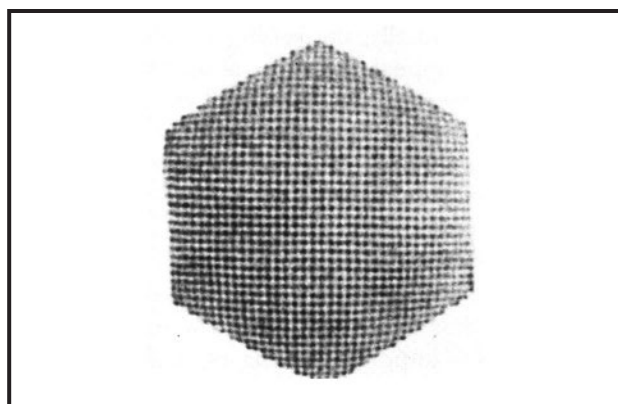


Figure 4.11: Image of an orthogonal-hole phantom acquired in the same fashion as described for Figure 4.9

Resolving the holes provides an assessment of resolution. The space between holes should be at the resolution limit of the camera. Linearity can also be assessed by the degree of distortion of the entire alignment.

appearance of the bars or the alignment of the holes in the resolution phantom. In a properly functioning camera, all groups of bars or holes should appear linear or parallel. Some distortion is often seen at the edges of the image. In general, the distortion of the LFOV gamma camera should be less than 5%.

Sensitivity

Gamma camera sensitivity is the parameter that characterizes the ability of the gamma camera to detect incident gamma rays efficiently. Sensitivity serves as an easily reproducible procedure for verifying the response of the entire system. Sensitivity will be affected by many factors that include the sodium iodide crystal, light pipe, PMTs, and a PHA. An accurate assessment of sensitivity requires that the radionuclide source be accurately measured and there are no geometric influences of source position that may artificially decrease the sensitivity measurement. The NEMA procedure for measuring sensitivity is as follows:

- ☐ Place the collimator on the detector (detector face and collimator pointing toward the ceiling).
- ☐ Peak the camera over the 140 keV photopeak of ^{99m}Tc and use a 20% window.
- ☐ Invert the detector (so that the camera face is a preset distance from the ground, ie, 36 inches).
- ☐ Place 1 to 2 mCi of ^{99m}Tc in a standard 100 mm diameter petri dish. A dose calibrator should be used to measure the source and the empty syringe to determine the exact amount of activity.
- ☐ The volume of solution should fill the petri dish to 3 mm depth and should be standardized (ie, always use the same volume of fluid specific to the petri dish plate). Place the standard on the floor in the central field of view of the camera. Acquire an image for 1 minute. Determine the total number of counts.
- ☐ Counts should be less than 10,000 per second.
- ☐ The results are expressed as counts per minute per microcurie of radioactivity (CPM/ μCi).

The intrinsic sensitivity can be measured during routine quality control if the geometry and distance of the source to the detector are standardized. The ^{99m}Tc source is measured in the dose calibrator immediately before acquisition of the flood image. The counts recorded per minute of acquisition are determined and divided by the activity of the source.

Off-Peak Flood Images

Images of the flood field when the window of the PHA is skewed off-peak will cause the area over each PMT to be either hot or cold relative to the spaces between the PMTs. There is slightly better light collection efficiency directly under each PMT and events that occur adjacent to the tube produce a slightly higher Z pulse. Those that occur between each PMT (intertube space) produce slightly lower Z pulses. If the manufacturer does not compensate for this effect, a pulse height window set to the high side of the photopeak will preferentially accept events under tubes producing a “hot tube pattern” whereas a window set to the low side of the photopeak will produce a “cold tube pattern.” Manufacturers of analog cameras frequently tune their cameras in a compensatory fashion resulting in a reversal of the expected pattern of high-side or low-side peaking (Figure 4.12).⁸ Whether the above-peak setting causes a “hot” or “cold” spot defect is a manifestation of the camera design and not the direction of the window offset relative to the peak. Ideally, a uniform count density over each tube should be the same as the spaces between the PMTs. Off-peak images are more sensitive in detecting abnormalities than on-peak images. Off-peak images are useful to differentiate between PMT imbalances versus defects associated with the NaI crystal or optical coupling. Following is a procedure for acquiring off-peak images.

- ☐ Use the same setup as described for acquiring flood images.
- ☐ Record the count rate with the window of the PHA centered over the photopeak.
- ☐ Move the window above or below the photopeak until the count rate drops to half.
- ☐ Acquire the flood image as previously described.

Count Rate Performance

Every radiation counting system exhibits a characteristic dead time or pulse-resolving time that is related to the time required to process individual detected events. The pulses produced by a radiation detector have finite time duration so that if a second pulse occurs before the first has disappeared, the two pulses may overlap to form a single pulse. In this event the second pulse is not recorded; or if the PHA is used, the summed effect of the two

pulses would cause both to be rejected due to their summed energy. It is assumed that as the amount of radioactivity increases, the counts recorded by the gamma camera should also increase. In actuality, as the true count rate increases, the count recorded by the gamma camera goes through a maximum and eventually drops off. The system will be paralyzable at very extreme count rates. In addition to the loss of count, high counting rates also result in a loss of spatial resolution.

Camera dead time can be calculated by using two sources of 300 μCi of $^{99\text{m}}\text{Tc}$ each. The collimator is removed and the first source (R1) is positioned 1 meter from the camera. A 1-minute static image (256 x 256 x 16) is acquired. The first source is removed and the process repeated using the second source (R2). A third image is acquired using both sources at the preset distance from the camera (R12). One records the total counts for each of the R1, R2 and R12 images. Camera dead time is calculated by the

following equation:

$$\text{Camera dead time} = \left[\frac{2 \times (R12)}{(R1 + R2)} \right] \times \ln \left[\frac{(R1 + R2)}{(R12)} \right]$$

The maximum count rate of the older gamma cameras (mid 1980s) ranged from 80,000 to 250,000 cps. The dead-time loss with count rates of 100,000 cps was around 20%.

Quality Control of the Dose Calibrator

Quality control of the dose calibrator is necessary to ensure the patient is administered the proper dose of the radionuclide.^{5,8} The dose calibrator is subject to following four quality control tests: accuracy, precision, linearity, and geometry (specified in 10 CFR, Part 35). For all tests, the model and serial number of the dose calibrator is recorded along with other pertinent information described next. The dose calibrator is evaluated regularly to assure its accuracy and constancy. The proper dosage of the radiopharmaceutical delivered is directly dependent on a properly functioning dose calibrator.

Daily Quality Control of the Dose Calibrator

1. Zero Calibration

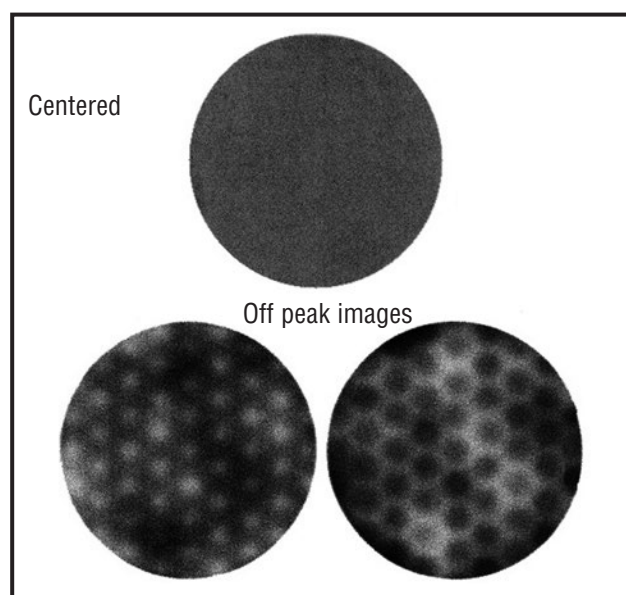
The first daily check of quality control is to ensure zero calibration that will correct for any background activity in the radiopharmacy. All radionuclides should be placed in their lead shields to minimize background activity around the dose calibrator. The background is adjusted to read zero. Many dose calibrators will do this automatically, or by the zero calibration button can be used to make manual adjustments.

2. Precision or Constancy Testing

The precision or constancy test ensures that radioactivity the dose calibrator records is reproducible over a long period of time. Regulations regarding human use require daily testing of precision. Precision is the ability to measure a source of constant activity repeatedly within a stated degree of reproducibility. Satisfactory performance of this test will assure that the dose calibrator is operating consistently from day to day. The constancy test is performed at the beginning of each day using a certified sealed source of not less than 50 μCi . A typical sealed source for

Figure 4.12: The top image is a flood image with the window of the PHA centered on the photopeak of $^{99\text{m}}\text{Tc}$

The images in the lower half were made with the window set eccentric to the photopeak. These images were acquired after the count rate was decreased to half by moving the window above (lower left image) and then below (lower right image) the photopeak. Note the mottled appearance of the off-peak flood images.



this test is ^{137}Cs . After decay correction, the measured activity should not vary by more than 5% of the calculated radioactivity. The record of the test includes the radionuclide identity, date, radioactivity measured and initials of the tester.

- ☐ Place the calibration source, (^{137}Cs , ^{60}Co , or ^{57}Co) into the dose calibrator.
- ☐ The source must be accurate to within 5% of the known radioactivity, have a photon energy between 100 keV and 700 keV, and have radioactivity of at least 50 μCi .
- ☐ Adjust the radionuclide selector to the proper setting for the specific radionuclide used.
- ☐ Determine the reading three times and calculate the average value. This average value should be within 5% of the decayed certified value (supplied with the sealed source when purchased).

Quarterly/Annual Quality Control for Dose Calibrator Linearity Testing

Accuracy Testing

This test ensures that the measured radioactivity is equivalent to the true radioactivity. Accuracy is defined as the closeness of a measured value to its true value. Accuracy is tested at installation and annually with at least two different radionuclide sources. These sources must not be less than 50 μCi . One source must be a gamma emitter and have a photon energy between 100 and 700 keV. Typical sources are ^{57}Co , ^{133}Ba , and ^{137}Cs . After decay correction, the radioactivity measured should not vary by more than 5% of the calculated radioactivity. The record of the test includes the source identities, radioactivities, serial numbers, date, results of the test, and signature of the radiation safety officer or individual radionuclide license holder.

- ☐ Place a sealed radioactive source that has a long physical half-life (^{137}Cs , ^{57}Co , or ^{133}Ba) into the dose calibrator.
- ☐ Adjust the radionuclide selector to the radionuclide that is being used.
- ☐ Record the displayed radioactivity level.
- ☐ Adjust the radionuclide selector to the other radionuclide setting and then measure and record

the displayed radioactivity level.

- ☐ Compare the two values to the previous days' values. The values should not change more than 5%. If the values vary by more than 10%, then the dose calibrator should be serviced.

Linearity

Linearity is an assessment of the dose calibrator's ability to measure radioactivity accurately over a wide range of activities. The dose calibrator should have a linear response below radioactivities of 3.7 GBq (100 mCi). At very high radioactivities (greater than 200 mCi or 7.4 GBq), however, the dose calibrator response does become nonlinear. Nonlinearity results in an artificially low reading compared to the amount of radioactivity that is actually present. This low reading is due to recombination of ion pairs in the ion chamber before they are collected at the electrodes. The linearity test is conducted over the range of radioactivities that are likely to be measured in the practice. Initially, the linearity of the dose calibrator can be established by a decay method. The linearity test is performed at installation and quarterly. The records include the measured and calculated activities, date of test, and signature of the radiation safety officer, or individual radionuclide license holder.

- ☐ Place 7.4 GBq (200 mCi) of a $^{99\text{m}}\text{TcO}_4^-$ source into an appropriate counting vial. Record the initial activity and the time and date.
- ☐ Measure the source twice daily until the radioactivity reaches 100 μCi (72 hours later).
- ☐ Calculate the expected decay curve using the decay equation:

$$A_t = A_0 e^{-\lambda t}$$

- ☐ Compare the displayed radioactivity to the calculated decay radioactivity. Linearity is characterized by dose calibrator readings that are within 5% of the decay-corrected values.

Geometry Test

The geometry test determines whether the source configuration, volume, or position in the dose calibrator well has any significant effect on the accuracy of measurement. Weak gamma sources, such as ^{125}I (35 keV) are characterized by low readings in higher density materials (eg, glass vials versus

plastic syringes); and appropriate corrections are made to obtain accurate readings. Volumetric variations are evaluated by placing 37 MBq (1 mCi) of the sample radionuclide into a vial. An initial reading and all subsequent readings are made after one mL increments of water are added. Discrepancies in the radioactivity would indicate whether or not correction factors are needed for various volumes of the radionuclide. Variations of radioactivity can be checked with respect to position in the ion chamber by measuring a 1 mCi (37 MBq) source at prescribed distances from the bottom to the top of the dose calibrator well. Readings at the bottom and top of the well will be inaccurate due to loss of photon detection in the ion chamber. This test is used to establish the position of greatest accuracy, and this position should be used for routine measuring of all radionuclides. The geometry test is performed at installation and again following dose calibrator repair, movement, or adjustment. Records include the source measured, radioactivity for each volume measured, date of the test, and signature of the radiation safety officer or the individual radionuclide license holder. All dose calibrator records for accuracy, precision, linearity, and geometry are maintained for 3 years.

Radiopharmaceutical Quality Control

Quality control of the radiopharmaceutical includes evaluation for radionuclide, radiochemical, and chemical impurities.¹³⁻¹⁷ Radionuclide purity measures the fraction of the total activity that is in the form of the stated radionuclide. Radiochemical purity is the fraction of the radionuclide present in the stated chemical form.^{16,17} Chemical purity (rarely done in veterinary nuclear medicine) is the proportion of the drug in the specific chemical form regardless of the radionuclide.¹⁷⁻¹⁸

Daily determination of radionuclide purity is required for human use and will be performed by the nuclear pharmacy prior to delivery of the radionuclides. Veterinary nuclear medicine laboratories with their own $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator should measure radionuclide purity at least once a week or when there are multiple elutions of the generator in any given day. Routine quality control of commercial radiopharmaceuticals will be performed by the nuclear pharmacy prior to delivery of the radiopharmaceuticals. In veterinary laboratories that prepare the radiopharmaceutical in-house, the radiochemical purity measured

is rarely performed unless the biodistribution of the radiopharmaceutical deviates from normal. In that case, the radiochemical purity is determined from the residual volume of the radiopharmaceutical in the vial. When a radiopharmaceutical is to be used for quantitative research, then the radiochemical purity of each radiopharmaceutical should be tested prior to the study.

Radionuclide Purity

The most common radionuclide impurity in sodium $^{99\text{m}}\text{Tc}$ -pertechnetate is ^{99}Mo (Figure 4.13). To determine the radionuclide purity of a solution:

- ❑ Place the elution vial of $^{99\text{m}}\text{TcO}_4^-$ into the dose calibrator making sure the radionuclide selector is on the $^{99\text{m}}\text{Tc}$ setting and record the radioactivity.
- ❑ Remove the elution vial and place it into the lead ^{99}Mo assay canister.
- ❑ Insert the lead canister into the dose calibrator and set the radionuclide selector to ^{99}Mo .
- ❑ Record the displayed activity. Radionuclide purity is calculated as the number of μCi of ^{99}Mo per mCi of $^{99\text{m}}\text{Tc}$.

The NRC allowable limits (see Table 1.4 in Chapter 1) include the fact that the percent of the desired radionuclide must be greater than 90%. The amount of molybdenum must be less than 0.15 μCi of ^{99}Mo /mCi of $^{99\text{m}}\text{Tc}$ at the time of injection, and there cannot be more than a total of 5 μCi of ^{99}Mo per dose administered.

Radiochemical Purity

The most common method of assessing radiochemical purity is instant thin layer chromatography (ITLC).¹⁵ ITLC is performed by placing a small quantity of the radiopharmaceutical (a drop from a 26-gauge needle) near the end of an ITLC strip (called the origin of the support column; Figure 4-14). The support column varies with the radiopharmaceutical but is typically either cellulose filter paper or silica gel-impregnated chromatography paper. The support column is placed into a chromatography chamber, or alternately into a 10 mL test tube containing a specific solvent. It is important that the deposition site of the radiopharmaceutical is above the level of the solvent. The solvent will then wick up the support column by absorption and capillary action (Figure

4.15). The radiopharmaceutical is separated from the radiochemical impurities based on their solubility. Constituents that are insoluble in the solvent stay at the origin and those that are soluble move up the support column with the solvent front. In this manner, the radiochemical impurities are separated from the pure radiopharmaceutical. The distribution of radioactivity along the support column is determined by scanning the column or cutting it into sections and measuring the radioactivity in a well counter for each section. The location of the radiopharmaceutical and the impurities along the support column are denoted by their respective R_f value. The R_f value is defined as the percent migration from the origin to the solvent front (Figure 4.16). A two-strip ITLC system is

Figure 4.13: Photograph of the lead canister used to measure ^{99}Mo

The elution vial is placed in the lead canister then both are put into the dose calibrator. The lead canister is designed to absorb most of the 140 keV photons from technetium-99m but not the higher energy (740 and 780 keV) photons of ^{99}Mo . The dose calibrator determines the amount of ^{99}Mo in the elution.



necessary to evaluate radiochemical impurities of most radiopharmaceuticals (Figs 4.15 and 4.16).

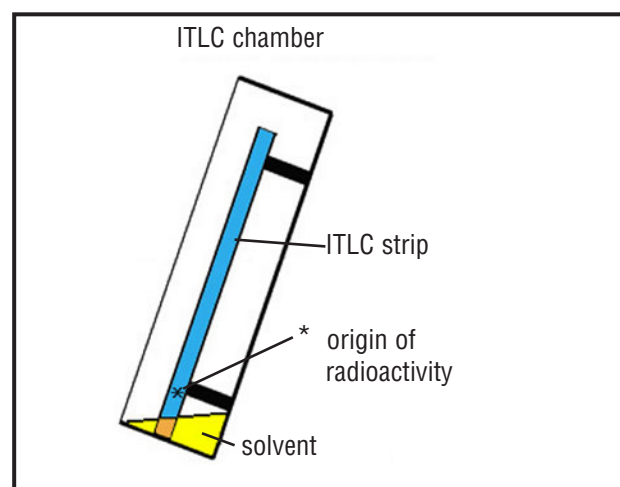
Common radiochemical impurities include free $^{99m}\text{TcO}_4^-$ and reduced hydrolyzed $^{99m}\text{TcO}_2$.¹⁵⁻¹⁷

Free or unbound ^{99m}Tc pertechnetate ($^{99m}\text{TcO}_4^-$) is the most common radiochemical impurity. $^{99m}\text{TcO}_4^-$ is normally concentrated in the thyroid gland, choroid plexus, salivary glands, and stomach and is excreted by the kidneys. The biologic clearance of $^{99m}\text{TcO}_4^-$ is relatively slow, resulting in persistent soft tissue activity. Free $^{99m}\text{TcO}_4^-$ as a radiochemical impurity is often the result of oxidation of the radiopharmaceutical kit's reducing agent (stannous chloride) by air entering the vial when the radiopharmaceutical is made. In this case, the kit is no longer capable of reducing the ^{99m}Tc (VII as $^{99m}\text{TcO}_4^-$) to a lower oxidation state ^{99m}Tc (IV of $^{99m}\text{TcO}_2$) and will therefore not chelate with the pharmaceutical (MDP, DTPA, etc.).

Hydrolyzed, reduced ^{99m}Tc ($^{99m}\text{TcO}_2$) is the second most common radiochemical impurity and is caused by moisture within the reaction vial. The moisture will cause stannous hydroxide to form, which results in a colloidal impurity. When this radiocolloid is

Figure 4.14: Diagram of an ITLC chamber

Solvent is placed in the bottom of the chamber. A strip of paper containing a spot of the radiopharmaceutical is placed into the solvent. The radiochemical constituents that are soluble in the solvent will migrate up the paper strip leaving the insoluble constituents at the bottom of the strip, thus separating the various radiochemical impurities.



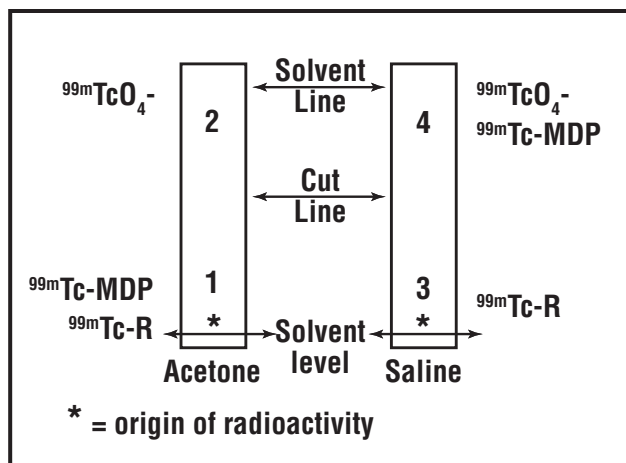


Figure 4.15: Diagram of ITLC strips for determining the radiochemical impurities in ^{99m}Tc MDP

$^{99m}\text{TcO}_4^-$ is soluble in acetone and will migrate with the solvent front. ^{99m}Tc MDP and ^{99m}Tc R are insoluble in acetone and will stay at the origin. $^{99m}\text{TcO}_4^-$ and ^{99m}Tc MDP are soluble in saline and will migrate with the solvent front. ^{99m}Tc R is insoluble in saline and will stay at the origin.

injected intravenously, it will localize via monocytic phagocytosis within the liver and secondarily in the spleen and bone marrow. In cats and pigs there is a large resident population of mononuclear phagocytes in the lungs, so increased lung radioactivity would be expected. The solvents used for detecting radiochemical impurities for each radiopharmaceutical are shown in Table 4.2.

Other Artifacts

Improper or inadvertent extravascular injection of radiopharmaceuticals that are intended for intravenous administration will produce a persistent intense area of radioactivity at the injection site.¹⁸ The radiopharmaceutical is cleared by the lymphatic system and will result in regional lymph node uptake. This has been reported for ^{99m}Tc MDP and ^{99m}Tc sestamibi (Figure 4.17).

As many radiopharmaceuticals are cleared from the body via the urinary system, the urine will contain a significant portion of the injected dose. High specific activity within the urine will be present for hours after the study. If the body surface is contaminated with radioactive urine, "hot spots" will be seen corresponding to the extent of contamination.^{18,19} If the animal ingests the radioactive urine, gastrointestinal

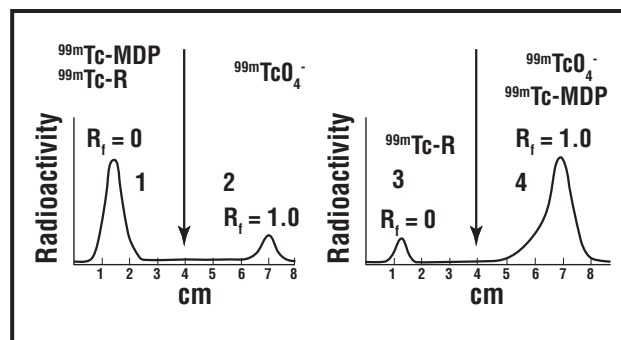


Figure 4.16: Rf values used for determining the radiochemical impurities in ^{99m}Tc MDP

The strips are scanned to determine the location of the radionuclide on the strip. The peaks on the graph show the location and the relative concentration of the radionuclide. The Rf indicated the degree of migration from the origin. A Rf of 0 means no migration and a Rf of 1 means complete migration of the radioactivity with the solvent.

radioactivity will occur.

Various drugs can sometimes alter the biodistribution of radiopharmaceuticals. One of the more notable effects is that of iodinated radiographic contrast media on thyroid uptake (Figure 4.18). The iodinated contrast saturates the iodide receptor of the thyroid gland and reduces the uptake of $^{99m}\text{TcO}_4^-$ or radioiodine.^{20,21} Because cats with hyperthyroidism have hypertrophic cardiomyopathy or renal disease, they may have either had nonselective angiocardiograms, computed tomography or excretory urograms prior to thyroid scintigraphy. Other drugs that will block thyroid uptake of radiopharmaceuticals in humans, (although unproven in animals), include some anti-thyroid medications, oral iodine (Lugol's solution or potassium iodine), and exogenous thyroid hormone supplements.

Artifacts Associated with the Gamma Camera

Septal Penetration

Septal penetration is a result of not matching the collimator energy characteristics with the radionuclides that are being imaged. Collimators are designed for specific photon energies. Thinner lead septa are used in low-energy collimators. The characteristic appearance of the image with septal penetration is one of poor anatomic detail. Areas of high radiopharmaceutical concentration will have a characteristic "star"

Table 4.2 Radiopharmaceuticals and Their Quality Control ITLC Reagents, Including Expected Positions on the ITLC Strips So That Radiochemical Purity and Percent Labeling Can Be Calculated

Radiopharmaceutical	Solvent	Solid Support (ITLC column)	Free $^{99m}\text{TcO}_4^-$	$^{99m}\text{TcO}_2$	Tc-Labeled Agent	Cut Location Rf Value
Sulfur Colloid	Acetone	Whatman 31 ET	1.0	0.0	0.0	0.60
MAA	Acetone	Whatman 31 ET	1.0	0.0	0.0	0.60
PYP	Acetone Distilled water	Whatman 31 ET ITLC-SG	1.0 1.0	0.0 0.0	0.0 1.0	0.60 0.40
DTPA	Acetone Distilled water	Whatman 31 ET ITLC-SG	1.0 1.0	0.0 0.0	0.0 1.0	0.60 0.40
GHA	Acetone Distilled water	Whatman 31 ET ITLC-SG	1.0 1.0	0.0 0.0	0.0 1.0	0.60 0.40
HDP	Acetone Distilled water	Whatman 31 ET ITLC-SG	1.0 1.0	0.0 0.0	0.0 1.0	0.60 0.40
MDP	Acetone Distilled water	Paper ITLC-SG	1.0 1.0	0.0 0.0	0.0 1.0	0.60 0.40
DMSA	20% acetone	ITLC-SG	1.0	0.0	0.0	0.50
Disofenin	20% NaCl Distilled water	ITLC-SA ITLC-SG	1.0 1.0	0.0 0.0	0.0 1.0	0.60 0.25
Mebrofenin	20% NaCl Distilled water	ITLC-SA ITLC-SG	1.0 1.0	0.0 0.0	0.0 1.0	0.60 0.25
Teboroxime	0.9% NaCl Saline/acetone	Whatman 31 ET Whatman 31 ET	1.0 1.0	0.0 0.0	0.0 1.0	0.60 0.30
Sestamibi*	100% ethanol	Whatman 31 ET	0.0	0.0	0.60-1.0	0.25
HMPAO†	Saline 50% acetonitrile MEK	ITLC-SG Whatman 31 ET ITLC-SG	1.0 1.0 1.0	0.0 0.0 0.0	0.0 1.0 1.0	0.63 0.13 0.29

*Strip must be air dried before placing in chromatography chamber.

†Secondary HMPAO Rf = 0.0 with MEK/ITLC-SG.

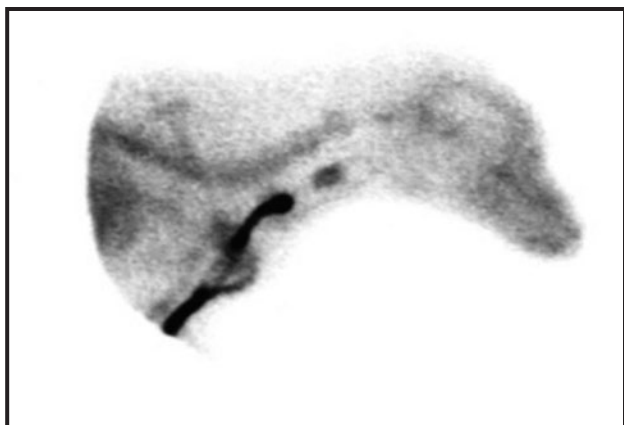


Figure 4.17: Right lateral image of the neck and head of a dog taken 2 hours following a perivascular injection of ^{99m}Tc -MDP

Note the linear activity representing lymph vessels of the front limb. The focal uptake cranial to the scapula represents the superficial cervical lymph node. Also, note the thyroid uptake that indicates poor radiopharmaceutical binding and the presence of free sodium pertechnetate in the circulation.

appearance.²⁰ If a low-energy collimator is used with radionuclides emitting high-energy photons (such as ^{111}In or ^{131}I), the photons will penetrate the collimator septa.²⁰ This will result in degradation of overall image quality. The number of artifact rays that are seen originating at the center of the star artifact is dependent on the collimator hole configuration. The rays of the star originate from the photon penetrating the thinner walls of the low-energy collimator (Figs 4.19 and 4.20). A star artifact can also be seen if there is a focal area of intense radiopharmaceutical accumulation within the patient (see Figure 4.28). This occurs because the photon flux is high enough that some photons will penetrate the collimator septa, degrading image resolution and creating the star pattern.

The way to correct this artifact is to use the collimator designed for the energy of gamma emissions from the radionuclide that is being imaged.

Poor Camera Resolution

Distance

Poor resolution will result if the patient is too far from the surface of a parallel-hole collimator. Resolution



Figure 4.18: Ventral view of the cervical region of a cat 20 minutes after injection of sodium pertechnetate

The thyroid gland uptake is suppressed but can still be visualized. The poor thyroid uptake is due to prior administration of radiographic contrast medium.

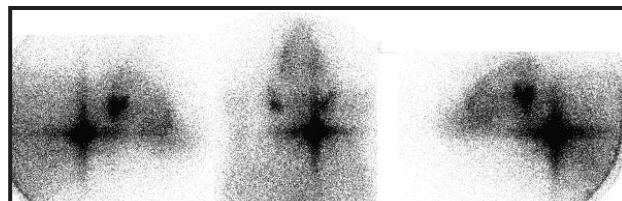


Figure 4.19: Thyroid scan in a dog 24 hours following injection of 500 μCi of ^{131}I

These images were acquired using a low-energy collimator with the window of the PHA centered at 364 keV. Note the star artifact originating from the thyroid. Also, note the poor resolution of the image. These artifacts indicate septal penetration of the collimator by the gamma rays. A medium energy collimator should be used for imaging ^{131}I .

is best when the patient (source of radioactivity) is near the collimator surface.²¹ Resolution decreases as the collimator-to-patient distance increases because a larger percentage of photons are allowed to pass through the collimator holes and reach the detector. This results in misregistration of photon origin because the angle of incidence allowed the photons to pass through the collimator holes (Figs 4.21, 4.22, and 4.23).

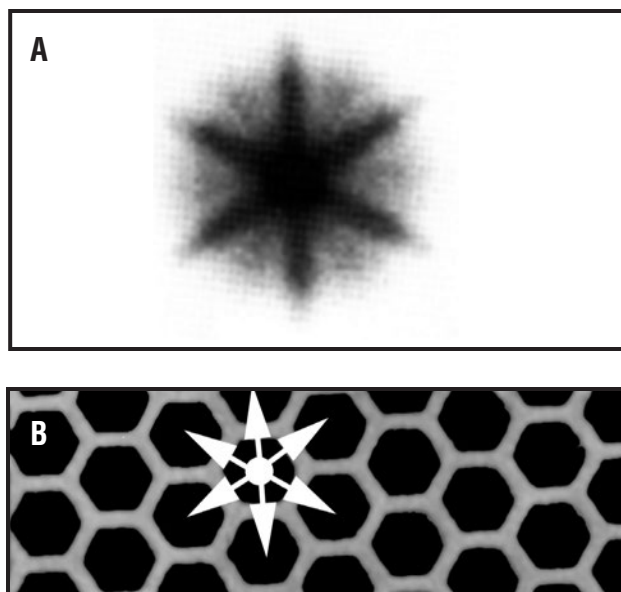


Figure 4.20: Image of a high energy radionuclide, ^{111}In using a low-energy collimator

A, The star pattern is typical of septal penetration and can be seen if the collimator is rated for an energy lower than the radionuclide imaged. It can also be seen with a proper energy-rated collimator if the source of radioactivity is high. B, Photograph of a parallel hole collimator showing how the star pattern is generated by septal penetration. The gamma ray photon can penetrate the thinner section of the collimator septa resulting in rays of the star artifact. The number of rays seen on the star is dependent on the collimator hole configuration.

Window Setting

An incorrect pulse height analyzer (PHA) setting will result in poor resolution. When the window is centered below the photopeak, then the recorded image is created from photons from scatter radiation and not from primary photons (Figure 4.24).

Patient Movement

Movement results in a blurred scintigraphic image or multiple image patterns (Figure 4.25).^{19,20} Movement is more common with long acquisition times. Movement is the most common artifact in equine scintigraphy (Figure 4.26). Motion blurring is a bigger problem when imaging the equine upper extremity, pelvis, and spine. Many of the newer imaging computers do have motion correction software that will realign a dynamic series of images. The aligned

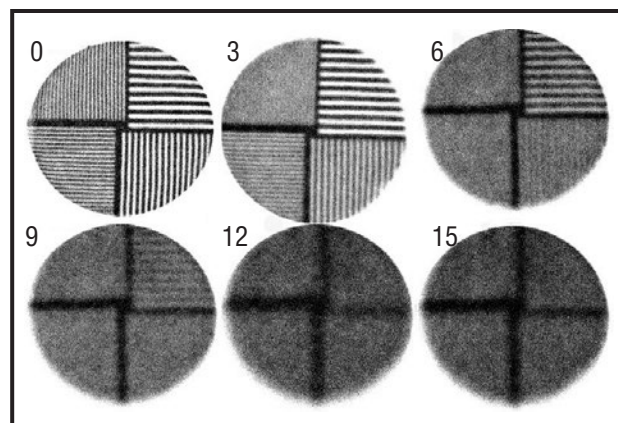


Figure 4.21: Four-quadrant bar phantom images taken at increasing distances from a parallel-hole collimator

The distance in inches is noted beside each image. Note how the resolution decreases as the distance from the camera increases.

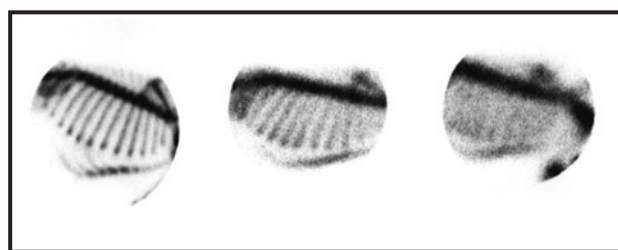


Figure 4.22: Lateral images of a dog taken 2 hours following injection of $^{99\text{m}}\text{Tc}$ -MDP

The images were taken with the dog at different distances from the parallel-hole collimator. The best resolution is obtained with the dog in contact with the collimator (image on left). Note the clarity of the ribs in this image compared to the image on the right.

images are summed to create a motion corrected composite image.

Camera Malfunction

Camera resolution is affected by intrinsic and extrinsic factors of the camera, such as spatial circuitry, crystal thickness, number of PMTs, and linearity.

5. Collimator Artifacts

The presence of a high-energy gamma emission can decrease resolution. Sources of high-energy radionuclides include: (1) incomplete clearance from the

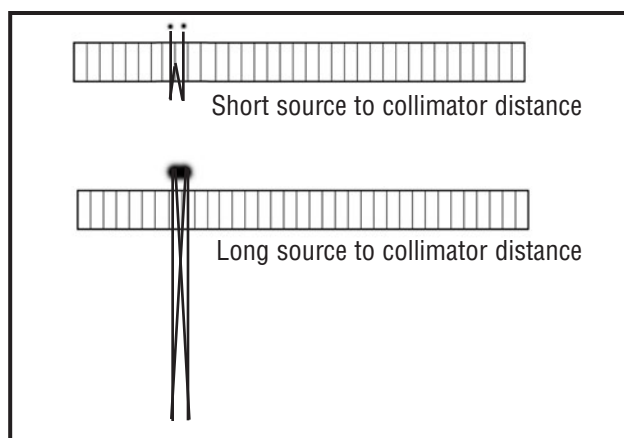


Figure 4.23: Line diagram showing how resolution decreases at increasing source to collimator distances

When the two objects are adjacent to the collimators, only those gamma ray photons traveling parallel to the collimator hole can pass through therefore the two objects appear separate. Gamma rays traveling at a higher incident angle are absorbed by the collimator septa. At the long source to collimator distance, more gamma ray photons with a higher incident angle can pass through multiple collimator holes, thus blurring the image and making it impossible to resolve the objects as separate.

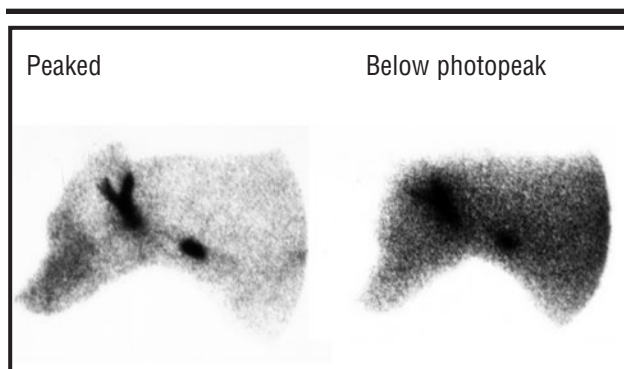


Figure 4.24: Left lateral images of a dog taken 20 minutes following injection of sodium ^{99m}Tc pertechnetate

The image on the left was taken with the window of the PHA centered over the technetium photopeak. The image on the right was taken with the window of the PHA centered below the photopeak. Note the poor resolution of the image on the right. This is an image of scatter radiation.

body of a higher energy radionuclide (^{131}I) as may be seen if imaging a dog or cat following treatment with radioiodine or (2) a radionuclide impu-

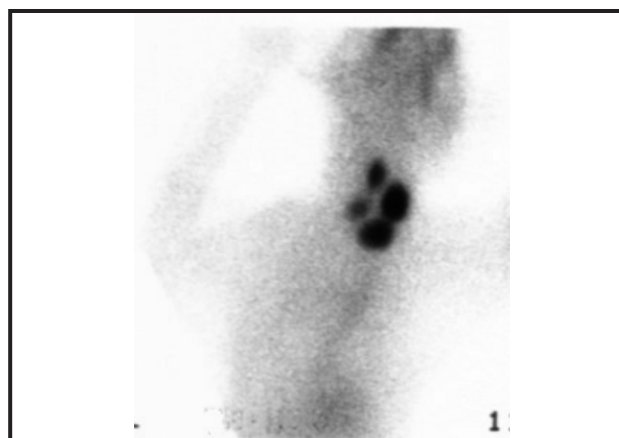


Figure 4.25: Ventral view of a cat taken 20 minutes following injection of pertechnetate

The cat moved once during the acquisition. There is a double image of the hyperactive thyroid lobes giving the appearance four foci of uptake where as the cat only had two foci of uptake seen on repeat images.

urity, such as ^{124}I contamination in a sample of ^{123}I . A damaged collimator can affect resolution if the collimator openings are not aligned or if the septa have been crushed. Medium energy collimators have larger holes with thicker lead septa than low-energy collimators (Figs 4.27 and 4.28). This septal pattern will be seen in the image, especially if the image is magnified.

Low Count Density Image

An image containing a low total number of counts will have poor spatial resolution.⁸ Because of the random nature of radioactive decay, a large number of counts are necessary to assure good statistical certainty of the distribution of radioactivity within the body. If the number of recorded counts is low, then lesion detectability will be decreased (Figs 4.29 and 4.30).

Pixel-Limited Resolution

The number of pixels defines the resolution of the digital image.²³⁻²⁵ A small matrix size results in large individual pixels that may inhibit lesion detection because the lesion is averaged with the neighboring areas (Figs 4.31 and 4.32). For most 15-inch diameter camera systems, a 128×128 matrix will have pixel sizes smaller than the spatial resolution limits of the camera; but with smaller matrix sizes

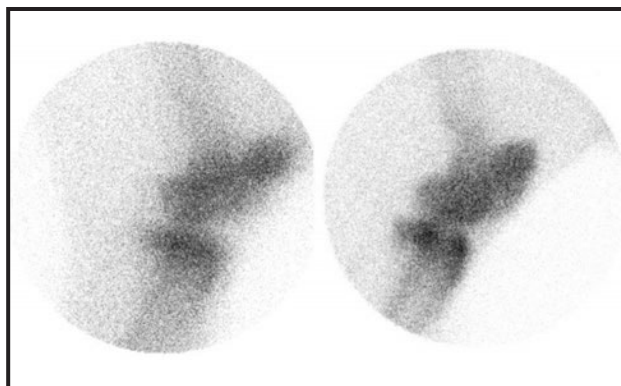


Figure 4.26: Lateral views of the right stifle of a horse taken 1 hour following injection of ^{99m}Tc -HDP

The image of the left was made with back and forth (swaying) movement during the acquisition. Note the improved resolution of the tibial plateau, patella, and distal femur on the image at the right compared to the image at the left. Small movements can result in a significant decrease in image quality and resolution.

(64×64), resolution may be limited by the size of individual pixels.

Correction of Gamma Camera Poor Resolution

The correction of gamma camera poor resolution is dependent on the cause. The cause of poor resolution can be identified by the image appearance and sort through the list of possible causes. Distance between the patient and the collimator must be minimal; the PHA setting must be checked and the proper collimator used for the radionuclide imaged. The patient must remain still during the acquisition. The intrinsic resolution of the camera should be evaluated prior to calling for the camera to be serviced. Keep in mind that changing acquisition times or matrix size could alter resolution. For low count density images, overall count density should be increased without increasing acquisition times, by the following:

- ☐ Using a smaller acquisition matrix (such as a 128×128 matrix versus a 512×512 matrix).
- ☐ Injecting a larger dose of the radiopharmaceutical.
- ☐ Using a general-purpose, low-energy collimator.
- ☐ Use of image filters, such as a median smooth or a Metz filter.



Figure 4.27: Photograph of a medium-energy collimator

Note the relatively large size of the collimator holes and the thick collimator septa.

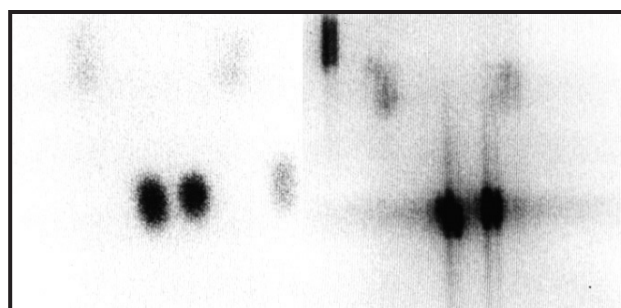


Figure 4.28: Ventral view of a dog obtained 24 hours following injection of 400 μCi of ^{131}I

The image on the right side was acquired using a pinhole collimator. The patient-collimator distance was equal to the cone length so there is no magnification of the thyroid gland. The image on the left was acquired with a medium-energy collimator. Note the mottled appearance of the thyroid that is due to the course-hole pattern of the collimator. There is also a star artifact caused by septal penetration. Septal penetration can be seen with the proper-energy-rate parallel-hole collimator if there is a focal high-intensity accumulation of the radionuclide.

Gamma Camera Field NonUniformity

Crystal Abnormalities

A nonuniform detector response may be due to an area of NaI crystal hydrolyzation. The sodium iodide crystal in a gamma camera is hermetically sealed

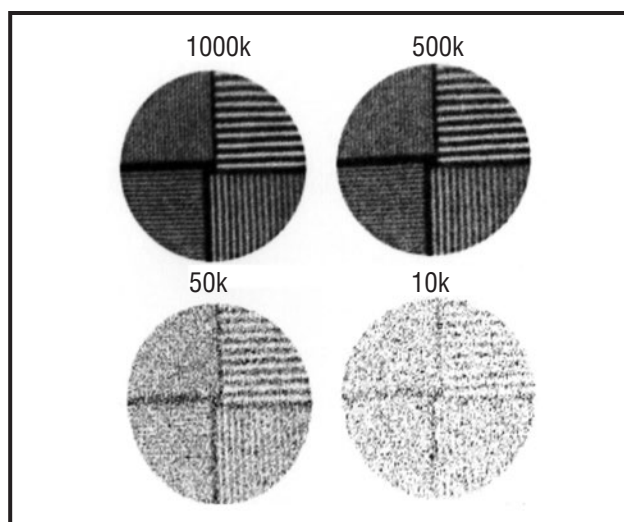


Figure 4.29: Bar phantom images acquired for different total numbers of counts

Note how resolution decreases with lower counts. Due to the random nature of radioactive decay, there is poor statistical certainty of the distribution of radioactivity.

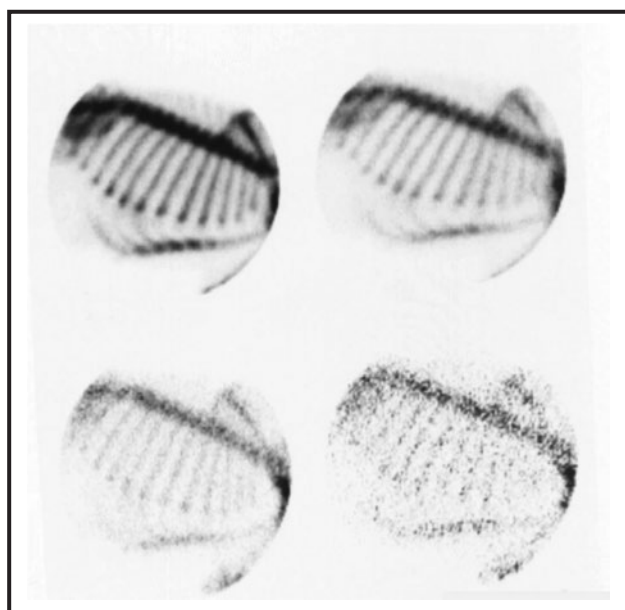


Figure 4.30: Right lateral images of a canine thorax taken 2 hours following injection of ^{99m}Tc -MDP

These images were acquired for different numbers of counts. Note the better image quality in the higher-count-density images.

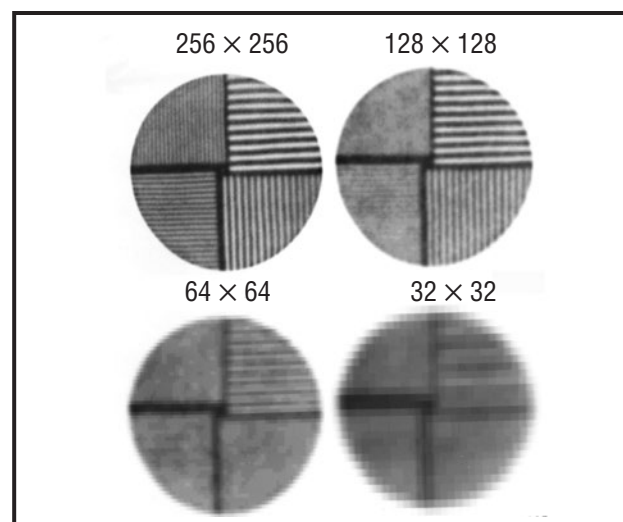


Figure 4.31: Bar phantom images acquired for the same total numbers of counts but in different sized matrices

Note how resolution decreases with smaller matrix size. Resolution becomes pixel limited.

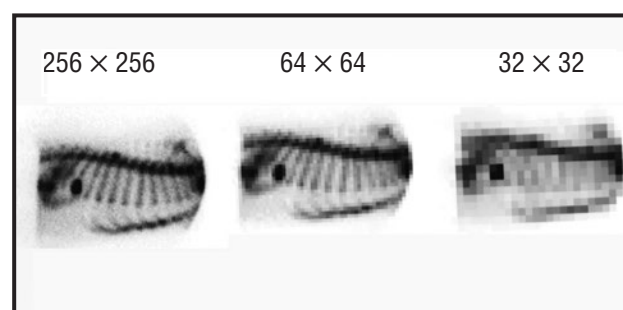


Figure 4.32: Right lateral images of a canine thorax taken 2 hours following injection of ^{99m}Tc -MDP

These images were acquired for the same numbers of counts. Note the poor resolution in the $64 \times 64 \times 16$ and the $32 \times 32 \times 16$ matrix sizes.

in an aluminum case to prevent exposure to light and moisture. If the seal is broken or the aluminum penetrated by a hard sharp object, moisture will enter the crystal resulting in hydrolyzation. Hydrolyzation of the crystal causes yellowing and clouding, reducing the crystal's scintillation capability, and impedes normal light transfer to the photocathode. All of these

factors will result in area(s) of decreased sensitivity. Hydrolyzation usually involves a large region of the crystal and will cover the area over many PMTs. A cracked sodium iodide crystal will produce a sharply demarcated, high contrast, photopenic defect corresponding to the defect in the crystal (Figure 4.33).

Light-Pipe Defects

The sodium iodide crystal is optically coupled to the photocathode of the PMTs. This optical coupling limits the reflection and refraction of the light. The optical couple is achieved by the use of light pipe or coupling grease made of atomized glass. A defect in the coupling by the light pipe or coupling grease results in ineffectual light transfer and therefore focal area of decreased sensitivity. Gamma cameras should be stored with the crystal parallel with the floor (face up or face down) to prevent gravitational settling of the coupling grease or separation of the light pipe. Poor coupling of the crystal to the photocathode will cause a photopenic defect similar to crystal hydrolyzation. A decoupled crystal interferes with light transfer and can also cause image distortion.

PMT Imbalances

Poorly balanced or nonfunctional PMTs, amplifiers or both will result in field nonuniformity. Each PMT should produce the same amplitude electrical pulse in the presence of a homogenous photon flux. Variations in PMT signal amplitude results in a non-uniform field. PMT malfunctions, or lack of amplifier calibration, will result in a flood field image that will have “hot” or “cold” regions over the unbalanced units (Figure 4.34). The resulting image is mottled and irregular. A nonfunctional PMT or preamplifier will produce a high-contrast photopenic defect at the position of the damaged unit (Figure 4.35).

Nonlinearity

The spatial circuitry determines the x and y locations of the absorbed incident photon. If the incident photon position is incorrectly registered, there will be “cold” areas in the actual location of absorption and “hot” areas where the photon is incorrectly placed. Loose connectors or a defective circuit board will cause incorrect positioning circuitry. This problem will result in image distortion and loss of linearity.

Pulse Height Analyzer (PHA) Setting

If the window of the PHA is above or below the

photopeak, a honeycomb or PMT pattern is seen. Inappropriate PHA settings result in a honeycomb pattern similar in size to the PMTs units (Figs 4.3 and 4.12).

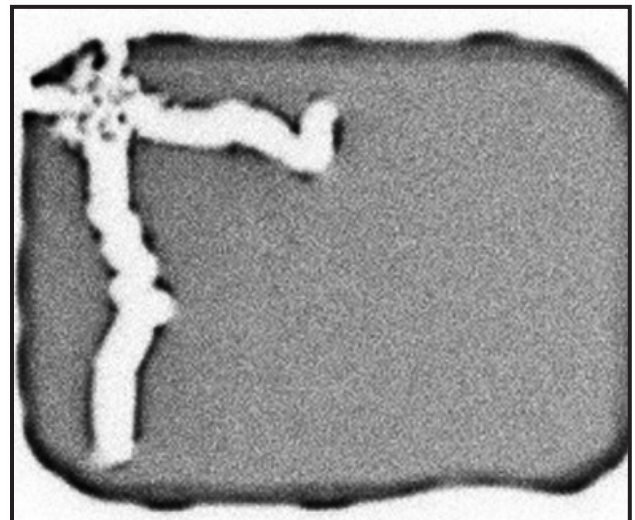
Correction

All of the preceding problems require service personnel to correct the camera problems, except for an improper PHA setting. The gamma camera is peaked to the correct energy window of the radionuclide in use and reacquiring the quality control (flood uniformity).

Edge Packing

Edge-packing artifacts result when peripheral PMTs incorrectly register counts at the edge of the field of view. Normally, an incident photon is absorbed in the center of the NaI crystal and emits a light flash.¹⁸ The photocathode from a number of PMTs will detect the light flash. The PMT closest to the incident photon will have the highest amplitude signal. The PMTs farther from the incident photon will have a proportionally smaller amplitude signal. The location of the incident photon is determined by plotting the signal intensities from all PMTs and the center of the line spread function will determine the location of the incident photon. If the incident photon is absorbed near the edge of the crystal, the PMTs will record only part of the light spread func-

Figure 4.33: Flood image of a NaI (TI) crystal that has been cracked (courtesy of Dr. Anne Bahr, Texas A & M University)



tion. As the camera cannot register the entire light spread function, the location of the event will be incorrectly recorded along the crystal edge (Figure 4.36). Edge packing has a characteristic appearance of high count intensity at the edge of the image field (Figure 4.34). If the area of increased uptake is at the edge of the image, one should reposition the animal so that the area in question falls in the central field of view. This will avoid misinterpretation of the edge-packing artifacts as a pathologic lesion.

Summary

Quality control of the gamma camera and other pieces of equipment is critical to normal operation of a nuclear medicine facility. Without a quality control

Figure 4.34: Flood image from a gamma camera with poor uniformity

The PMTs are not balanced. The black rim around the image represents an edge-packing artifact.

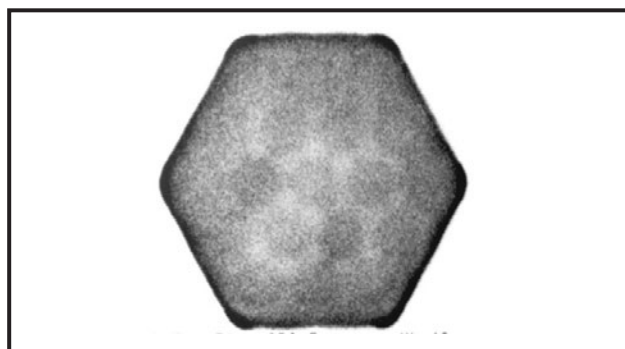
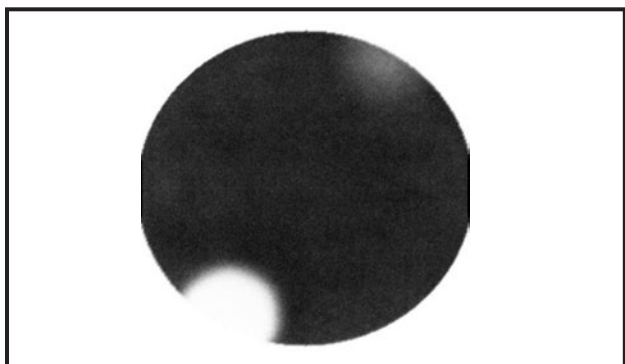


Figure 4.35: Flood image from a gamma camera with a nonfunctional PMT (7 o'clock position) and a PMT that has a low output (1 o'clock position)



program in place, research and clinical applications are in jeopardy of producing images that are meaningless. The recommendations in this chapter summarize what it takes to ensure the gamma camera is functioning properly and at maximum efficiency.

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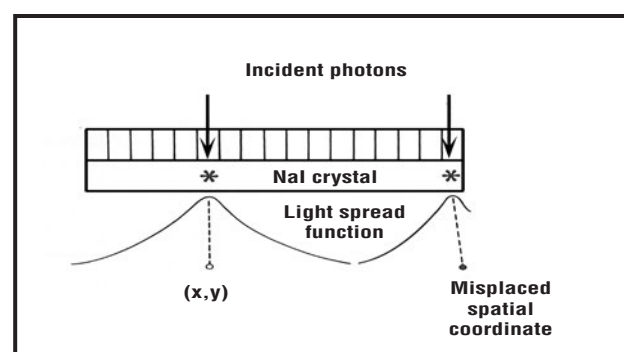


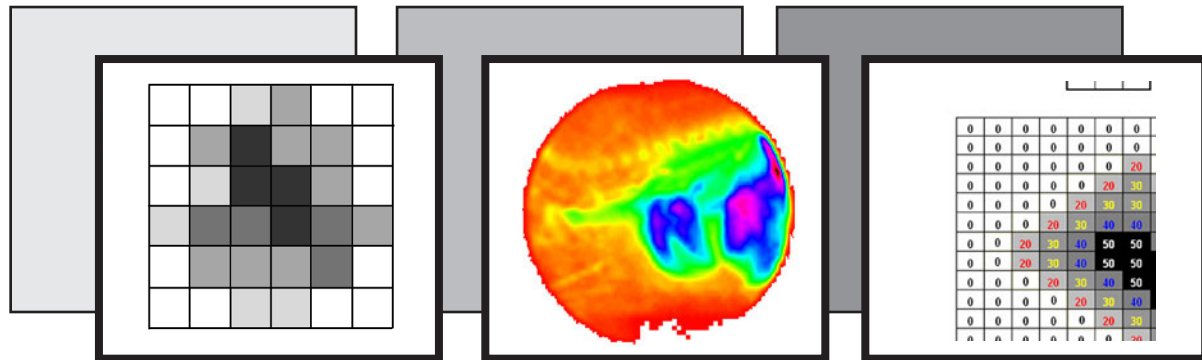
Figure 4.36: Schematic representation of edge packing

This schematic shows a section of a collimator and the NaI crystal from a gamma camera. When a photon is absorbed into the NaI crystal, a light flash is emitted that spreads isotropically from the point of origin. The spatial coordinates of the incident photon are determined from the center of the light spread function. If the photon is absorbed near the edge of the crystal, then the entire light spread function is not created and the resultant distortion causes the center point to be misplaced along the edge of the image, resulting in the artifact called "edge-packing."

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Digital Image Processing

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Introduction

Today the modern gamma camera is intrinsically interfaced with an image computer. Simple image processing has been available on even the most basic nuclear medicine computers since the 1980s. As scintigraphic images contain relatively little information, compared to a digital color photograph, a video, or a computed tomography (CT) image, computer processing was possible before the advent of powerful computer processors. As computer power and speed improved, so did the sophistication of the image processing algorithm. Gamma cameras are now sold in combination with a computer as part of the total camera system.¹ An understanding of basic principles of computers and computer processing of the digital image is necessary for quantification of the scintigraphic image.

Image interpretation and quantification has given rise to interest in image manipulation and processing. Techniques used in digital image processing were greatly advanced by NASA, the CIA, and the Department of Defense. This, combined with the advent of large-scale digital computers in the 1960s and 1970s, brought about major improvement in digital image processing. The end of the Cold War and the declassification of many of these techniques, along with the widespread availability of microcomputers, have made very advanced image processing techniques universally available. Computer processing software (Photoshop, Adobe) is available in computer stores and through vendors who cater to the scientific community (SigmaScan Pro, SPSS Inc). Free software is also available on the US government's Web site (NIH Image or Image J Home Page, <http://rsb.info.nih.gov/nih-image/>). Techniques needed to enhance and manipulate a scintigraphic image are relatively simple. The majority of techniques use simple mathematics, but more advanced methods require Fourier transformation of the images.

To understand digital image processing, one must think of an image in terms of mathematics. The image is represented as a two-dimensional light-intensity function.

$$f(x,y)$$

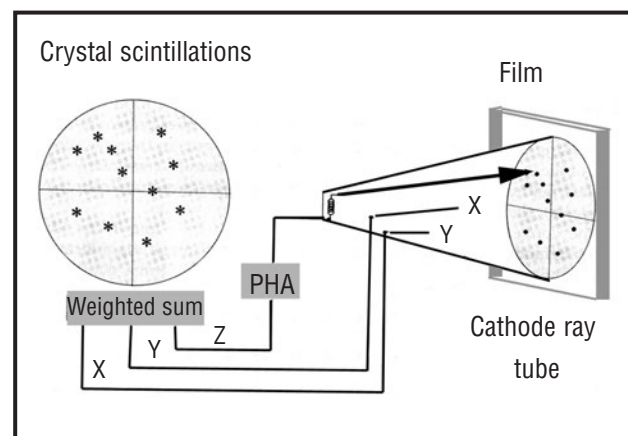
In this case, the x and y are the spatial coordinates and the value of f at the point (x,y) represents a color or brightness.² In a digital image, each point of the image and level of brightness is a discrete value. In the analog image, these are continuous functions.³

The Analog Image

Older gamma camera systems created images by exposing a piece of photographic film to light flashes from a cathode ray tube. The image was composed of multiple dots of film exposure, each representing a photon absorption of acceptable photon energy detected by the gamma camera. The locations of these light flashes on the cathode ray tube were determined by the output signal from the gamma camera.⁴ There are three analog signals coming from the gamma camera detector: one proportional to the X location of the event, one proportional to the Y location, and the third one proportional to energy (Z).⁵ The cathode ray tube is composed of an electron gun, focusing diodes, and the photocathode (Figure 5.1) If the Z pulse passes the pulse height analyzer

Figure 5.1: Formation of an analog nuclear medicine image

The X and Y signals from the gamma camera determine the voltage applied to the focusing diodes of the cathode ray tube. If the height of the Z pulse is within the acceptance range of the PHA, the electron gun will fire, sending an electron forward. The voltage on the focusing diodes directs the path of the electron. When the electron strikes the phosphor, a light flash is emitted. The light exposes the film. e^- = the electrons accelerated toward the cathode ray tube.

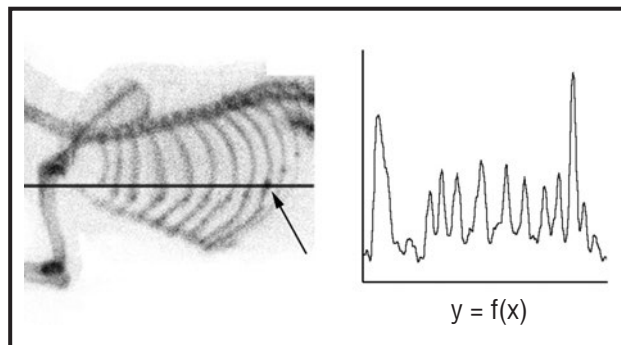


(PHA), it will trigger the electron gun to accelerate electrons toward the photocathode by electrostatic forces. When the electrons hit the photocathode, they separate and a flash of light exposes a small portion of the film. The path of the electron is altered by the electrical charge applied to the diodes on the sides of the tube.⁶ The degree of electron deflection in the horizontal plane is determined by the intensity of the X signal from the gamma camera. The degree of electron deflection in the vertical plane is based on the intensity of the Y signal from the gamma camera. As a result, each primary photon absorbed by the gamma camera crystal results in a flash of light in a corresponding position on the output phosphor of the cathode ray tube, if the energy deposited matches the Z pulse requirements. Thus, the degree of exposure (blackness) of any point on the film is proportional to the number of counts detected at that location. The disadvantage of this method is that only a visual estimate of the relative radioactivity is possible.

Figure 5.2 is an analog image from a bone scan of a canine thorax. This image is made up of varying light intensities. The gray scale is inverted; thus, the greater the concentration of the radionuclide, the blacker the portion of the image. To look along a horizontal line through this image, would reveal a profile of the varying light intensities. Note there is no scale on the

Figure 5.2: Analog image of a canine thorax taken 2 hours after the injection of ^{99m}Tc -MDP

The horizontal line shows the position of the line profile seen to the right. The peaks of the graph correspond to the high intensity regions of the image (ribs). The line is continuous with an infinite number of points and intensities which are only limited by the speed and the H & D (characteristic) curve of the film. The line profile is a one dimensional function $y = f(x)$.



horizontal or vertical axis because this is an analog image. The peak on the left of the graph is created by the higher intensity uptake in the humerus. Note that the cranial cortex has a higher intensity than the caudal cortex as can be seen by the shape of the first peak. In the graph, multiple smaller peaks denote the uptake of each rib. The highest intensity region is from the costochondral junction of the ninth rib (arrow). The line profile seen on the graph represents a one-dimensional function or $y = f(x)$. The number of shades of gray and the spatial resolution are determined by the film characteristics. If one considers the entire image as composed of many line profiles in both the horizontal and vertical directions, the image then becomes a two-dimensional light intensity function as just described. Therefore, any point in the image could be defined as $f(x,y)$.

The Digital Image

The digital image is composed of a matrix containing a specific number of rows and columns that define its individual cells.¹⁻³ Each cell of the matrix has a set of discrete spatial coordinates that indicate a specific address defined using a Cartesian coordinate system. The coordinates are formed by taking two perpendicular lines that intersect at an origin. The first coordinate is the abscissa, which is the distance from the vertical line; and the second coordinate is the ordinate, which is the distance from the horizontal line. Using this system, the coordinate at the lower left-hand corner of the image becomes (0,0). The light intensity at each of these points is also given a discrete numerical value. Each address or spatial coordinate is called a picture element, or pixel. Figure 5.3 is a lateral image from a canine bone scan of the thorax. The area of increased radioactivity at the ninth costochondral junction is located at the spatial coordinates (214,121). This pixel is 214 pixels from the left limit of the image and 121 pixels from the bottom of the image. The intensity or the number of counts recorded in this pixel was 176 counts or light flashes. Using this method, any point of the image can be defined.

To create a digital image, the analog signal from the gamma camera is converted through an analog-to-digital converter (ADC).^{1,7} The location of each recorded event is boxed into a specified matrix. Notice in Figure 5.4 how the exact location of each event is lost but is grouped together with all of the

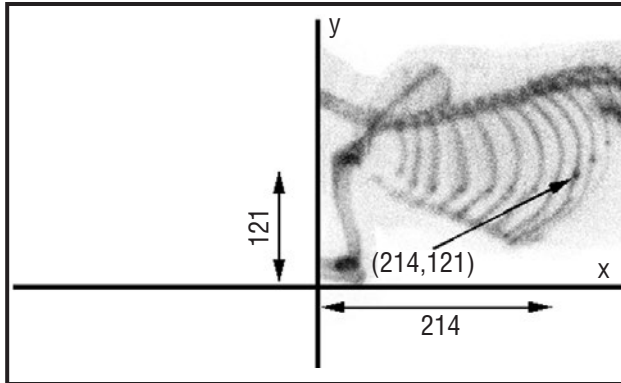


Figure 5.3: Image of the canine thorax seen in Figure 5.2 after digitalization

This image is composed of a finite number of points or picture elements (pixels). Each pixel has a specific location or address and a specific intensity. The hot spot seen on the ninth rib is located in the pixel address (214,121) and the intensity is 176, which means there were 176 gamma rays collected within the area of this pixel.

other events recorded in the cell (pixel). The number of photons recorded in the cell is denoted by the numerical value assigned to the specific cell.

Matrix Size

The number of rows and columns (matrix size) defines the spatial resolution of the image.¹ When the matrix size increases (more pixels), the displayed resolution also increases. The smallest object represented in the digital image occupies the space of one pixel. To observe two such objects, they must be separated by at least one pixel.¹ The term *line pairs* is frequently used to specify the spatial resolution in imaging systems. Thus, the line pair resolution in a digital image is three times the pixel width. An analog image can be thought of as an infinite number of pixels. Figure 5.5 is a set of images from a canine gated cardiac study that has been digitized into varying sized matrices. Note the resolution becomes severely pixel limited in the smaller matrix sizes, (32×32 and 16×16).

Types of Image Acquisitions

The computer controls the image acquisition. The parameters of the acquisition are specified before the study is begun. The two major types of computer acquisition are frame mode and list mode.^{1,8,9}

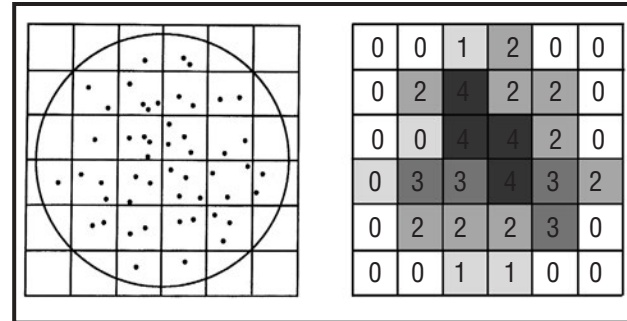


Figure 5.4: Difference between an analog image and a digital image

The image on the left represents an analog image, with the superimposed frame representing the location of the digital matrix. Note the location of each of the events (dots) shown in the analog image. Once the image is digitized, all events recorded within the area of a pixel are summed to give an intensity value. Assigning a shade of gray or color to the entire pixel creates an image. The number of events recorded in the pixel determines which shade of gray or color is assigned. The exact location of the record event within the pixel is lost. Resolution of the digital image would logically be improved by decreasing the size of each pixel.

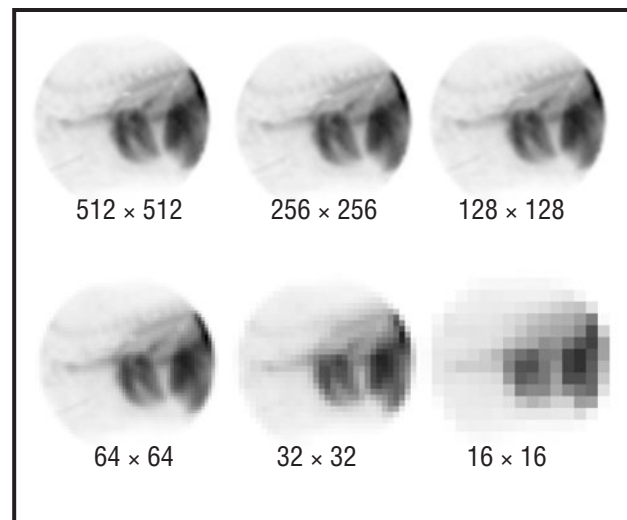


Figure 5.5: Images from a gated cardiac study, or radionuclide ventriculogram in a dog

The study images are displayed in various matrix sizes. At the small matrix size, the pixels are larger and the image appears “boxy.” Resolution is limited by the size of the pixels in the digital image.

Frame Mode

In a frame mode acquisition, the matrix size is specified before the image is acquired. The recorded events (counts) are collected and distributed into the digital matrix of the image. After the acquisition is complete, the entire matrix is stored as a single image file. The exact location of the event within each pixel and the time it arrives is lost when the image is stored as a frame mode.

There are several types of frame mode acquisitions.

Static Frame Mode

In a static frame mode acquisition, images are acquired one at a time.⁸ The camera may need to be repositioned for the next image or may remain in the same position but acquire another image later. The end point or termination of the acquisition can be based on time of acquisition, total number of counts collected, or reaching a maximum number of counts per pixel. This is the standard acquisition type for static imaging studies, such as bone scans, or thyroid scans. In a static frame mode acquisition, the main consideration is spatial resolution; therefore, matrix size is an important issue and a 256×256 matrix is the most commonly used matrix size used.

Dynamic Frame Mode

A dynamic frame mode acquisition is a series of images taken at specified frame rate.⁸ These sequential dynamic imaging studies are used to monitor changes in radioactivity over time within a single gamma camera imaging field. The computer is set to acquire a total number of frames, which are acquired sequentially until the end of the study. The parameter that determines the end of one frame and the beginning of the subsequent frame is usually based on a time interval, but the frame rate can also be based on reaching a maximum number of counts within the frame or reaching a maximum count density within a least one pixel within the frame. As the vast majority of dynamic frame mode acquisitions are based on time, the most important feature of this type of acquisition is the frame rate. The frame rate is determined by rate of change of the physiologic process that is being evaluated. If the physiologic process changes quickly, then a faster frame rate is needed. For example, in a cardiac first-pass radionuclide angiogram, the camera records the passage of

a radioactive bolus through the chambers of the heart and the lung. Because this entire cardiopulmonary transit can occur in a few seconds, a rate of at least four frames per second is necessary to resolve these processes temporally.

In another example of a dynamic frame mode acquisition, the canine glomerular filtration rate (GFR) scan, the accumulation of the radiopharmaceutical occurs over a 1-minute to 3-minute interval, therefore the frame rate can be much slower (10 frames/min). Dynamic frame mode acquisitions are used for quantitative studies, such as GFR, portal scintigraphy, and first-pass radionuclide angiogram. The matrix sizes of dynamic acquisitions are usually much smaller than for static frame mode acquisitions. The concern with most dynamic acquisitions is how the radioactivity within a region of the image is changing over time; therefore, temporal is more important than spatial resolution and 64×64 or 128×128 matrix sizes are the most common.

Gated Frame Mode

Many physiologic events, such as respiration and cardiac contractions, occur cyclically. Each cycle may be relatively brief, and the number of counts that could be recorded from a single event may be inadequate for image formation and quantification. However, if counts from multiple cycles could be added together, then an image of higher count density could be created. To do this, the acquisition from each cycle must be synchronized. If the beginning of each cycle can be identified, then the event can trigger the acquisition. A gated frame mode acquisition uses an electrical signal from a physiologic input to initiate each acquisition.⁹ Each frame of the acquisition is begun or terminated by the signal from this physiologic input. The most common gated study is a cardiac study in which the R wave of the electrocardiogram is used as a marker for each new cardiac cycle. On the next cardiac cycle, a new set of images is acquired and added to the existing images. Counts from several hundred cardiac cycles are added sequentially to form composite images representing the cardiac cycle (Figure 5.6). Gated acquisition can be initiated by any physiologic process that can trigger an electrical signal. Other examples of gated acquisition include respiratory or arterial pulse pressure gating.

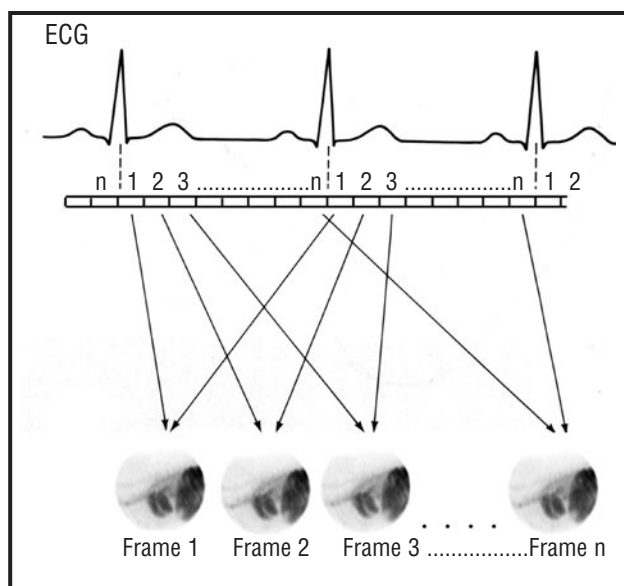


Figure 5.6: Formation of images from a gated frame-mode acquisition (radionuclide ventriculography)

A series of images are initiated by an electrical signal. In this case the height of the R wave of the ECG exceeds the set threshold or trigger, which started an acquisition. A set number of image are acquired starting at the R wave of the cardiac cycle. The frame rate is based on the length of the R to R interval and the number of frames to be recored. These images are stored. The next R wave begins another set of images, which are added to the existing set of stored images. This is repeated over and over until each frame has an adequate number of counts. Each frame represents a specific time point during a cardiac cycle.

List Mode

A list mode acquisition is fundamentally different from the frame mode acquisition just described. In a list mode acquisition each scintigraphic count is recorded separately. The data are essentially listed as all scintillation events recorded as their x and y coordinates along with the relative time each event was counted. List mode data can be used to create one frame or a sequence of frames, and the frame rate does not have to be specified before initiating the study. List mode acquisitions give the computer operator considerable flexibility to reconstruct the data at different frame rates.⁹ The ability to reframe the images at various rates facilitates optimal analysis of the scintigraphic data. List mode acquisitions

are especially useful for initial evaluative studies when the kinetics of a given radiopharmaceutical are not known. Thus, the frame rate is not known but the specific physiologic process of interest must be temporally resolved.

Event marks are placed in the list of data whenever a physiologic event occurs. In a gated cardiac study, a marker is placed in the stream of data wherever an R wave deflection is recognized. This marker allows reconstruction of the gated study in a “forward” direction by compiling the counts at time increments following each QRS complex or “backward” by assembling the counts at time increments preceding the QRS complex.⁹ Gated list mode acquisition can also be used to create images of a cardiac cycle with a specific heart rate. A disadvantage of list mode acquisition is that data must be reconstructed before the image can be reviewed. List mode data also require more computer memory than frame mode studies.

Considerations of Matrix Size

Matrix size decisions are based on the requirements for spatial and temporal resolution. As the matrix size becomes larger, each pixel becomes smaller. The individual pixel size in a 256×256 matrix in a gamma camera with a 15-inch or 38.1 cm diameter crystal would be 1.49 mm.

$$\begin{aligned}\text{Pixel size} &= 381 \text{ mm} \div 256 \\ &= 1.49 \text{ mm}\end{aligned}$$

The individual pixel size in a 128×128 matrix in a gamma camera with a 15-inch or 38.1 cm diameter crystal would be 2.98 mm.

$$\begin{aligned}\text{Pixel size} &= 381 \text{ mm} \div 128 \\ &= 2.98 \text{ mm}\end{aligned}$$

The individual pixel size in 64×64 matrix in a gamma camera with a 15-inch or 38.1 cm diameter crystal would be 6.0 mm.

$$\begin{aligned}\text{Pixel size} &= 381 \text{ mm} \div 64 \\ &= 6.0 \text{ mm}\end{aligned}$$

To avoid loss of resolution from digitization, the pixel width should be less than one-third the resolution limit of the gamma camera.¹ Most gamma cameras have an intrinsic resolution between 3 and 5 mm. Using a parallel-hole collimator, resolution decreases with increased object to collimator distance. In most imaging studies, the target organ is several centimeters from the camera face. Considering this, the typical resolution limits for imaging an organ in vivo are 4 to 6 mm. Assuming a resolution of 4.5 mm, the pixel size of 1.5 mm is required to prevent loss of information during digitization. To meet this requirement, a 256×256 matrix size is needed. Spatial resolution is an important factor for static frame mode images. The 256×256 matrix is the most common size used because, with that matrix, resolution of the image is not pixel limited.

Count density or counts per pixel is an important factor in good image quality. The more counts per pixel, the better the image quality.¹⁰ The larger matrix sizes have smaller pixels, thus fewer counts in individual pixels. If one considers a flood field image with a uniform distribution of counts throughout the image field the total number of counts would be divided equally amongst the pixels of the digital matrix. A 256

$\times 256$ matrix would have 262,144 pixels. A flood field image of 3,000,000 counts digitized into a 256×256 matrix will have 45.8 counts per pixel.

That same 3,000,000 count flood image digitized into a 64×64 matrix will have 732 counts per pixel.

$$\begin{aligned}\text{Count density} &= 3,000,000 \text{ cts} \div (256)^2 \text{ pixels} \\ &= 3,000,000 \text{ cts} \div 65,536 \text{ pixels} \\ &= 45.8 \text{ cts/pixel}\end{aligned}$$

The advantages of spatial resolution obtained by a large matrix could be lost if the count density is low. Figure 5.7 shows the impact that count density has on resolution. To have good statistical certainty for each pixel within an image, a high count density is required. The best image quality is obtained by using a large matrix size with a high count density, but that requires a large number of total image counts. Count densities in the range of 40 to 100 counts per pixel result in images of high quality but are difficult to obtain in some studies, such as equine bone scintigraphy. High count density using a large matrix could be obtained by giving a larger dose of the radiopharmaceutical or by acquiring the image for a longer

Figure 5.7: Images of a bar phantom and a canine thorax taken for various numbers of counts

Note that the bars are difficult to resolve in the images with the lower number of counts. Anatomic detail of the canine thorax is also severely compromised in the low-count images. The number of counts acquired can limit resolution of the image.

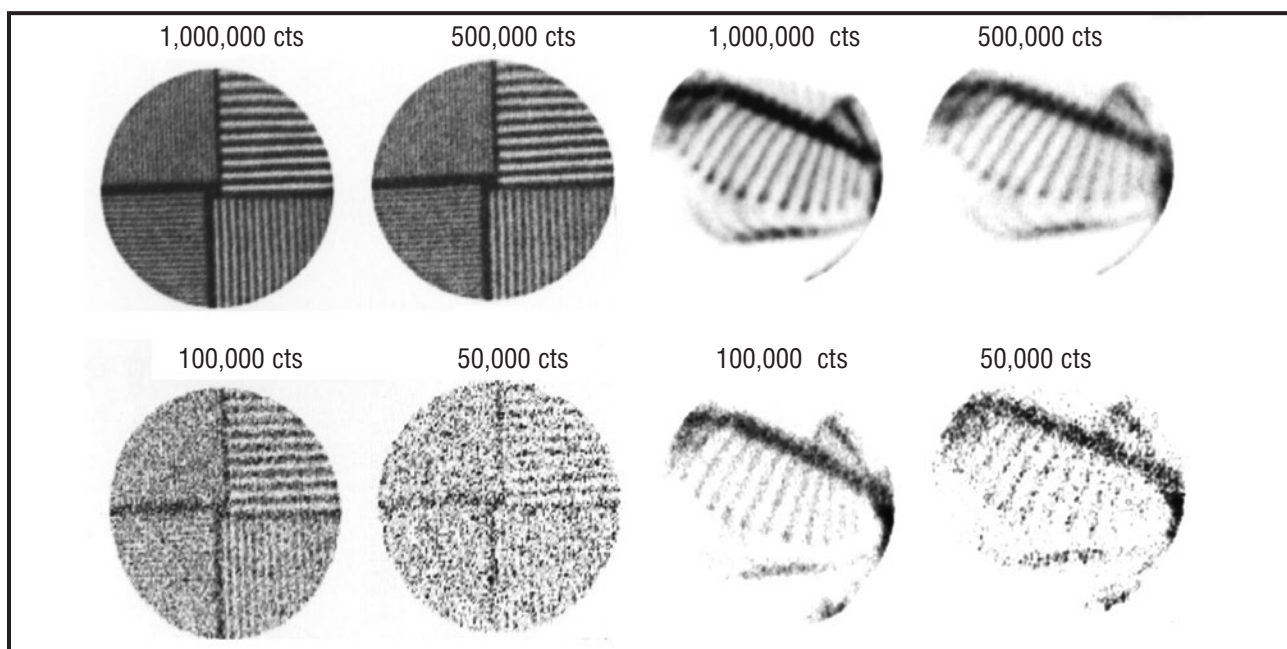


Table 5.1: Comparison of One, Two, and Three Flip-flop Circuits (bits) and Possible Numbers Assigned by a Binary Code

Image Depth	Numbers	Binary Code
1 bit	0 - 1	0 or 1
2 bits	0 - 3	00, 01, 10, 11
3 bits	0 - 7	000, 001, 011, 110, 010, 100, 101, 111

Table 5.2: Range of Digital Values That Can Be Captured According to the Number of Bits Inherent in the Computer System or Image

Calculations are complete through 8 bits: 8 bits = 1 byte; 2 bytes = 1 word (16 bits)

# Bits	Calculation	Number	# Bits	Calculation	Numbers
1	$2^1 = 2$	0 - 1	5	$2^5 = 32$	0 - 31
2	$2^2 = 4$	0 - 3	6	$2^6 = 64$	0 - 63
3	$2^3 = 8$	0 - 7	7	$2^7 = 128$	0 - 127
4	$2^4 = 16$	0 - 15	8	$2^8 = 256$	0 - 255

time. In veterinary medicine, neither of these options is realistic.

Image Depth

The number of counts recorded within an individual pixel is saved as part of the digital matrix. The maximum number of counts saved to a pixel address is limited by the computer memory assigned to each pixel. Image depth refers to the amount of computer memory assigned to each pixel. Computers use a transistor circuit called a “flip-flop” to store information. Each flip-flop circuit can be turned either off or on and can be assigned a value of 0 or 1, respectively. The flip-flop circuit is the basis of the binary code used to store information in the computer. One bit of computer memory (one flip-flop circuit) can store two different numbers (0 for “off” or 1 for “on”) using a binary code. Two bits of computer memory (two flip-flop circuits) can store up to four different numbers and so forth (Table 5.1 and Table 5.2). The maximum number that can be saved is equal to 2^n , where n is the number of bits of computer memory.

There are terms used to describe image depth. A byte represents 8 bits of computer memory. A word is 2 bytes or 16 bits of computer memory. The highest value that can be stored in 1 byte is 2^8 or 255.¹¹ Note that the maximum number is 255, as the first number is considered to be 0. The highest value that can be stored in 1 word is 2^{16} or 65,535.¹¹

As described above, a pixel in an 8-bit image can hold up to 255 counts per pixel. If this pixel receives another count (256), then the binary code starts over at 0. This is referred to as rollover, and the artifact can be seen in Figure 5.8, a feline thyroid stored as an 8-bit image (byte mode).¹² Note the central portions of the right thyroid lobe have several areas that are white. These pixels have exceeded 255 counts and have started counting over beginning with 0.

Image Designation

The designation for a digital image indicates the matrix size and the image depth. A $64 \times 64 \times 8$ designation for an image means the matrix has 64 rows and 64 columns for a total of 4,096 pixels. Each pixel

has 8 bits of image memory assigned, which allows it to store count densities from 0 to 255. A $64 \times 64 \times 16$ designation means the matrix has 64 rows and 64 columns or 4,096 pixels. Each pixel has 16 bits, allows it to store count densities from 0 to 65,535. A $256 \times 256 \times 8$ designation means the matrix has 256 rows and 256 columns or 65,536 pixels. Each pixel has 8 bits which allows it to store count densities from 0 to 255. A designation of 64×64 (word) has the same meaning as a $64 \times 64 \times 16$ matrix. Likewise

a 256×256 (byte) has the same meaning as a $256 \times 256 \times 8$ matrix.

Digital Image Memory Requirements

The product of the total number of pixels in the image and the image depth in bits gives the approximate amount of computer memory required for each digital image. The image depth (per pixel) multiplied by the number of pixels in an image matrix will equal the total image size (bytes). In addition to the information content of the image, there is non-image information stored in the file header. This non-image information contains information about the matrix size, image depth, image acquisition date and time, patient name, medical record number, etc. In a typical study, this could account for an additional 1,024 bytes of storage space (Table 5.3).

Storage Devices and Computer Hard Disk

An evolution of media used to store digital images has led to storage media that has gotten small and storage capacity that has greatly increased. Table 5.4 shows common types of storage media used for storing nuclear medicine studies. Table 5.5 shows the total storage capacity (number of actual images) of various hard disk drive sizes, depending on the type of study matrix used.

Image File Formats

The file header information is used to record patient demographic information and image acquisition parameters. The nuclear medicine computer manufacturer determines the storage format of the images and header, and for that reason image files cannot be freely exchanged between computers. Because

Figure 5.8: Ventral image of the cervical region of a cat 20 minutes after injection of $^{99m}\text{TcO}_4^-$

The number of counts in the pixels representing the thyroid gland has exceeded the amount of memory assigned to this image. The numeric value assigned to these pixels has rolled over to 0 resulting in the count loss in the thyroid region. In an 8-bit image, rollover will occur if the counts in the pixel exceed 255.



Table 5.3: Image Size According to Matrix Used and Image Depth (byte or word mode)

Matrix Size	Image Size and File Header (1 byte = 8 bits)	Image Size and File Header (1 word or 2 bytes = 16 bits)
64×64	$4,096 + 1,024 = 5.1$ kilobytes	$8,192 + 1,024 = 9.2$ kilobytes
128×128	$16,384 + 1,024 = 17.4$ kilobytes	$32,768 + 1,024 = 33.8$ kilobytes
256×256	$65,536 + 1,024 = 66.5$ kilobytes	$131,072 + 1,024 = 132.1$ kilobytes
512×512	$262,144 + 1,024 = 263.1$ kilobytes	$524,288 + 1,024 = 525.3$ kilobytes
$1,024 \times 1,024$	$1,048,567 + 1,024 = 1$ megabyte	$2,097,152 + 1,024 = 2$ megabytes

Table 5.4: Memory Available for Different Storage Devices

Media Type	Storage Capacity	Number of Images Stored (256 x 256 x 8)	Number of Images Stored (256 x 256 x 16)
5.25-inch floppy disk	360 kilobytes	5	2
3.5-inch diskette	1.44 megabytes	21	10
Syquest drive	88 megabytes	1,322	666
Zip drive	250 megabytes	3,756	1,892
Jazz drive	2 gigabytes	30,048	15,140
CD-ROM	700 megabytes	10,516	5,299
DVD	4.7 gigabytes	71,612	35,580

Table 5.5: Total Storage Capacity (number of images) of a Hard Drive*

	6 gigabyte disk	20 gigabyte disk	40 gigabyte disk	60 gigabyte disk	100 gigabyte disk
Matrix Size	No. of Images (16-bit depth)	No. of Images (16-bit depth)	No. of Images (16-bit depth)	No. of Images (16-bit depth)	No. of Images (16-bit depth)
64 × 64	651,042	2,170,139	4,340,278	6,510,417	10,850,694
128 × 128	177,557	591,856	1,183,712	1,775,568	2,959,280
256 × 256	45,422	151,405	302,810	454,215	757,025
512 × 512	11,422	38,073	76,145	114,218	190,363
1,024 × 1,024	2,837	9,458	18,916	28,374	47,290

*Assumes that the hard drive is a secondary drive and does not hold the computer operating system.

of the need to exchange images between different manufacturers, systems, file conversion programs are now commonly found on nuclear medicine computers.

DICOM

The interchange of digital images beyond closed proprietary architectures became important in the 1980s with the development of digital imaging systems, such as computerized radiography, ultrasound, nuclear medicine, computed tomography (CT), and magnetic resonance imaging (MRI). A standardized file exchange protocol was developed by a joint committee of the American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA; <http://www.nema.org/nema/medical/dicom>). DICOM (Digital Imaging and Communications in Medicine) defines a communication protocol that determines how images and header information are transferred from one computer to another. All types of radiology equipment use DICOM: x-ray, CT, MRI, ultrasound, and nuclear medicine. Images can be sent to a Picture Archival and Communication System (PACS) for image comparison or fusion of images, such as nuclear medicine scans and radiographs.

Other Image File Formats

Digital images can also be stored as predefined bit maps that are commonly used on personal computer systems.¹ Header information, other than that describing the physical layout of the image, is not included unless it is part of the image bit map. The bit map image format allows for easy transfer and display on computer systems that are not specifically for radiology or nuclear medicine. Common bit map image formats that are currently used include GIF, TIFF and JPEG.

GIF

- ☐ GIF stands for Graphics Interchange Format.
- ☐ Developed by CompuServe, Inc.
- ☐ Image format uses the Lempel-Ziv-Welch (LZW) algorithm for lossless data compression.
- ☐ Compression can be 2:1 or 4:1.

TIFF

- ☐ TIFF stands for Tag Image File Format.
- ☐ International standard format.
- ☐ Formats differ for Windows versus Macintosh operating systems.

3. JPEG

- ☐ JPEG stands for Joint Photographic Experts Group.
- ☐ Developed by Institute of Electrical and Electronics Engineers.
- ☐ Uses a data compression algorithm that can result in loss of quantitative information.
- ☐ Data compression can be up to 20:1, and the images are within acceptable limits for display on computer monitors and printing to files.

Image Display

To display an image on a computer monitor, the image must be loaded into the display memory. Every pixel is referred to an intensity lookup table (LUT) that translates the pixel count value to an intensity or a color value.¹ For a gray scale image, each pixel is assigned a gray scale value from the LUT based on the number of counts it contains. The higher the pixel value, the more intensely the pixel is displayed on the monitor. Images can be displayed as black on a white background (inverse gray) or white on a black background. For an image display to appear relatively smooth to the eye, a range of at least 100 intensity levels is required.²

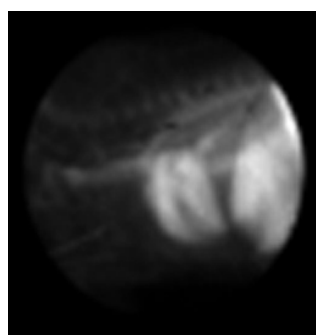
The standard black and white monitor for nuclear medicine computers provides for a display of 256 shades of gray. This corresponds to an 8-bit LUT. A color system will have varying intensities of red, green, and blue on the monitor. A 24-bit color LUT has 8 bits dedicated to each of the colors, allowing for the display of 256 shades of each color or 16 million colors.¹ If red, green, and blue are displayed at their maximum intensity, the color produced is white. If these three colors are of equal intensity but less than their maximum intensity, then a shade of gray is displayed. A 24-bit color monitor is able to display 256 shades of gray. There has been considerable debate as to the best LUT for viewing nuclear

medicine images. A linear gray scale is the most commonly used LUT for nuclear medicine, assigning the lowest intensity pixel as black and the pixel with the greatest number as white. This produces an image that is white with a black background. To create an image that is black with a white background, the LUT is inverted (Figure 5.9).

In a linear gray scale the highest pixel value is assigned white, and the pixels with a 0 value are assigned black. The number of shades of gray between these extremes is extrapolated in a linear fashion. If, for example, there are 1,000 pixel levels within the image and the display is 8-bit (capable of displaying 256 shades), each display level is achieved by dividing the range of counts by the number of shades of gray. In this case, the range of counts in the image (0 to 1,000) is divided by 256 yielding four counts per intensity level. This means that all pixels with a range of 0 to 3 will be given the lowest intensity, those with a range of 4 to 7 are given the next intensity, and so forth. This scheme is fair in that it does not favor a particular range of counts; however, this LUT can be a problem if there is a high intensity area within the image field of view but

Figure 5.9: Lateral image of a canine thorax following injection of a blood pool agent (^{99m}Tc -RBC)

An inverted linear gray scale is used to display the image. The pixels with 0 counts are black and with the highest number of counts are white. Varying shades of gray are assigned to pixels with values in-between. There is a linear relationship in the assigned shades of gray. The image to the right is an inverted gray scale in which pixels with no recorded counts are white and the pixels with the highest counts are black.



Linear gray scale



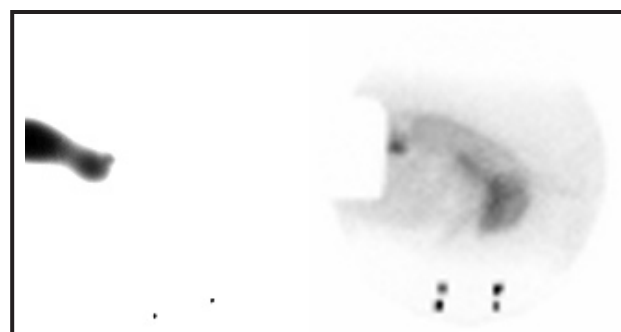
Inverted linear gray scale

the area of interest is of much lower intensity. This example is commonly encountered with per-rectal portal scintigraphy in which the area of deposition of the radionuclide is within the field of view. The count density within the colon may be 500/pixel, but the count density within the liver and heart is 8/pixel. As a result, only the colon is visible making it impossible to see the liver or heart (Figure 5.10). This is also seen with thyroid scans in hyperthyroid cats. The count density in the thyroid may be over 200 counts/pixel and the count density in the soft tissues in the range of 10 to 20. As a result the display will show the thyroid glands, but the outline of the cat is not seen and, therefore, location of the thyroid lobes is difficult to determine (Figure 5.11).

The intensity and contrast of the image may be altered by two techniques, namely windowing and thresholding.¹ The principle of window levels is common in CT and MRI. The intensity of the display is set between specified pixel values. In a true windowing system, all pixels with values outside this

Figure 5.10: Summed images from per-rectal portal scintigrams in two dogs

An inverted linear gray scale is used to display the images. The image on the left shows the unshielded area of the colon within the field of view. A lead shield between the dog and the camera blocked the area of the colon in the image on the right. The number of counts per pixel in the area of the colon is 500. The number of counts in the area of the thorax is 10. If the gray scale is expanded from 0 to 500, the shade of gray assigned to the thorax is so light these structures are not seen. By blocking the area of the colon from the field of view, the highest intensity pixel is 20 and is assigned black. Those pixels with 10 counts are assigned shades of gray halfway between white and black. Note how much better structures in the thorax are seen on the image to the right.



range are not displayed. Thresholding is a more common technique in nuclear medicine, and it defines a count range to which all the display levels will be allocated. Pixels outside this range are displayed at a level identical to the minimum or maximum of the range. The limits of the range are usually expressed as a percentage of the maximum pixel in the image.⁵

Examples of Linear Gray Scales and Thresholding Adjustments

Linear Gray Scale (Inverted)

Pixels with a value of 0 are assigned the lowest intensity setting, (0 cts/pixel = white). The pixel with the highest value n is assigned the highest intensity setting (n cts/pixel = black). The remaining pixels are assigned proportionally increasing gray scale values (Figure 5.12).

Linear Gray Scale (Inverted) with Threshold

Gray scale can be adjusted by assigning all counts above a specific point the highest intensity gray scale setting. In Figure 5.13, the threshold level was

Figure 5.11: Ventral images of a hyperthyroid cat (left) and a normal cat (right) acquired 20 minutes following injection of pertechnetate

An inverted linear gray scale is used to display the images. The outline of the hyperthyroid cat is difficult to see because the upper limit of the scale (black) is assigned to the high count density pixels of the thyroid. The count density of the soft tissues is so much lower that they are assigned a very light shade of gray. In a normal cat, the upper limit of the gray scale is a value that is not much higher than the values for soft tissues of the body, so the tissues are assigned an intermediate shade of gray that is easily seen.

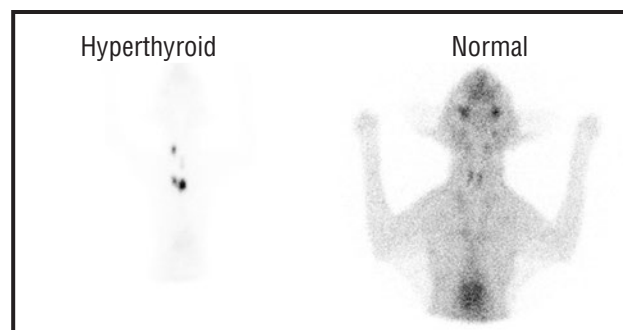


Figure 5.12: Lateral image of a canine thorax following injection of a blood pool agent ($^{99m}\text{Tc-RBC}$)

The graph on the right shows the relationship between counts per pixel and the assigned intensity (shade of gray). The LUT is an inverted linear gray scale. Pixels with a value of 0 have the lowest intensity (white) and pixels with the highest value (65) are assigned the highest intensity (black). The pixels with intermediate values are assigned intensities (shade of gray) that are proportional to their values.

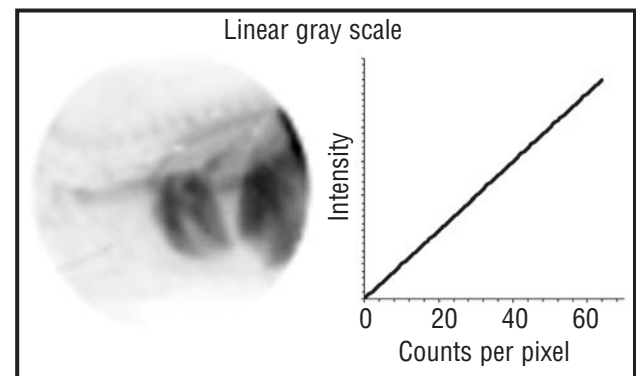
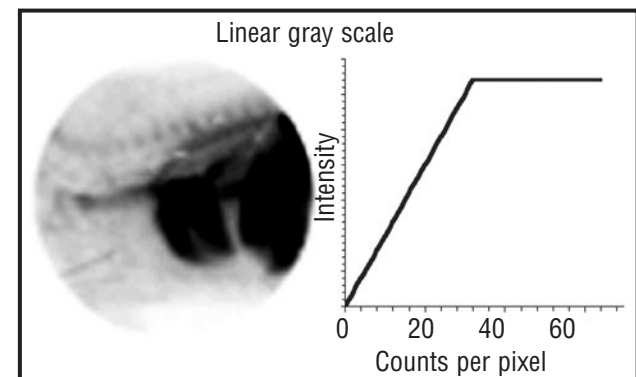


Figure 5.13: Lateral image of the canine thorax shown in Figure 5.12

The graph on the right shows the relationship between counts per pixel and the assigned intensity (shade of gray). The LUT is an inverted linear gray scale. Pixels with a value of 0 have the lowest intensity (white). The upper level of the gray scale is set at 30, which means that all pixels with a value of 30 or greater are assigned the highest intensity (black). Pixels with values between 0 and 30 are assigned intermediate shades of gray.



set to 30 counts per pixel. In this case, all pixels with a count density greater than 30 counts per pixel are assigned the highest intensity setting or black.

Nonlinear Lookup Tables

The LUT scale does not have to be linear. If all of the pixel intensities need to be displayed in a graduated fashion but the gray scale needs to be expanded over certain intensity ranges, then a nonlinear gray scale LUT may be used. In a logarithmic gray scale LUT, the display intensity increases by the log of pixel counts. The display intensity is set to equal the log of the pixel density. This type of scale expands the number of shades of gray in the low count density regions (Figure 5.14). There are also fewer intensity shades in the high count density range, which deemphasizes hot spots in the image.¹ This nonlinear display is used for images with very high count density pixels where there is a need to see portions of the image that have low count densities. An example would be a hyperthyroid cat with a high-intensity nodule. A logarithmic gray scale could be used to emphasize the low-intensity regions of the image without removing the gradient of pixel intensities.

If the intent is to expand the number of shades of

gray in the high count density range, then an exponential gray scale can be used. With an exponential gray scale LUT, the display intensities increase in an exponential fashion. In that case, the display intensity becomes the power value of the natural log of e (2.718 raised the power of the pixel intensity).¹² This results in a greater number of shades of gray in the high count density regions and fewer shades of gray in the low count density region (Figure 5.15).

Today, nuclear medicine computers come with a variety of color lookup tables (LUTs). In a color LUT, different colors are assigned to the various pixel densities (Figure 5.16). Color LUTs are popular because they offer increased perception of lesions. It is well established that the human eye can distinguish several hundred different colors but far fewer shades of gray.³ It has been demonstrated that color display can increase sensitivity in detecting lesions.¹³ Color LUTs are helpful in analyzing dynamic studies or assisting in drawing regions of interest, but some caution must be exercised in using color displays for interpretation of static images. With bone scintigraphy, where there is low count density and the statistical certainty of individual pixel values is often suspect, insignificant changes in count density can be artificially amplified using a color LUT. Color

Figure 5.14: Lateral image of the canine thorax shown in Figure 5.12

The graph on the right shows the relationship between counts per pixel and the assigned intensity (shade of gray). The LUT is a logarithmic gray scale. Pixels with a value of 0 have the lowest intensity (white), and pixels with the highest value (65) are assigned the highest intensity (black). The intensity of the display increases by the log of the pixel counts. This type of gray scale expands the number of shades of gray in the low count density range.

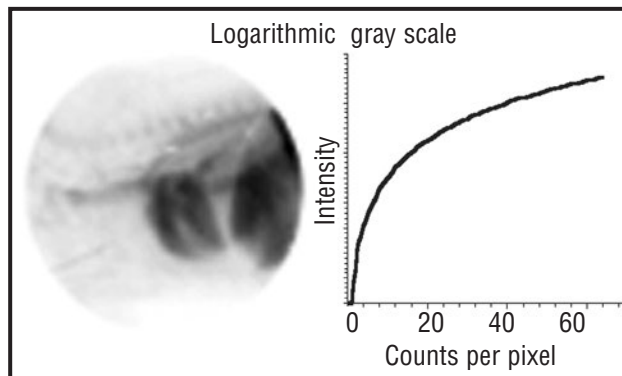
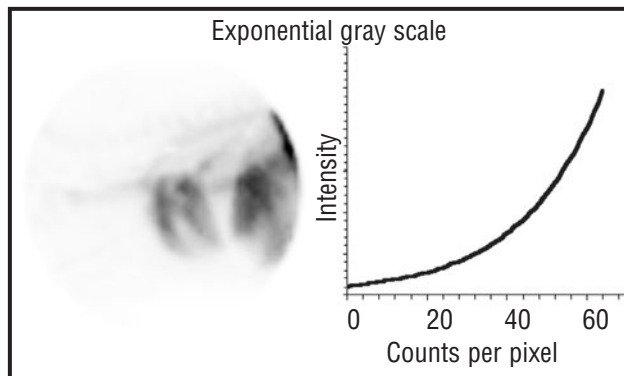


Figure 5.15: Lateral image of the canine thorax shown in Figure 5.12

The graph on the right shows the relationship between counts per pixel and the assigned intensity (shade of gray). The LUT is an exponential gray scale. Pixels with a value of 0 have the lowest intensity (white), and pixels with the highest value (65) are assigned the highest intensity (black). The intensity of the display increases in an exponential fashion. This type of gray scale expands the number of shades of gray in the high count density range.



LUTs would enhance detection sensitivity but often at the cost of lower specificity and false-positive diagnoses.

Image Interpolation

Interpolation is an important technique in many areas of image processing and display. Linear interpolation

Figure 5.16: Lateral image of the canine thorax shown in Figure 5.12

The graph on the right shows the relationship between counts per pixel and the assigned color. The LUT is a multicolor scale. Pixels with a value of 0 are assigned red, and the pixels with the highest value (65) are purple. Pixels in the intermediate ranges are assigned various other colors.

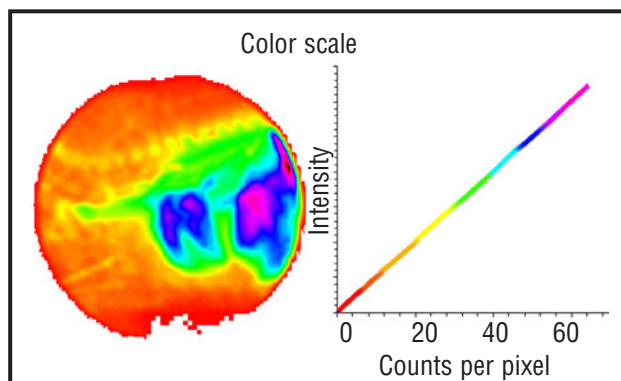
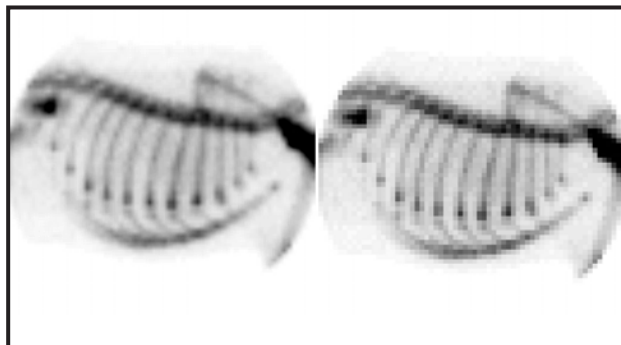


Figure 5.17: Lateral images of a canine thorax acquired 2 hours following injection of ^{99m}Tc -MDP

Both images were acquired in a 64×64 matrix. The image on the left has been interpolated into a 256×256 matrix. Because of the large size of the pixels in the 64×64 matrix, the image on the right appears boxy. The pixels are too small to be seen on the image on the right, and the image appears smoother.



makes the assumption that values between any pair of adjacent samples lie on a straight line connecting them. In the case of image display, the matrix size used for the display may be larger than the original acquisition matrix.⁸ In that case, an individual pixel value must be subdivided into smaller units. The value for each new pixel is influenced by the value of the neighboring pixels. The new values are a linear extrapolation between the values of the adjacent pixels. It must be noted that interpolation makes an image appear smoother by removing the boxy appearance from the pixels, but the resolution is no better than that of the original image (Figure 5.17).

Image Processing in the Spatial Domain

Because a digital image is no more than a matrix of numbers, simple mathematical manipulations of images can be used to change their appearance or location with the image frame. By changing the addresses of pixels, the position and orientation of the image can be altered. Changing the orientation is useful to standardize the display of images. The standard orientation for viewing nuclear medicine images is to position the image as if one were inside the gamma camera looking at the patient. For a right lateral view, this means the animal's head is toward the right. For a dorsal view, the animal's right side is on the right side of the image and for a ventral view, the animal's right is on the left side of the image (Figure 5.18). Ideally, the image should be acquired in the correct orientation; but if it is not, then computer processing can be used to correct the orientation. Also, image math can be performed by mathematically combining two or more images to create a new image. Finally, the pixel values themselves can be altered by comparing them to their neighboring pixels, thereby either enhancing or blurring edges. The following section describes various operations that can be performed on an image.

Geometric Operations

Geometric operations are techniques used to change the orientation of an image. The addresses of the individual pixels are identified using the Cartesian coordinate system. Consider the original image shown in Figure 5.3. Note the spatial coordinates of the high intensity pixel at the ninth costochondral junction. This pixel address is (214,121). If the

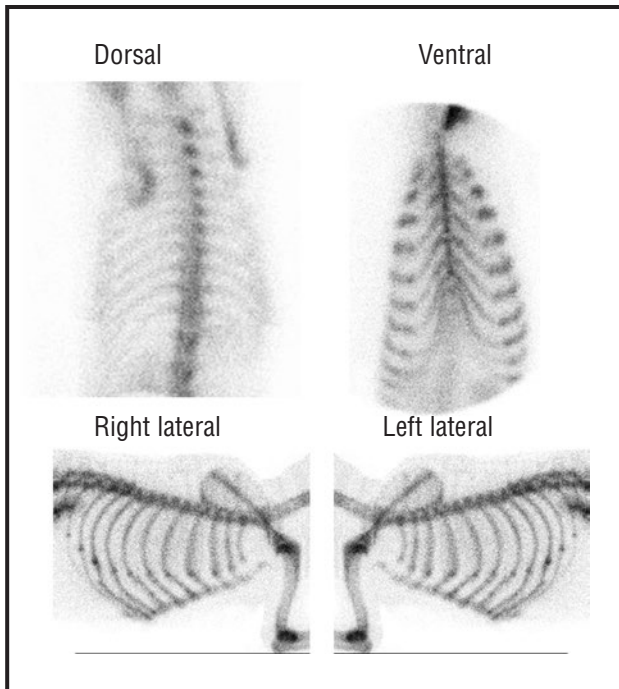


Figure 5.18: Images of a canine thorax acquired 2 hours following injection of ^{99m}Tc -MDP

Standard nuclear medicine orientation specifies that the image should be displayed as if one were inside the camera looking at the animal. From the dorsal perspective, the animal's right is on the viewer's right. From the ventral perspective, the animal's right is on the viewer's left. From a right lateral perspective the animal is facing to the right, and from a left lateral perspective the animal is facing to the left.

origin of the image (0,0) is considered to be in the lower left-hand corner, a pixel address of (214,121) means the pixel is 214 columns from the left and 121 rows up from the bottom. As the cursor moves over many nuclear medicine computer displays, the pixel address of the cursor appears along with the counts per pixel at a specific location. The pixel addresses are altered when performing geometric operations. Notice how these spatial coordinates change during the following geometric operations used to change image orientation.

Flip Horizontal

The location of each x coordinate is inverted into a negative number and the new image created using the new coordinates (Figure 5.19).

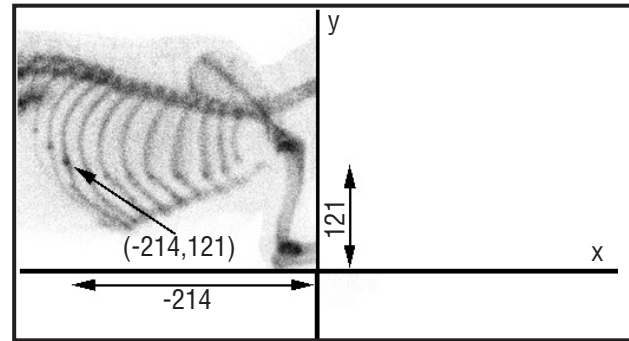


Figure 5.19: Lateral image of the canine thorax shown in Figure 5.3

Each pixel has an address designated as (x,y). The image has to be flipped horizontally by reassigning each pixel address throughout the image as a negative of the original x value. Original image $a(x,y)$ to new image $b(-x,y)$.

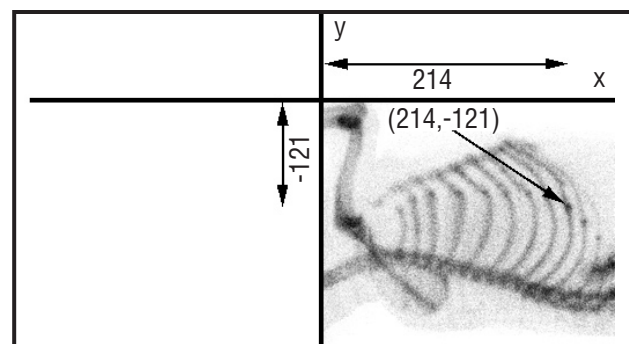


Figure 5.20: Lateral image of the canine thorax shown in Figure 5.3

Each pixel has an address designate as (x,y). The image has be flipped vertically by reassigning each pixel address throughout the image as a negative of the original y value. Original image $a(x,y)$ to new image $b(x,-y)$.

Original (a)	→	New (b)
a (x,y)		b (-x,y)

Flip Vertical

The location of each y coordinate is inverted into a negative number and the new image created using the new coordinates (Figure 5.20).

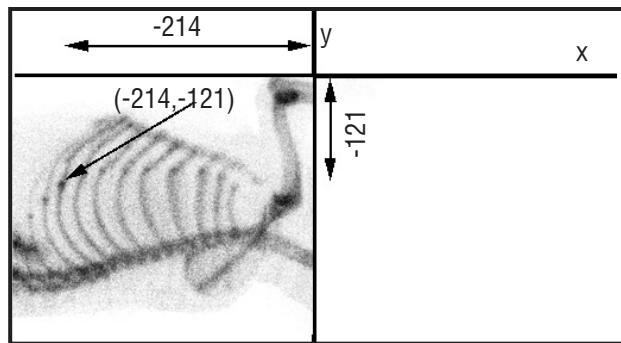


Figure 5.21: Lateral image of the canine thorax shown in Figure 5.3

Each pixel has an address designated as (x,y) . The image is rotated 180° by reassigning each pixel address throughout the image as a negative of the original x and y values. Original image $a(x,y)$ to image $b(-x,-y)$.



Rotate 180°

The location of each x and y coordinate is inverted into a negative number, and the new image is plotted using the new coordinates (Figure 5.21).



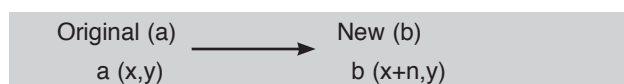
Rotate 90°

The values for the x and y coordinates are exchanged and the new image is plotted using the new coordinates (Figure 5.22).



Shifting Position of the Image

The address of the pixel is shifted by a specific number of pixels by any integer, n (Figure 5.23).



If $n = 11$, then this operation would shift the image to the right by 11 pixels as in Figure 5.23. The 11

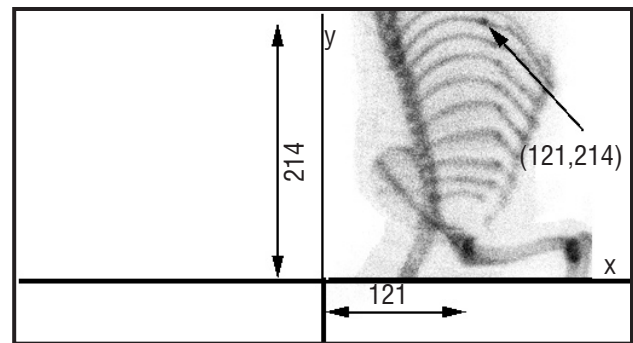


Figure 5.22: Lateral image of the canine thorax shown in Figure 5.3

Each pixel has an address designated as (x,y) . The image is rotated 90° by exchanging x and y values. Original image $a(x,y)$ to new image $b(y,x)$.

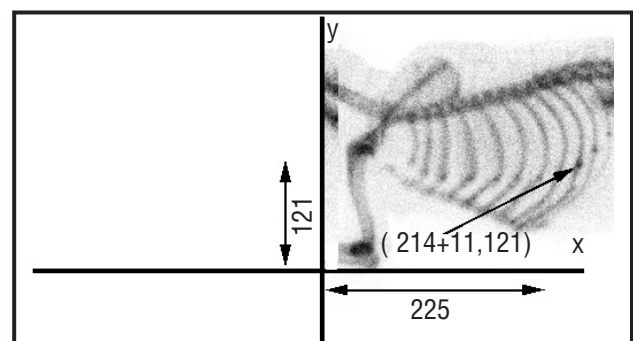


Figure 5.23: Lateral image of the canine thorax shown in Figure 5.3

Each pixel has an address designated as (x,y) . The image has been shifted to the right by reassigning each x pixel address throughout the image by $x + 11$. Original image $a(x,y)$ to new image $b(x + 11, y)$. Note the image has been shifted to the right 11 pixels. The 11 pixels on the far right side of the images have wrapped around to the far left side of the image.

rows of pixels on the far right end of the image are usually repositioned in the first 11 columns on the left (compare Figure 5.23 with Figure 5.3). In this manner, images can be shifted up or down by a specific amount.

Shifting or rotation of an image is relatively simple as just described, because each new pixel address fits neatly into an existing address. Rotation of an image

to an angle other than 90°, 180°, or 270° is much more difficult because the value of the original pixel must now be interpolated to several adjacent pixels.

Algebraic Operations

Algebraic operations are essentially image math. Two or more images are combined mathematically to create a new image.¹² Because each image is a matrix of numbers, mathematical operations are done on a pixel-by-pixel basis to create the new image. Algebraic operations are easily applied to dynamic frame mode images because the position of the animal should not change between image frames. If algebraic operations are to be used on static images, the images may need to undergo geometric operations to register (or align). If the anatomic parts of the image are not aligned, then misregistration artifacts can result from the algebraic operation.

Summing Images

Summing is an algebraic operation in which many images are added together to create a composite image. This procedure is routinely performed if regions of interest are to be drawn around an area of interest from a dynamic acquisition. In the case of per-rectal portal scintigraphy, each frame of the dynamic acquisition is of low count density making it difficult to discern the borders of the heart and liver. If all of the dynamic images are summed together, the new composite image has a much higher count density and the certainty of accurately identifying the borders of specific organs is greatly enhanced (Figure 5.24).

$$\sum_{k=1}^n (x_k, y_k) = 1(x,y) + 2(x,y) + \dots + n(x,y) = \text{summed } (x,y)$$

Adding Images

Algebraic operations can be used to add two images to create a third. For example, when creating a composite image of the heart by adding the RV phase image to the LV phase image (Figure 5.25).

$$a(x,y) + b(x,y) = c(x,y)$$

Subtracting Images

Algebraic operations are used to subtract one image from another to create a third. An example is when one is creating an ejection volume image of the heart by subtracting the end systolic image from the end diastolic image (Figure 5.26).

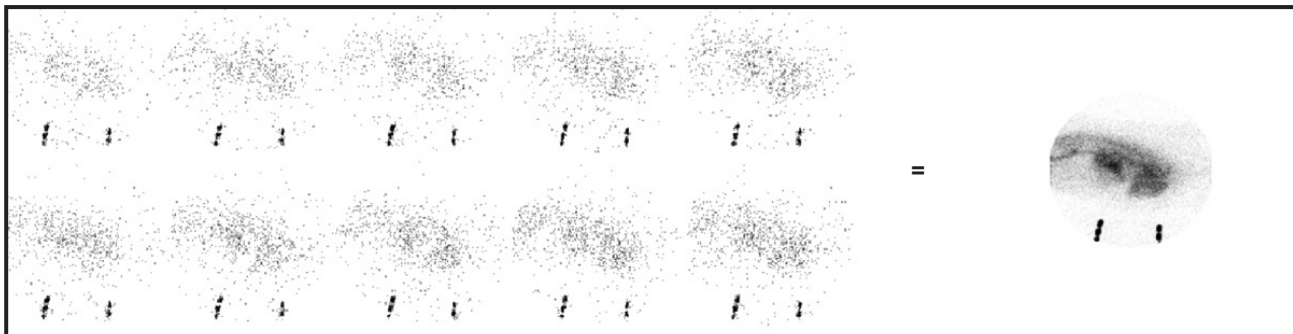
$$a(x,y) - b(x,y) = c(x,y)$$

Parametric (Division) Images

Algebraic operations are used to divide one image by another to create a third image. An example of a parametric image is when one is trying to demonstrate an area of ventilation and perfusion (V/Q) mismatch. A point operation is first performed to normalize each image to the same number of total counts. Then the ventilation image is divided by the perfusion image on a pixel-by-pixel basis (Figure 5.27).

Figure 5.24: Images of a per-rectal portal scintigraphy in a dog with a portosystemic shunt

The sequential frames to the left were taken at 4-second intervals. The number of counts within each frame is low resulting in poor anatomic detail. The images of each frame of the dynamic acquisition were summed to create the image to the right. This is an example of an algebraic operation. Note the improvement in image quality in the summed or composite image.



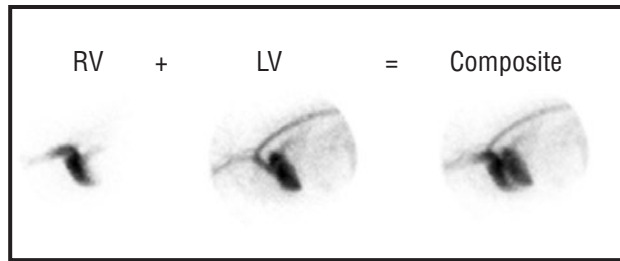


Figure 5.25: Images of a first-pass radionuclide angiocardigram in a normal dog

The image on the left was acquired during the passage of the radioactive bolus through the right ventricle (RV). The image in the middle was acquired during the passage of the radioactive bolus through the left ventricle (LV). By adding the RV and LV images together on a pixel-by-pixel basis, a composite image is created showing both sides of the heart and their relationship to each other. This is an example of an algebraic operation (image addition).

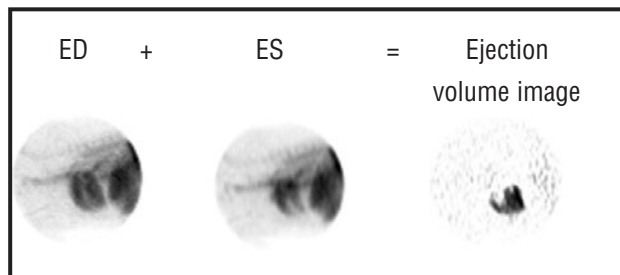


Figure 5.26: Images from a gated cardiac study in a normal dog

The image on the left was acquired at end diastole (ED). The image in the middle was acquired at end systole (ES). The ejection volume image on right was made by subtracting the ED image from the ES image on a pixel-by-pixel basis. This technique is best used to show the differences between two images. Here the difference represents the ejection volume image.

$$a(x,y) \div b(x,y) = c(x,y)$$

Point Operations

Point operations are normalization procedures that enable images that were taken with different acqui-

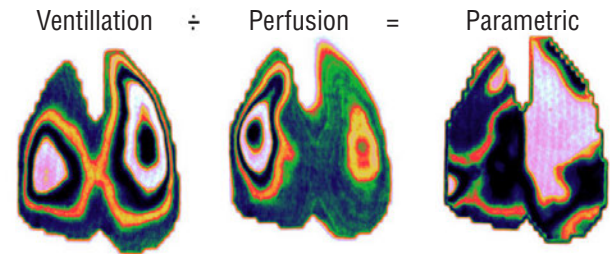


Figure 5.27: Dorsal ventilation and perfusion images in a dog with decreased perfusion of the right lung

The image on the left is the ventilation image. The image in the middle is the perfusion image. The image on the right is a parametric image made by dividing the ventilation image by the perfusion image on a pixel-by-pixel basis. The areas of the lung that have a V/Q match (corresponding pixels have similar values) will have assigned pixel values near 1. If a dog has less perfusion than ventilation (numerator much larger than the denominator), then the assigned pixel value in the parametric image will be large, extenuating the lesion.

sition times or a different total number of counts to be compared with one another. There are many situations in which it is difficult to compare one image with another because of these differences in total image counts; a good example is an equine bone scan. The image of a right metacarpophalangeal joint of a horse may have been acquired for 60 seconds, but the horse would not stay still longer than 45 seconds on the left side. To compare the intensity of the uptake, it would be necessary to make the images more equivalent. A point operation can be used to adjust the intensity of the left metacarpophalangeal joint image so that it can be compared to the right metacarpophalangeal joint.

Original image	→	New image
$a(x,y)$	→	$b(x,y) \times n$, where n is the scaling factor

In the above example, the original image would be multiplied by the appropriate scaling factors as shown below.

the original left metacarpophalangeal joint is scaled to the normalized left metacarpophalangeal joint.

$$a(x,y) \longrightarrow b(x,y) \times (1.33)$$

The scaling factor is a ratio of the acquisition times 60/45 seconds or 1.33. Because the left metacarpophalangeal joint would need to be increased in total counts, the larger number is placed in the numerator and the smaller number in the denominator.

Parametric lung imaging requires the ventilation scan to be divided by the perfusion scan. The ventilation scan will be of a much lower count density than the perfusion scan. Before the parametric image can be created, the count densities of the images must be made similar. To do this, a scaling factor is generated and is used to normalize the count density of the ventilation and perfusion scans prior to the algebraic operation to create the parametric image. Point operations are also used to normalize images before image subtraction. In another example, thallium-201

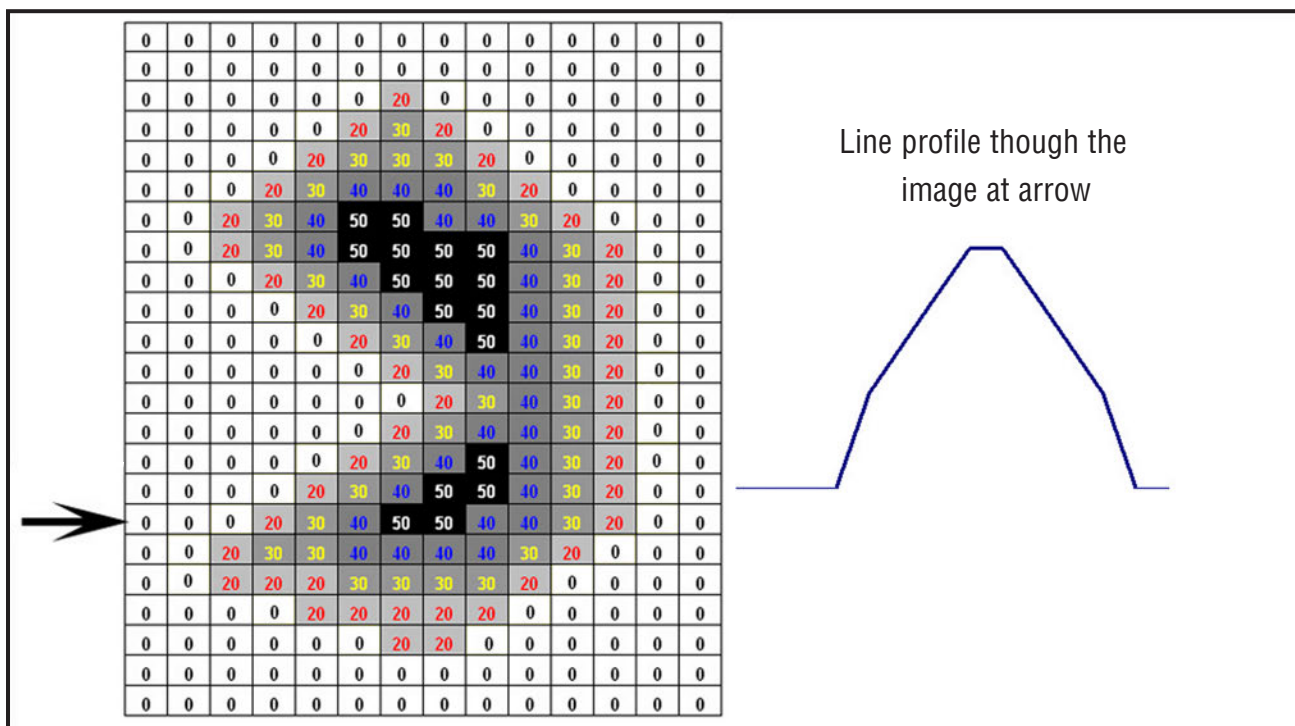
and sodium pertechnetate can be used to visualize the parathyroid glands. The thallium-201 image is subtracted from the sodium pertechnetate image of the thyroid glands. Before this is done, however, the images have to be normalized to account for differences in the count densities between the two images using a scaling factor that is calculated based on the two images.

Smoothing Operations

Scintigraphic images are usually of low count density and, therefore, of poor statistical quality.^{5,8,12} Pixels that should contain approximately the same value can vary, resulting in a grainy or cryptic appearance. Image smoothing enhances the image appearance by reducing noise from the varying pixel intensities. Smoothing will remove the high and low count density pixels that are common in low count images thus increasing the certainty of pixel values but also blurring the image. Smoothing is sometimes used to help

Figure 5.28: Diagram representing a digital image

The numbers in the pixel represent the pixel values or number of counts. A line profile is shown to the right, taken from the row of pixels indicated by the arrow. The 0 value pixels are represented by the flat baseline. At the edge of the object shown in the digital image, the line shows an abrupt increase to the maximum value in the center of the object.



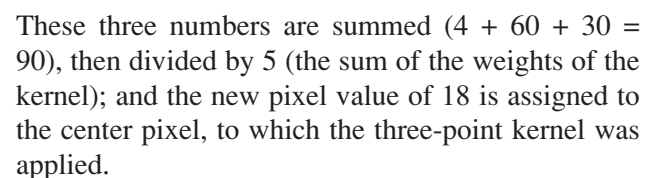


define a border of an organ to aid in region-of-interest placement. By smoothing the image, the borders are more even, without jagged margins. It should be noted that the smoothing operations described next will alter the pixel values in the image and will affect the quantification.

Weighted Averaging Smoothing

1	3	1

0	0	0	4	20	30	40	50	50	40	30	20	0	0	0



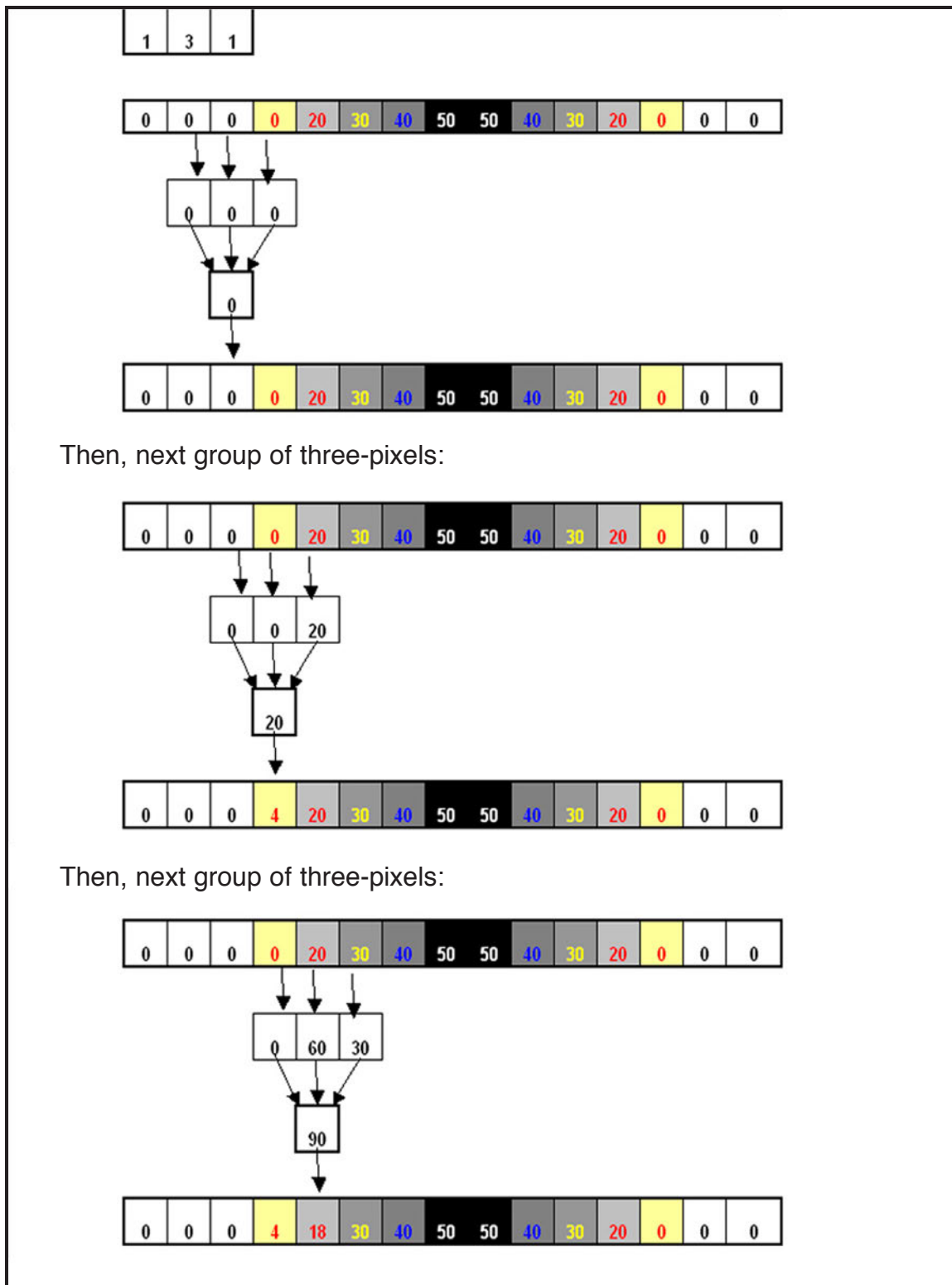


Figure 5.30: Diagram showing the process of a 1-3-1 weighted averaging smoothing

The kernel is positioned over the three adjacent pixels. The value of each image pixel under the kernel is multiplied by the value contained in the kernel. The three values are added together and divided by the sum of the kernel. This new number is then used to replace the value of the central image pixel under the kernel. The kernel is moved to the left one pixel and the process repeated over and over throughout the entire image.

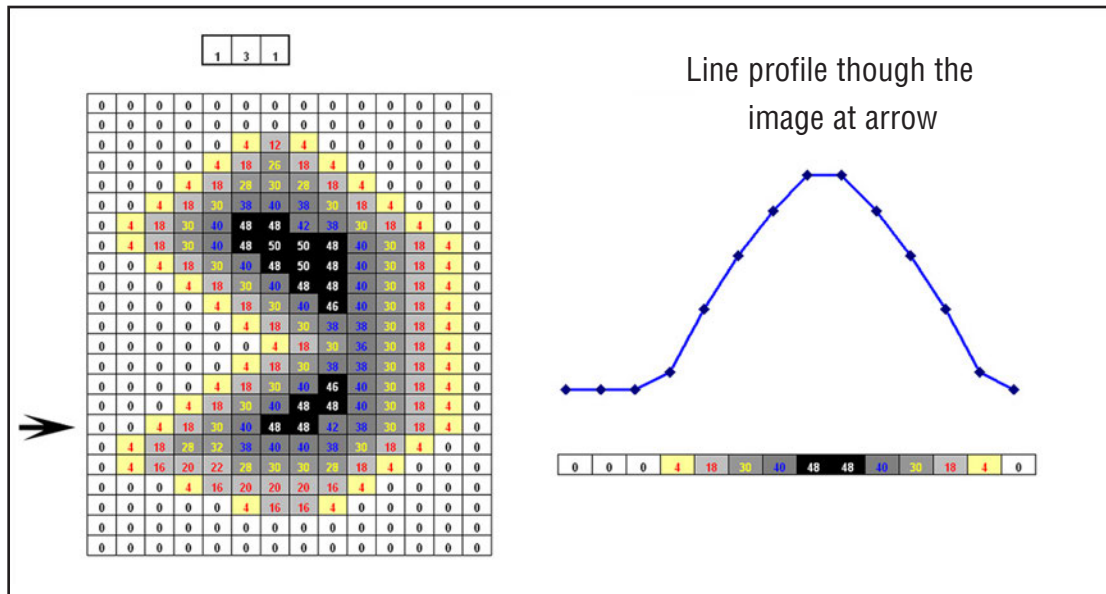


Figure 5.31: Diagram of a digital image and a line profile through that image

Same digital image shown in Figure 5.29 after being smoothed with a 1-3-1 weighted averaging smoothing. Compare the pixel values to figure 5.29. Note the edges of the line profile are more rounded. The resultant image would appear slightly blurred.

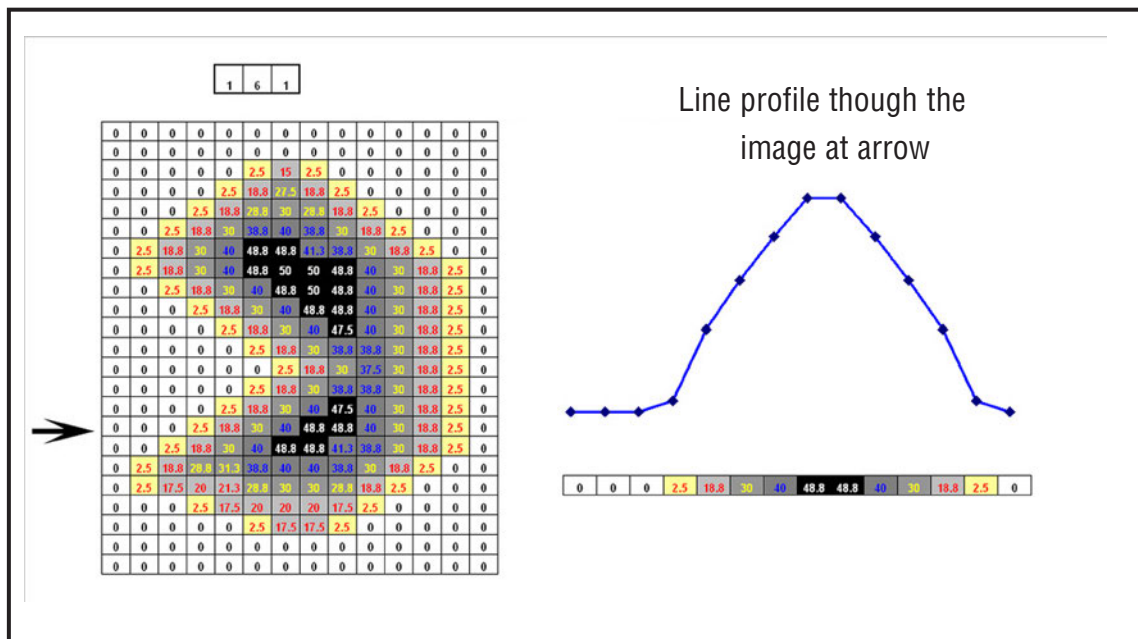


Figure 5.32: Diagram of a digital image and a line profile through that image

Same digital image shown in Figure 5.29 after being smoothed with a 1-6-1 weighted averaging smoothing. Compare the pixel values with those in Figure 5.29 and Figure 5.31. Note the values of pixels are not altered as much as with the 1-3-1 smooth. This is also visible at the edges of the line profile, which are less rounded. The higher the value in the center of the kernel, the more the image retains its original values.

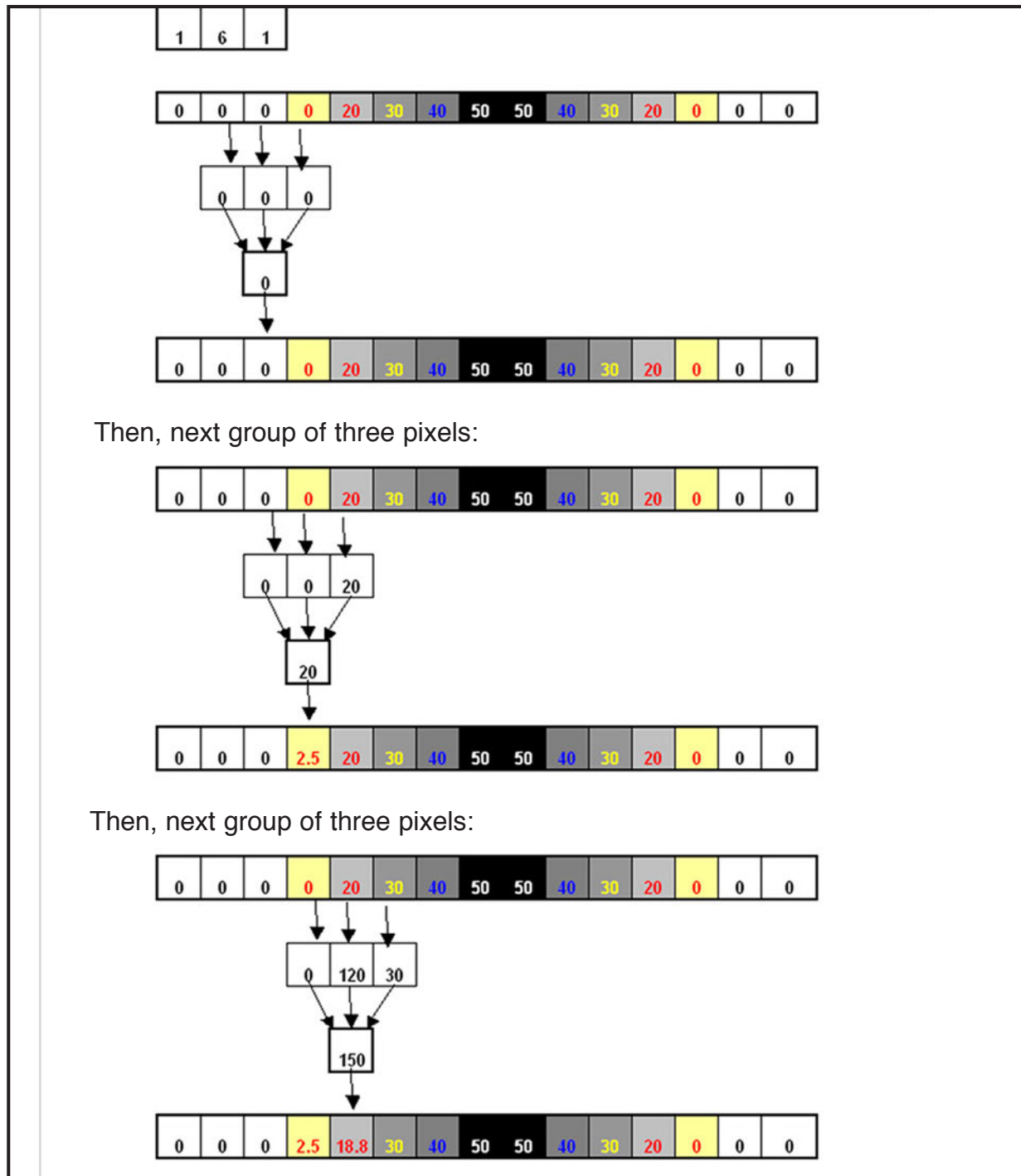


Figure 5.33: Diagram showing the process of a 1-6-1 weighted averaging smoothing

The kernel is positioned over the three adjacent pixels. The value of each image pixel under the kernel is multiplied by the value contained in the kernel. The three values are added together and divided by the sum of the kernel. This new number is then used to replace the value of the central image pixel under the kernel. The kernel is moved to the left one pixel and the process repeated over and over throughout the entire image as before (see Figure 5.32).

$$90/5 = 18$$

The kernel moves to the next cell and the process is repeated (Figures 5.30 and 5.31). The completed row after applying the 1-3-1 kernel to the entire original row would be:

0	0	0	4	18	30	40	48	48	40	30	18	4	0	0

By modifying the weight of the kernel, different degrees of smoothing can be achieved. The higher the central value of the kernel, the less the degree of smoothing because the central pixel value is given more weight in the process. If the number of the central pixel is the same as the other elements of the kernel, then the neighbors are given the same weight as the central pixel and the new value will be influenced to a greater degree by the neighboring pixels. Note the degree of blurring that is achieved by changing the central value to 6 in Figures 5.32 and 5.33.

Median Smoothing

Median smoothing is a type of image smoothing that replaces the original pixel value with the median value of the kernel. Median value kernels vary according to the number of cells in the array.

Below is an example of a three-cell median smoothing kernel. Initially, the values of the kernel have not yet been assigned. The original pixel values from the three-cells are placed into the kernel, and the median value of the three-cells is identified. The median value is then placed in the central pixel from the three cells within the row of pixel values that are being modified.

Consider the following array from the original image in Figure 5.28. The pixel value for each cell is shown, and a line profile is displaced on the right side of the image. The smoothing kernel slides over the array and is the template used to modify the pixel values at each cell by a median of it and its neighbors as shown:

0	0	0	0	20	30	40	50	50	40	30	20	0	0	0

Three-cell median smoothing kernel

0	20	30

The median of these three numbers is 20. In this case the value of the central pixel does not change. The kernel slides over the array and replaces the center pixel with the median of the array, represented by the new blue 20 (Figure 5.34).

0	0	0	0	20	30	40	50	50	40	30	20	0	0	0

Edge Detection (Pseudo Laplacian)

A pseudo Laplacian filter is used to highlight the edge of an object. The operation is the same as a weighted average smoothing operation except negative value numbers are used in the kernel. Each cell is multiplied by the value in the kernel. The numbers from the cells are added together and divided by the sum of the absolute values of the kernel. A negative value is obtained at the edge of an object, thus highlighting the edge.

-1	3	-1

Consider the same array (line profile or row of pixels) from the original liver image (Figure 5.29). The pixel values are below.

0	0	0	0	20	30	40	50	50	40	30	20	0	0	0

After applying the edge detection kernel (-1,3,-1) to the entire row, the new numbers are:

0	0	0	-4	6	6	8	12	12	8	6	6	-4	0	0

The kernel slides over the array and replaces the center pixel with the weighted average of the array as shown in Figure 5.35. Note how the numbers become negative at the edge of the object. Figure 5.36 is mock image of a right lateral view of a canine liver. A pseudo Laplacian operation was performed to create the image. There is a line profile through the image, shown to the right. Note how the line profile is negative on either side of the edge of the object.

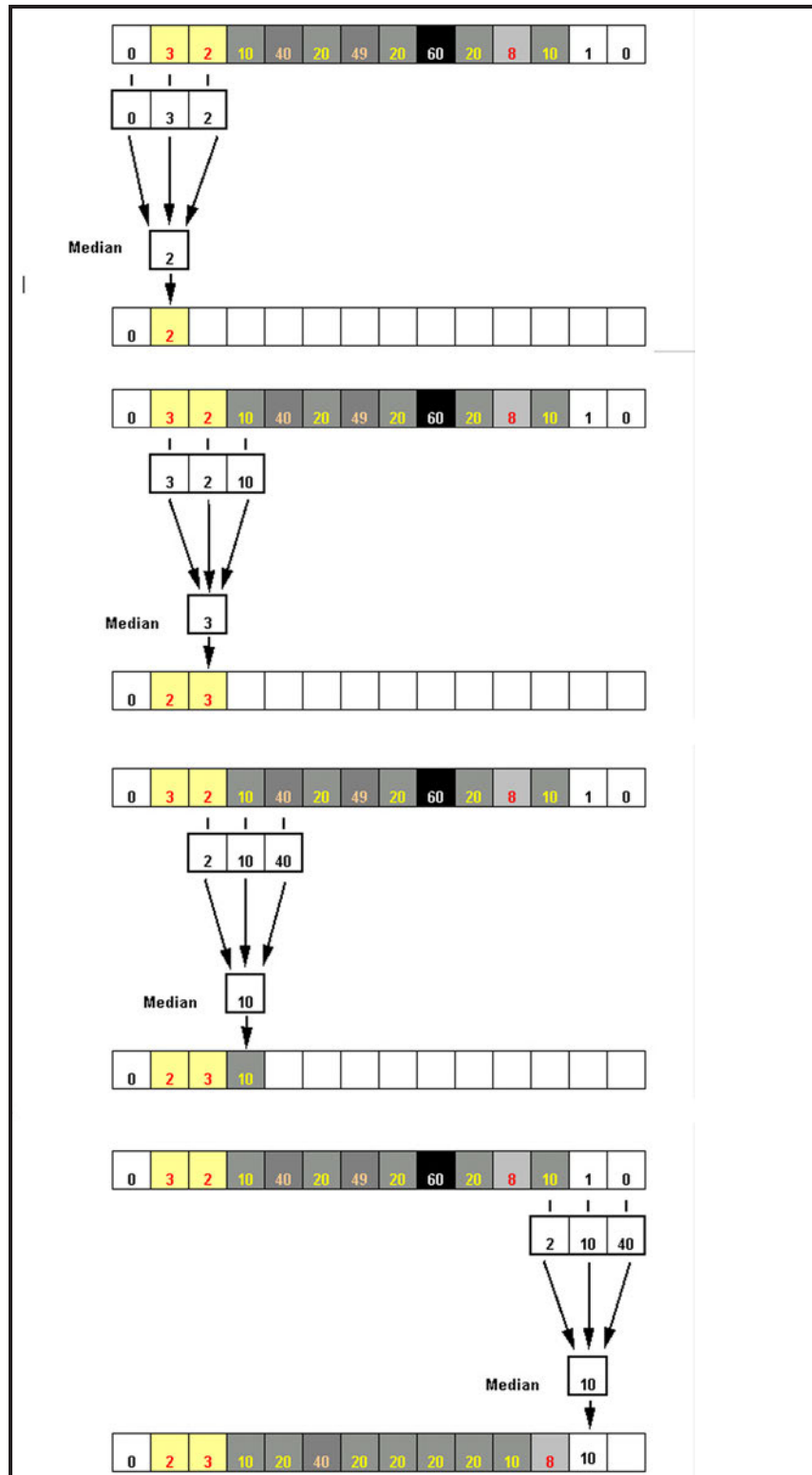


Figure 5.34: Diagram showing the process of a median smoothing

The kernel is positioned over the three adjacent pixels. The median value of the pixels under the kernel is used to replace the central image pixel. The type of filter will remove the high and low pixel values with minimal blurring of the image. This type of filter can improve the quality of a low count density image.

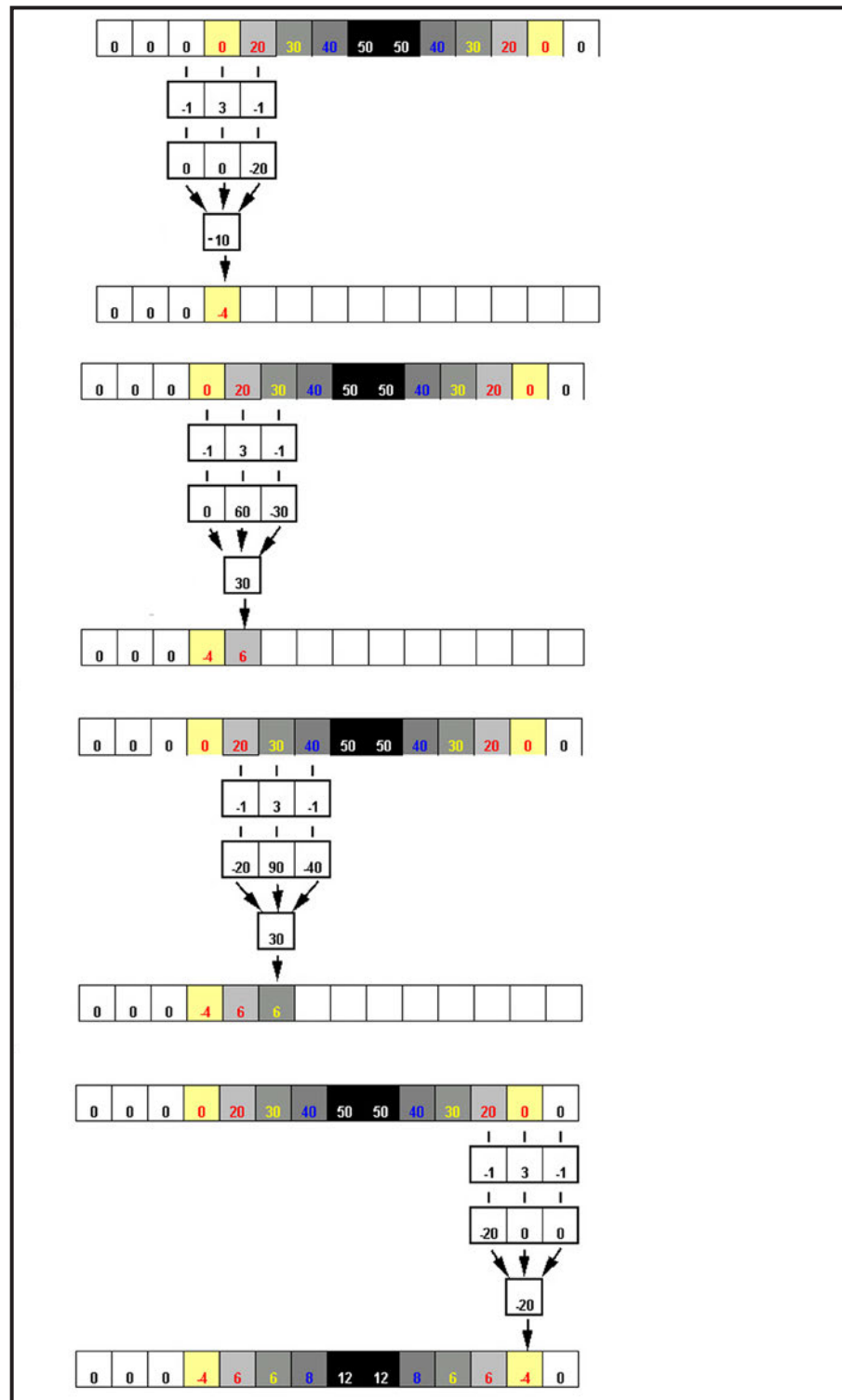


Figure 5.35 Diagram showing the process of a pseudo Laplacian filter

The kernel is positioned over the three adjacent pixels as with the weighted averaging smoothing. The kernel differs in that the central cell of the kernel has a positive number and the adjacent cells are negative. As this kernel moves across the image, a negative value is obtained at the edges of an object. This is a type of edge detection filter.

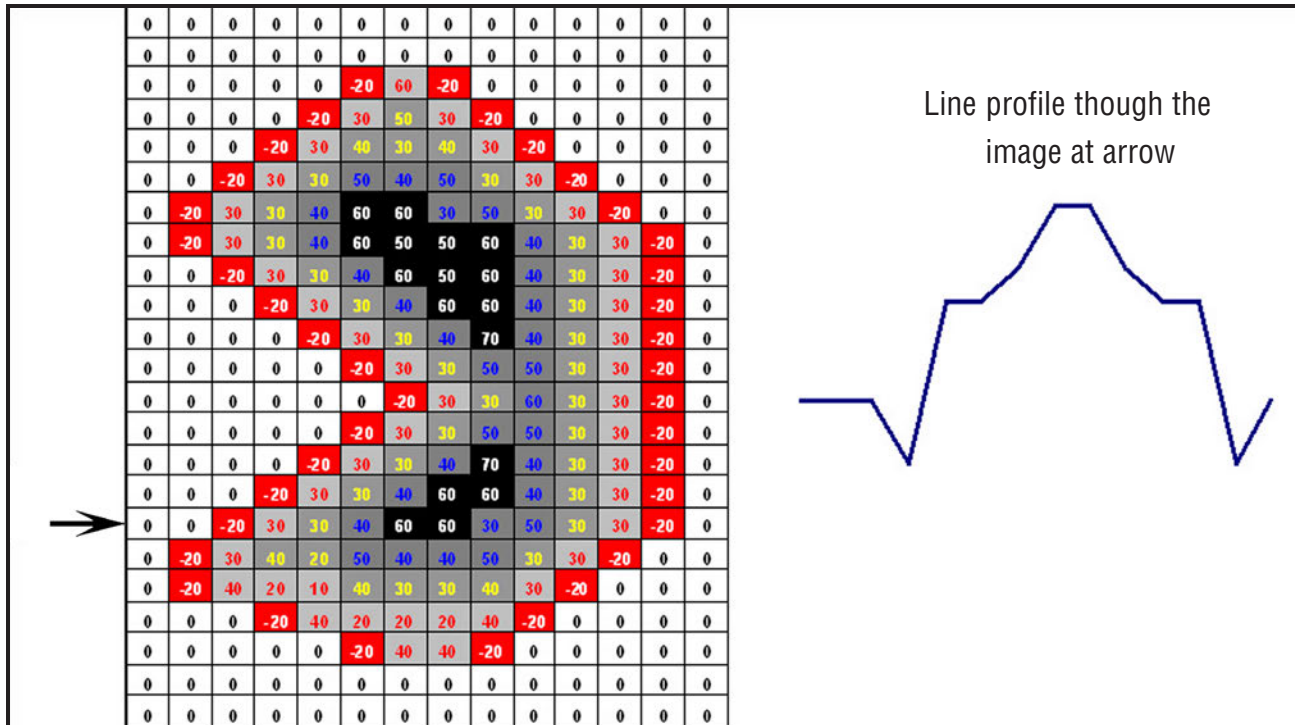


Figure 5.36: Diagram of a digital image and a line profile through that image

This is the same digital image shown in Figure 5.29 after a pseudo Laplacian filter has been applied. Compare the pixel values with Figure 5.29. Note the negative values of the pixels at the edge of the object. This is also seen on the line profile to the right.

Other Types of Filters

Filters vary in the number of cells in the kernel and the weighting assigned to each cell. Following are some examples of filtering kernels commonly used in nuclear medicine. A 1-6-1 smoothing kernel would look like:

1	6	1

A NEMA nine-point smoothing kernel would look like:

1	2	1
2	4	2
1	2	1

Temporal Filters

Temporal filters (or vertical filters) work the same as the spatial filters described above except the cells

that are averaged are the cells of the same spatial coordinates in the frames before and after the target frame. These types of filters are used in dynamic acquisition to remove the highs and lows in pixels from frame to frame.

Image Processing in the Frequency Domain

Transformations are techniques by which a complex mathematical process can be performed using simpler techniques. Consider the following example where transformations using logarithms are used to simplify a complex division problem as shown:

$$y = \frac{439.7103}{743.5421}$$

$$y = 0.591372$$

Before the days of calculators, this was a difficult

process. An alternative way to do this calculation is by using a logarithmic transformation. The log of the numerator and the denominator can be found in a table. Once the numbers are transformed into log functions, subtraction (which is easier than division) is used to determine the difference of the two numbers. An inverse log of the value provides the value of Y.

Logarithmic Transformation
 Log 439.7103 = 2.643167
 Log 734.5421 = 2.891396
 $2.643167 - 2.891396 = -0.22814$
 Inverse Log $-0.22814 = 10^{-0.22814} = 0.591371$

Image transformation uses this same principle. The images are transformed, a mathematical process is performed, and then the modified image is created by the inverse transformation (Figure 5.37).

The most common type of transformation used for image modification is called a Fourier transformation.^{2,3,12-15} An image is a two-dimensional line intensity function $f(x,y)$. Each row or column of pixels is an array of numbers that can be displayed as a line intensity profile or a line function. Each row or column of pixels can be viewed as a one-dimensional function $f(x)$ or $f(y)$.

Figure 5.37: Diagram showing the sequence of events in image processing in the frequency domain

The original image is transformed using Fourier transformation to the frequency domain. The image is modified by multiplying it by a filter. The modified transformed image is then converted back to the spatial domain by inverse transformation.

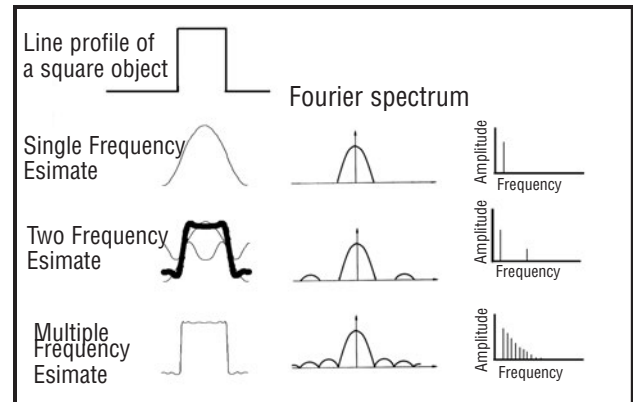
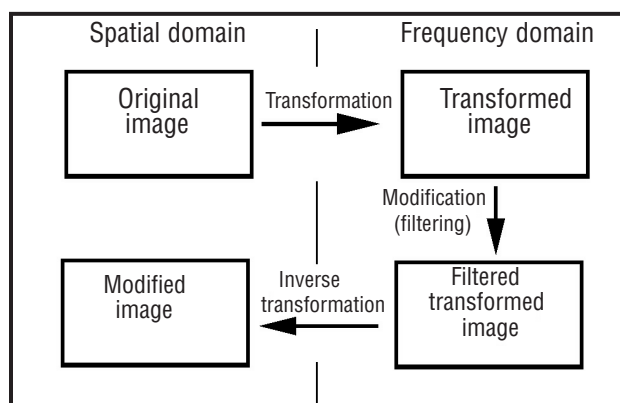


Figure 5.38: Diagram showing the process of Fourier transformation

The object being transformed is a square object being represented in one dimension by the line profile in the upper left. The shape of this line profile is first estimated by a low-frequency wave. Note the general size of the object is estimated, but the edges are not very defined. The edges become more evident by added a higher frequency wave. This process of adding more and more waves of different frequency continues until the transformation is complete. The Fourier spectrum shown in the center of the figure shows the frequency of waves used in the transformation. The low-frequency waves are near the center, and the higher frequency waves are placed peripherally in the spectrum. The amplitude and frequency of the waves used in the Fourier transformation are shown on the right side of the figure.

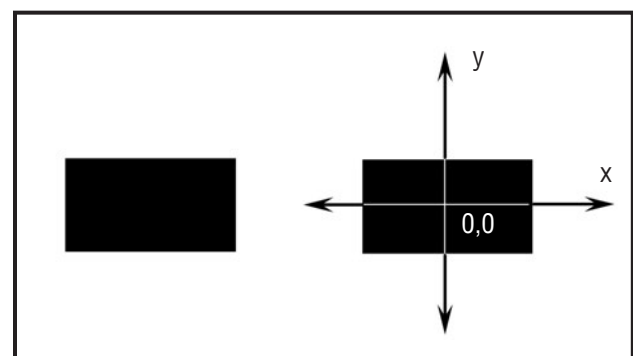


Figure 5.39: A simple image of a black box on a white background used to show the process of a two-dimensional Fourier transformation

The image to the right is the square function with the superposition of a Cartesian coordinate system.

A Fourier transformation fits the line function by a series of sine and cosine waves of different frequencies. The low-frequency waves fit the general shape of the object. By adding additional higher frequency waves, the sharper edges of the object are fitted. Figure 5.38 shows the fitting of a square function by adding waves of different frequencies. This process represents a one-dimensional Fourier transformation.

Because an image is a two-dimensional light intensity function $f(x,y)$, Fourier transformation would require a two-dimensional Fourier transformation. Figure 5.39 is a two-dimensional square function, ie, a square black box on a white background.

Figure 5.40 shows a Cartesian coordinate system overlaying the image. This is a three-dimensional representation of the lower right corner of the two-dimensional square function. The intensity or blackness of the image is shown along the z-axis. A two-dimensional Fourier transformation of the square function is performed, and the Fourier spectrum is shown to the right on the image below. Note the similarity to the Fourier spectrum of the one-dimensional square function.

The basic shape of the object is contained in the low-frequency waves toward the center (origin) of the

Fourier spectrum. The sharp edges of the image are fitted with the higher frequency waves that are further away from the center of the spectrum. The further away from the origin, the higher the frequency of the waves. Smoothing the image is accomplished by removing the high-frequency portions of the image. Remember the high-frequency waves were used to fit edges. Edge detection or enhancement can be accomplished by removing the low-frequency component of the image, thus leaving the high-frequency edges.

Filtering in the Frequency Domain

Filtering in the frequency domain is accomplished by multiplying the Fourier transformed image by a filter transform function. This is an algebraic operation performed in the frequency domain.^{2,3,12,14,15}

Low-pass Filter

A low-pass filter allows the low-frequency portion of the image to pass but removes all of the high-pass frequencies.² Figure 5.41 shows an ideal low-pass filter. The low-frequency portion is multiplied by 1, so that those frequencies pass unaltered ($1 \times n = n$), but the higher frequency portions are multiplied by 0 ($0 \times n = 0$) that removes them from the spectrum. The radius (r) of the low-pass filter function deter-

Figure 5.40: A representation of the square box shown in Figure 5.39

The processes of adding a series of sin and cos waves to approximate the shape of the object are the same as shown in Figure 5.38 except now they are being done in two-dimensions. A 2D Fourier transformation of this box yields the Fourier spectrum to the right. Note the low-frequency waves are near the origin of the spectrum, and the higher frequency waves are at the periphery of the spectrum. The higher the frequency, the further the waves are from the center of origin.

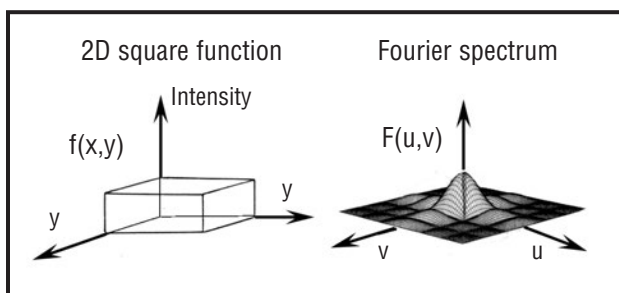
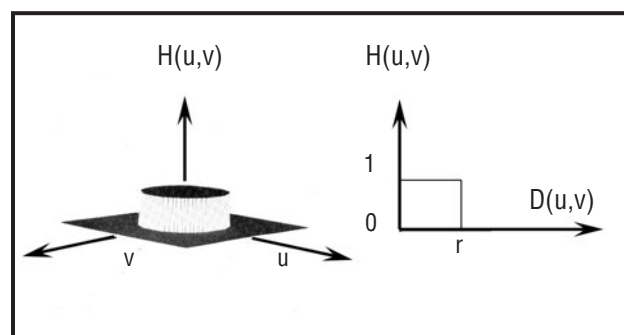


Figure 5.41: Perspective plot of an ideal low-pass filter and the filter cross section

Note the filter is composed of one of two numeric values, 1 or 0. If a transformed image is multiplied by this filter, areas multiplied by 1 retain their original value but those areas multiplied by 0 are removed. In this manner, the low-frequency portions of the image are allowed to pass but the high-frequency portions of the image are removed; thus, the name "low-pass filter." This type of filter will blur an image.



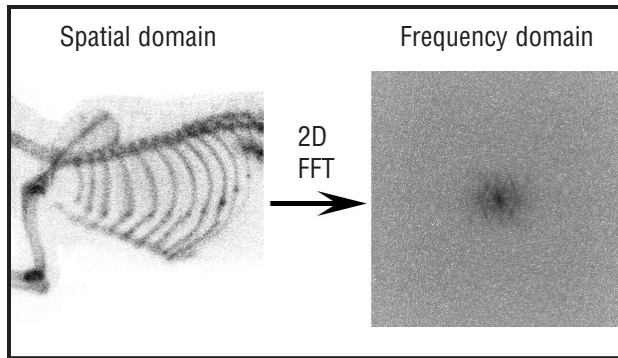


Figure 5.42: Digital image of the canine thorax seen in Figure 5.3

The image undergoes a two-dimensional Fourier transformation as outlined in Figures 5.38 and 5.40. The image to the right is the Fourier spectrum of the transformed image in the frequency domain. The low-frequency portions of the image are at the origin (center) of the spectrum, and the high-frequency portions are toward the periphery. The general shape of the spatial domain image is contained in the center of the Fourier spectrum, and the edges of spatial domain image are contained toward the periphery of the Fourier spectrum. 2D FFT = two-dimensional fast Fourier transformation.

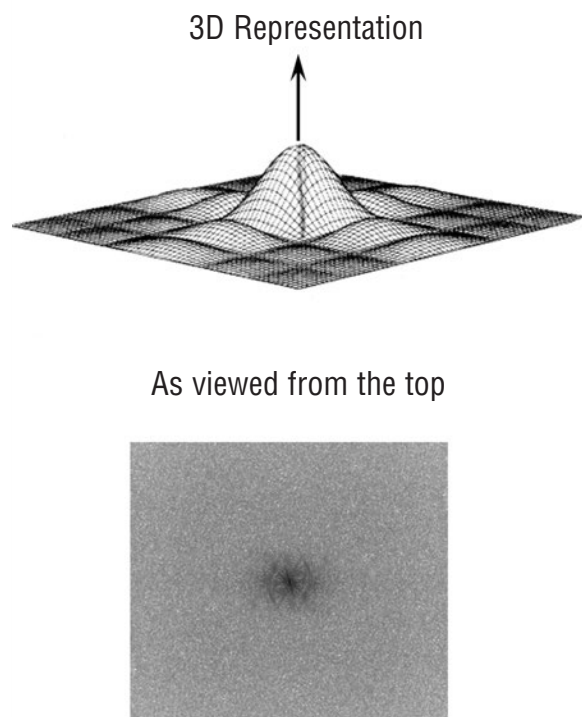


Figure 5-43: A three-dimensional wire frame plot of the Fourier spectrum in Figure 5.42

mines the cutoff frequency of the filter. The smaller the radius, the more high-frequency information is removed and the more severe smoothing (blurring) of the image will occur. A larger radius will retain more of the high frequency information and therefore there is a smaller degree of smoothing.

Figure 5.42 is a bone scan of a canine thorax. A two-dimensional Fourier transformation is performed, and the Fourier image is on the right. A theoretical surface plot of the transformed image of the canine thorax is shown in Figure 5.43. The Fourier transform of the dog thorax is multiplied by an ideal low-pass filter that retains the low-frequency information at the origin of the spectrum but removes a large segment of the high-frequency portion of the image. An inverse Fourier transform was performed to yield a smoothed image of the canine thorax (Figure 5.44).

High-pass Filter

A high-pass filter allows the high-frequency portion of the image to pass but removes all of the low frequencies.² An ideal high-pass filter transform function is shown in Figure 5.45. The high-frequency portion is multiplied by 1 so that these frequencies

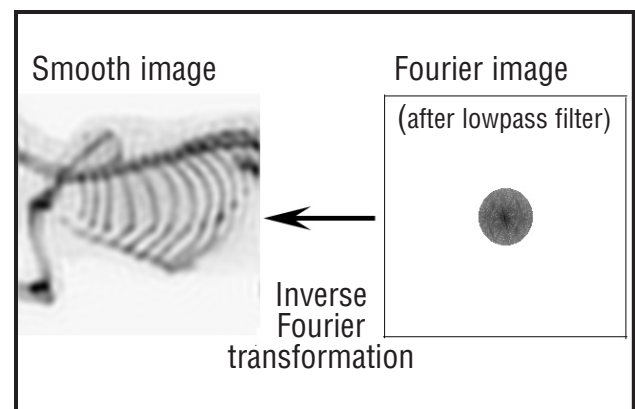


Figure 5.44 Fourier spectrum of the frequency domain image of the canine thorax in Figure 5.42 after being multiplied by an ideal low-pass filter (right image)

Note the origin or center of the Fourier spectrum is unaltered but the peripheral areas have been removed. An inverse transform is performed to return the image to the spatial domain. The resulting image retains most of its information content (low-frequency information), but the edges are removed (smoothed) slightly blurring the image.

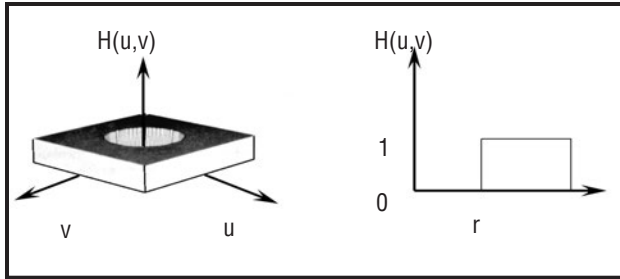


Figure 5.45: Perspective plot of an ideal high pass filter and the filter cross section

Note the filter is composed of only two numeric values, 1 or 0. If a transformed image is multiplied by this filter, areas multiplied by 1 retain their original value but those areas multiplied by 0 are removed. In this manner, the high-frequency portions of the image are allowed to pass, but the low-frequency portions of the image are removed, thus the name "high-pass filter." This type of filter would outline the edges of an image.

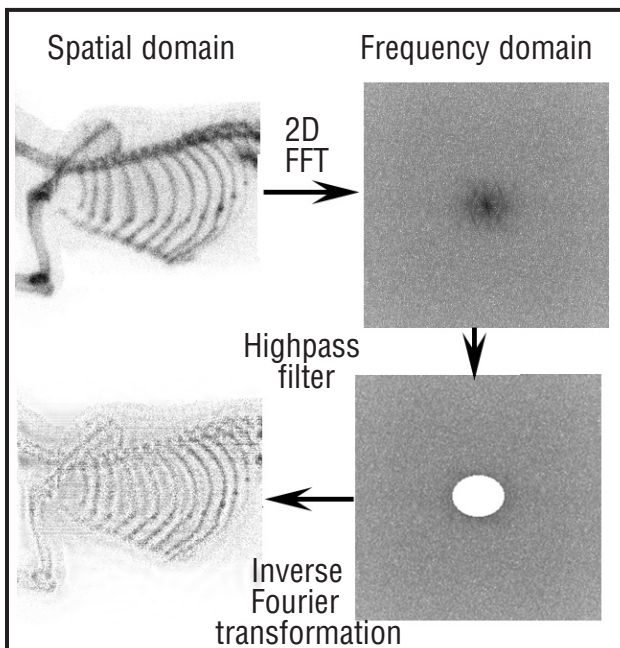


Figure 5.46 Digital image of the canine thorax seen in Figure 5.3

Fourier transformation changes the image into the frequency domain. The Fourier spectrum is multiplied by an ideal high-pass filter, which removes the low-frequency information. An inverse transformation changes the image back into the spatial domain where the margins or edges of the original image are outlined. 2D FFT = two-dimensional fast Fourier transformation.

will pass unaltered ($1 \times n = n$), but the low-frequency portions are multiplied by 0 ($0 \times n = 0$) and that removes them from the spectrum. The radius (r) of the low-pass filter function determines the cutoff frequency of the filter. The smaller the radius, the less low-frequency information is removed. A larger radius will remove more of the low-frequency information thus only highlighting the edges or margins. Figure 5.46 shows the image of the canine thorax before and after the application of a high-pass filter. Note the high-pass filter would be considered an edge enhancement algorithm.

Other Types of Fourier Transformation Filters

Ideal low-pass or high-pass filters can result in some image artifacts, such as "ringing."² Ringing is a symmetrical mottling that is superimposed over the image. It is due to the abrupt cutoff of frequencies. A more gradual cutoff will reduce this artifact. Figures 5.47, 5.48, and 5.49 show Butterworth, exponential, and trapezoid filters, respectively. Only low-pass filters will be shown but their high-pass counterparts do exist. The variables that can be adjusted are the cutoff frequency and the slope. The cutoff frequency refers to the distance from the center of the image (radius). Most filter functions are shown as the graph displaced to the right of each filter function.

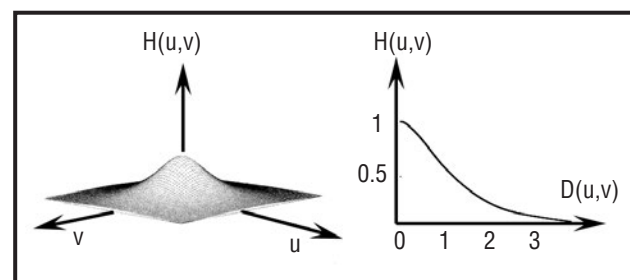


Figure 5.47: Perspective plot of a Butterworth low-pass filter and the filter cross section

Note the filter has a gradual transition from 1 to 0. If the Fourier spectrum of the transformed image is multiplied by this filter, areas multiplied by 1 retain their original value but those areas multiplied by 0 are removed. Frequencies in-between are multiplied by varying values. This type of filter is defined by N (slope of line or how fast the amplitude of the filter decreases toward 0) and the cutoff frequency (the frequency at which the amplitude of the filter is equal to 0.5). The further out the cutoff frequency is, the more the image retains its original appearance.

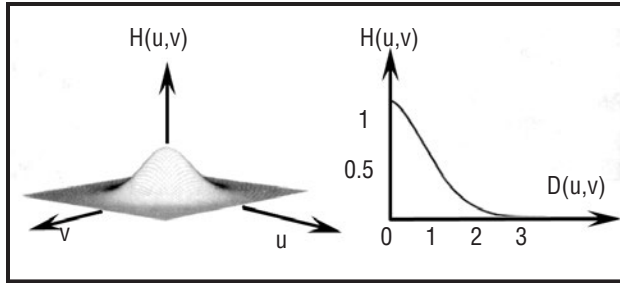


Figure 5.48 Perspective plot of an exponential low-pass filter and the filter cross section

Note the filter has an exponential transition from 1 to 0. If the Fourier spectrum of the transformed image is multiplied by this filter, areas multiplied by 1 retain their original value but those areas multiplied by 0 are removed. Frequencies in-between are multiplied by varying values. This type of filter is also defined by N (slope of line or how fast the amplitude of the filter decreases toward 0) and the cutoff frequency (the frequency at which the amplitude of the filter is equal to 0.5).

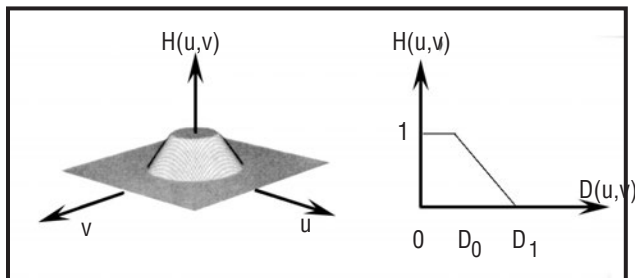


Figure 5.49 Perspective plot of a trapezoid low-pass filter and the filter cross section

Note the filter has a linear transition from 1 to 0 and has the shape of a trapezoid. It is defined by N and the cutoff frequency as described for the other low-pass filters.

Restoration Filters

Nuclear medicine images are inherently low resolution. There is blurring that is related to both extrinsic and intrinsic factors. In addition, there is considerable image noise that is due to the information content of the image (count density). Figure 5.50 is an example of an ideal image of a line source and the blurring of the image recorded by the gamma camera. The line spread function is to the left of the image and repre-

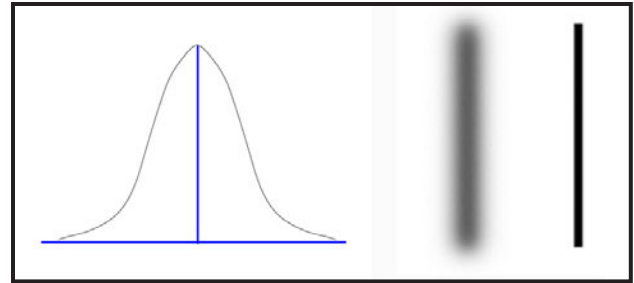


Figure 5.50 Image of a line source

The line on the far right is a representation of a discrete line source (ideal image). The image to the left is what the gamma camera records. The edges are blurred due to the resolution limitations of the gamma camera. The line profile to the right shows the blurring along the edges of the line.

sents a count profile taken through the blurred image of the line source. The Fourier transformation of the line-spread function is the modulation transfer function (MTF).^{12,15} The MTF is a quantitative index of the blurring that is inherent in the gamma camera. The MTF describes the ability to depict spatial frequencies (line pairs/cm). The MTF can be thought of as the relationship between the ideal image and the actual image recorded by the gamma camera. This MTF could be created for each gamma camera to take into account intrinsic and extrinsic features of the camera. Some computers have built-in restoration filters that take into account the typical blurring found in a gamma camera. If the modulation transfer function of the imaging system is known then a specific restoration filter can be created to correct for the blurring inherent in the gamma camera.

Part of the restoration filter is the inverse of the modulation transfer function.^{12,13,16,17} The frequency domain restoration filter combines the inverse of the modulation transfer function and a low pass filter to remove higher frequency image noise. Figure 5.51 is an example of a Metz filter. The Metz filter is a restoration filter, which combines the inverse filter and a low-pass filter. The formula for the Metz filter is:

$$M(u,v) = \frac{1}{\text{MTF}(u,v)} \times (1 - [1 - \text{MTF}(u,v)^2]^x)$$

Where x is a parameter that controls the cut off frequency to which the inverse filter is followed before

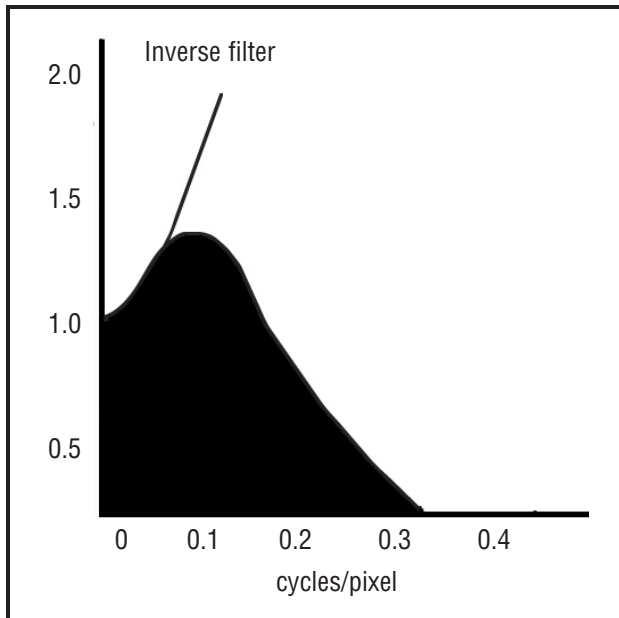


Figure 5.51: A cross section of a Metz filter

Note the values of the filter are greater than 1 in the low-frequency range. This is the restoration portion of the Metz filter and is designed to be the inverse of the MTF of the system. The other portion of the Metz filter is a low-pass filter that removes the higher frequency image noise.

the filter rolls off to suppress high-frequency noise. The first part of the equation is the restoration portion of the filter (inverse of the MTF). This portion corrects for the blurring of the image due to resolution limits of the imaging system. The second part of the filter is the smoothing portion of the filter. This is basically a low-pass filter that removes the high-frequency noise from the image. Metz filters are useful for low count density images. They improve image quality by noise reduction and contrast enhancement (Figure 5.52).

Analyzing the Nuclear Image: Processes Involved in Quantification

One of the advantages of nuclear scintigraphy is the ability to quantify the distribution of radioactivity within the body. The imaging computer can be used to quantify radioactivity within a certain region of the image. A Region of Interest (ROI) can be placed as an overlay on the image, and the computer will determine the numeric values assigned to the includ-

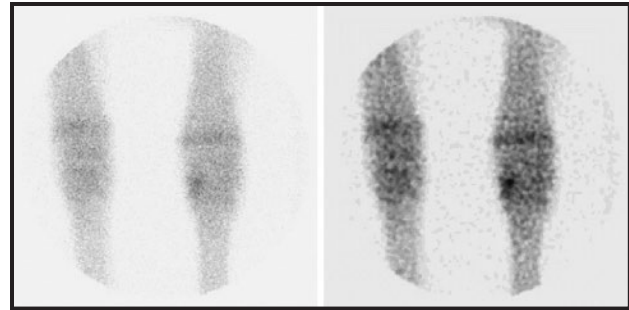


Figure 5.52: Dorsal images of equine carpi taken one hour after injection of ^{99m}Tc -HDP.

The image on the left is the original and the image on the right is after the application of a Metz filter. Note how the Metz filter increased the contrast of the lesion of the left third carpal bone.

ed pixels. There are a variety of options and shapes available for drawing ROI's. Figure 5.53 is an image of the tool bar window for the NucLear MAC imaging computer. A number of different types of ROIs can be selected prior to drawing the ROI.

Regions of Interest

Square ROI

The square ROI is selected from a tool menu bar. Typically the cursor is moved to an area of the image and the mouse button is depressed to activate the ROI. By dragging the cursor across the image, a box is created over the image. This type ROI is good for creating count ratio. This is especially true for bone imaging because the square ROI can be made to fit within the cortical margins of a long bone or vertebral body. In many cases, the ROI size can be held constant. This type ROI is not very good when the total number of counts from an organ is desired because its shape will not conform to the edges of the round or irregularly shaped organ.

Oval or Circular ROI

This type of ROI is selected from a tool menu bar. Typically, the cursor is moved to an area of the image and the mouse button is depressed to activate the ROI. By dragging the cursor across the image, an oval or circle is created over the image. This type of ROI is good for creating a count ratio. This is especially true for thyroid imaging because the oval

ROI can be made to fit over the thyroid gland or the salivary gland. Like the square ROI, the oval ROI size can be held constant or the ROI copied.

Free Form ROI

This type of ROI is selected from a tool menu bar. The cursor is moved to an area of the image and the mouse button is depressed to activate the ROI. An irregularly shaped ROI is created by either dragging the cursor around the area of interest or clicking the mouse button at each point on the edge of the area of interest. Connecting the points that have been selected creates the ROI.

Threshold ROI

Changing the threshold of detection on each side of the ROI alters the ROI around the area of interest. The threshold determines the minimal count density to be included within the ROI. Typically a box is set around the area of interest within the image field. The edge of the ROI will be contained within the box and contoured around the area of interest based on the number of counts per pixel. The threshold on each side is selected, and the edge of the ROI will form around pixels containing a greater number of counts than the threshold. Each side can be adjusted independently, and the operator can observe the change in shape of the ROI as each threshold is adjusted. This type of ROI is useful for drawing an ROI around the left ventricle during a radionuclide ventriculography analysis as shown in Figure 5.54. Because the background radioactivity along the septal wall and the dorsal edge adjacent to the left atrium is much higher than the background along the ventricular free wall, different thresholds can be

set to get the desired shape and size of the ROI. This type of ROI is also repeatable and consistent if the threshold values are known.

Isocontour ROI

This type of ROI will conform around high intensity regions of the image. Typically a box is placed over the area of interest, and the computer will map the radioactivity levels within the selected area of the image. This mapping is very similar to topographic elevation maps. If one thinks of the areas of high intensity as higher elevations, then the ROI will be placed over the peaks in the image and the size determined by the elevation level of counts.

Time Radioactivity Curves

If an ROI is applied to the images of a dynamic acquisition, a plot of counts per frame can be generated.¹⁴ Because each frame is acquired at a preset time interval, the resulting plot will have counts displayed on the y-axis and time on the x-axis (Figure 5.55). The time-activity curve graphically displays the changes in counts within the ROI over the time of

Figure 5.53: Tool palette from NucLear MAC imaging computer

Different types of ROIs can be selected from the tool palette.

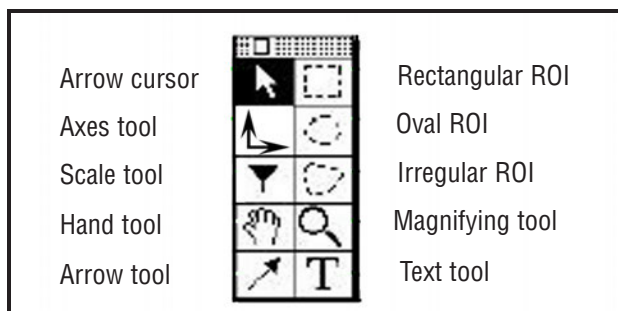
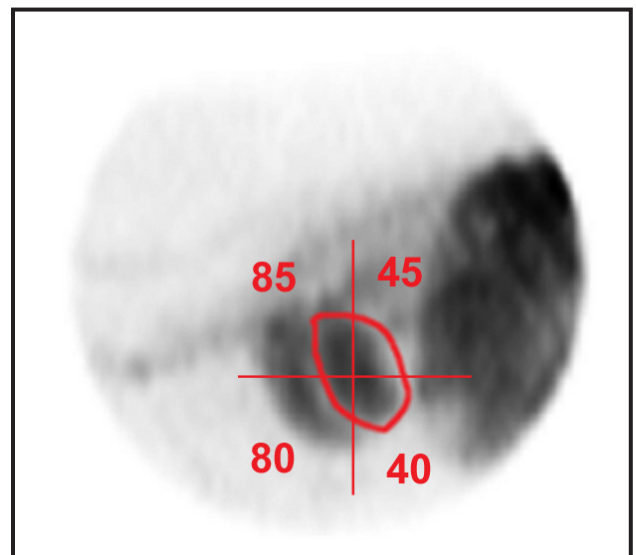


Figure 5.54: Image from a gated cardiac study showing the placement of a threshold ROI around the left ventricle in a dog

The size of the ROI is adjusted by setting the threshold for each quadrant. This is a type of semiautomated ROI. If the value for the threshold is known, then the ROI can be reset on subsequent analysis.



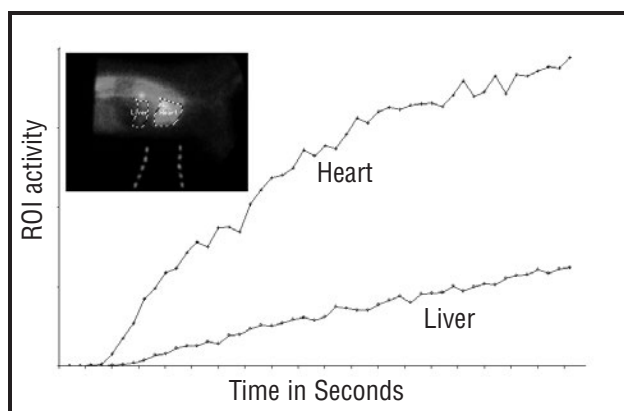


Figure 5.55: Per-rectal portal scintigraphy in a dog with a portosystemic shunt

The image in the upper left is a summed image of the dynamic acquisition. ROIs have been placed around the heart and liver. These ROIs are then applied to each frame of the dynamic acquisition and the counts from each ROI are plotted to create the time-activity curves. The y-axis represents the counts recorded from each ROI. The x-axis represents each frame of the dynamic acquisition. As the frames are acquired at specific time intervals, the values along the x-axis represent those times.

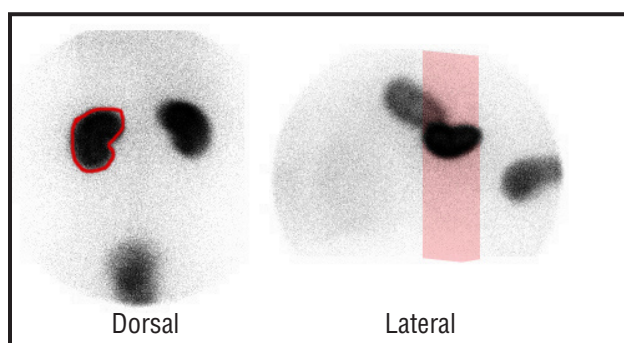


Figure 5.56: Dorsal image (left) and left lateral image (right) of a canine abdomen acquired 2 hours following injection of ^{99m}Tc DMSA

If a region of interest is placed around the left kidney on the dorsal view, the counts recorded by that ROI include the counts originating from the kidney plus the counts in the tissues dorsal and ventral to the kidney, as identified by the shaded area on the image to the left.

the dynamic acquisition. Time radioactivity curves are used in many types of analysis such as first-pass analysis, radionuclide ventriculography, renal studies, hepatobiliary scans and portal scintigraphy. Once the data is in a count versus time plot, various types of mathematical analyses, such as curve fitting, can be performed.

Background Correction

Planar nuclear medicine images are two-dimensional images of a three-dimensional object. When an ROI is placed over an organ in the image field, the radioactivity recorded includes the radioactivity within the organ plus all of the radioactivity above and below the organ¹⁴ (Figure 5.56). Background radioactivity will produce significant errors in quantification as it can account for as much as 50% of the total counts recorded in an ROI. As a general rule, if background radioactivity contributes more than 10% of the total ROI counts, then a background correction is necessary.

Some basic terms regarding background correction are as follows. Gross counts are the total numbers of counts that have not been corrected for background within a region of interest. Net counts are the total numbers of counts that have been corrected for background radioactivity within a region of interest. Background counts are the total numbers of counts that are determined to contain only background radioactivity in a region of interest, and no organs are within the ROI that might actively accumulate the radiotracer.

Methods

Perimeter Ring Background Correction

A background ROI is drawn around the target ROI. The background region is usually one or two pixels away from the target ROI. The background ROI does not have to be a ring encircling the target ROI. Other methods include drawing a semicircular or rectangular ROI on two sides of the target ROI. The mean count density of the background ROI is determined and this value is subtracted from each pixel of the target ROI using the following formula.

$$\text{Net ROI counts} = \text{Gross ROI counts}_{\text{target organ}} - \left[\left(\frac{\text{BKD counts}}{\text{No. of BKD pixels}} \right) \times \text{No. pixels in target ROI} \right]$$

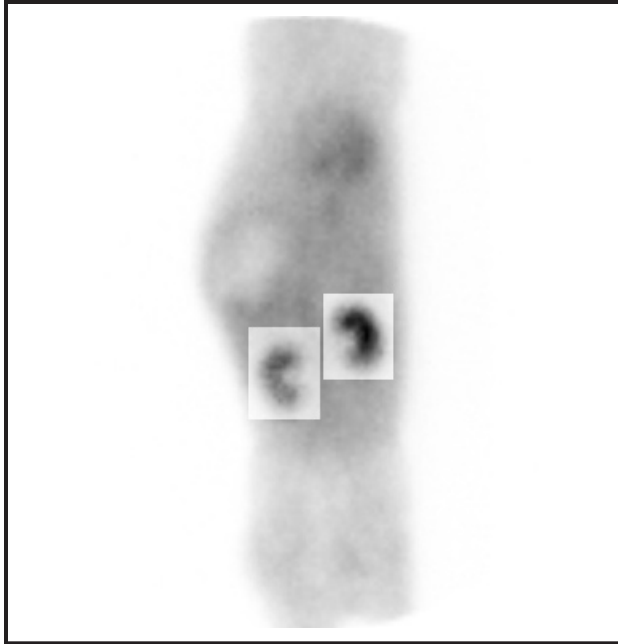


Figure 5.57: Summed dorsal image from a GFR scan in a dog

An interpolative background subtraction has been applied to both kidneys. Note the lower counts in the box around the kidneys.

Interpolative Background Subtraction

Interpolative background subtraction is helpful when the background is not uniform across the target organ. An example is a dorsal view of the canine kidney where body thickness (and, hence, background) increases from caudal to cranial. In this example, the pixels along the cranial pole have more background than the caudal pole. Sampling the ring of pixels just outside the kidney region and interpolating to the opposite side of the ring create a ramped background image. When this image is subtracted from the original, only the background subtracted kidney remains (Figure 5.57).

A third method assumes that the background counts within the ROI are those counts recorded before arrival of the radioactivity bolus. This method works well for dynamic studies, such as per-rectal portal scintigraphy.

Errors are created by improper background correction. If background is overestimated, the net counts within the region of interest will be underestimated.

Alternatively, if background is underestimated, the net counts within the region of interest will be overestimated.

Cross Talk

Cross talk represents counts that are recorded within a target ROI but originated from outside the target area. An example could be an ROI drawn over the peripheral region of the liver at the later stages of an hepatobiliary scan. The gallbladder may contain a high concentration of the radionuclide, and the bloom of this high intensity gall bladder may extend into the liver ROI. Another example would be portal scintigraphy in which radioactivity within the transverse colon extends into the liver ROI, falsely elevating the liver counts.

Percentage of the Injected Dose in an Organ

This procedure is used to quantify uptake of the radionuclide that accumulates within a target organ. To make these calculations, the dose of the radionuclide administered to the patient is converted to counts per minute. The number of counts recorded in the target organ ROI per minute must be corrected. The ROI counts must be decay-corrected to the time of injection of the radiotracer into the patient (the time the radiotracer was assayed using the dose calibrator). Second, depth correction is necessary to account for gamma rays emitted by the target organ but that are absorbed by the body tissue before the gamma rays leave the body. Finally, the counts of interest must be background-corrected to account for radioactivity recorded by the organ ROI but originating from tissues superficial or deep to the target organ ROI as previously described.

Determining the Injected Dose

To measure the administered dose accurately, the syringe is counted using a dose calibrator and/or the gamma camera prior to and immediately following injection. The difference in these values represents the dose injected into the patient. Counting the dose before and after injection is very important if the injection volume is less than 0.5 mL. A significant portion of the dose will remain in the syringe, and residual radioactivity will need to be accounted for in later calculations. Significant residual activity may also be present in the intravenous catheter. If the administered dose is counted in a dose calibra-

tor, then camera efficiency (counts/mCi) will need to be determined to convert the total mCi amount injected as recorded by the dose calibrator. If a quantity of radioactivity is low (less than 4 mCi), then the dose can be assayed by placing the syringe over the gamma camera and an image acquired so that the radioactivity (counts per minute) is recorded. If the dose is greater than 5 mCi, the photon flux will exceed the count rate limits of the gamma camera. The resultant dead-time loss causes an underestimation of the administered dose and, thereby, a falsely elevated percent dose uptake.

If doses greater than 5 mCi are used, then a radionuclide standard is prepared to determine the camera efficiency in terms of cpm/ μ Ci. The standard is prepared by placing a known quantity of radioactivity, approximately 0.5 to 2.0 mCi, of $^{99m}\text{TcO}_4^-$ into a plastic counting vial using a pipette. Alternately, an aliquot of the injected dose can be placed in a similar counting vial. The aliquot has to be recorded as a percentage of the entire injected dose. In either case, the counting vial is placed within the image field of view. An ROI is placed over the counting vial, and the counts per minute are recorded. As the quantity of radioactivity in the counting vial is known, the efficiency is determined by dividing the counts per minute recorded by the quantity of radioactivity in either μ Ci or mCi. The dose administered to the patient is then calculated by multiplying the preinjection minus the postinjection radioactivity (mCi) by the number of counts recorded per mCi in the standard.

Decay Correction

If the radioactivity within the dose is measured at the beginning of the study but the images of the target organ are obtained later, then an accounting of the radioactivity lost to decay is necessary.¹⁸ All measurements must be corrected to a specific time. For example, if the organ ROI is measured at 2 hours, then the administered dose has to be corrected for the 2 hours of decay. The formula for decay correction is as follows (standard decay equation; see examples in Chapter 1).

$$A = A_0 e^{-\lambda t}$$

Where A is the decay-corrected radioactivity, A_0 is the original radioactivity, λ is the decay constant for

the radionuclide, and t is the time interval that has passed since the original assay or A_0 was measured. The decay constant can be calculated from the radio-

$$\lambda = \ln(2)/T_{p1/2} = 0.693/T_{p1/2}$$

When using this formula, the units of time must be the same as those used for the physical half-life of the radionuclide.

Depth Correction for Soft Tissue Attenuation

Depth is defined as the distance from the skin surface to the middle of the organ of interest. The counts lost to tissue absorption are determined using the linear soft tissue attenuation coefficient (assuming soft tissue between the target organ and the camera). The soft tissue attenuation coefficient used for ^{99m}Tc is 0.153/cm. To calculate the soft tissue attenuation coefficient, a 1 mCi source of the radionuclide is placed at a fixed distance directly above an empty plastic beaker, centered over the gamma camera. A static image is acquired with the beaker empty, followed by a series of images obtained after the addition of 1 cm increments of water. A plot of cm of water versus decay-corrected counts is created. A nonlinear regression is used to fit the line using the equation:

$$Y = e^{-\lambda x}$$

Where Y is the decay-corrected counts, x is the cm of water, and λ is the attenuation coefficient for the specific radionuclide in question (0.153/cm for ^{99m}Tc). Once the attenuation coefficients for the particular radionuclide are known, then depth dose correction is performed using the following formula:

$$\text{Depth corrected organ counts} = \frac{\text{Organ ROI counts}}{e^{-\lambda x}}$$

Where λ is the soft tissue attenuation coefficient for the particular radionuclide and x is the organ depth in cm. Now it is possible to calculate the percent dose (%ID) uptake by the organ. This is determined by the following formula:

$$\%ID \text{ uptake} = \frac{\text{Corrected cts (target organ/cpm)}}{\text{Radionuclide dose (cpm)}} \times 100$$

Summary

Gamma camera images lend themselves to ease of manipulation via a number of mathematical operations in both the spatial and frequency domains. It is important for the clinician to know which of the operations will alter the interpretation in a negative fashion, thereby resulting in the potential for misdiagnosis. The digital image can be manipulated so that different filters can be applied to enhance target organ visualization. It should be remembered that the filter operations result in count information within the image data set that is no longer valid for quantification. A thorough understanding of the basic imaging filters and Fourier transformation image manipulations is critical to understanding SPE[C]T and PET reconstruction algorithms. The use of regions of interest when applied to dynamic data sets can generate time-radioactivity curves that can provide quantitative, physiologic information about an organ of interest. This quantification is at the heart of nuclear medicine and will be explored in detail in the applicable chapters of this text.

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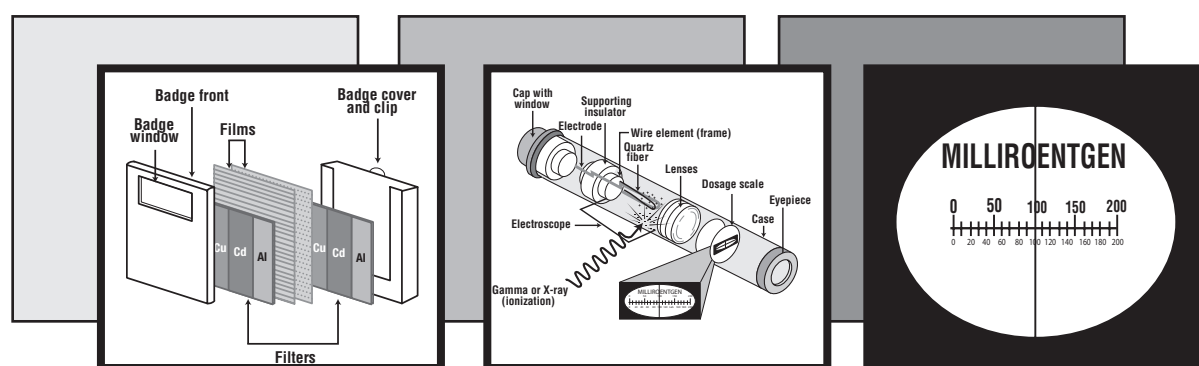
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Radiation Safety, Personnel Radiation Monitoring, and Licensing Issues

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Introduction

Radiation safety and concerns for personnel safety are of the utmost importance when handling radioactive materials. Radioactive contamination is the most common problem that the veterinarian will have to deal with regarding the handling of radioactive patients and their excreta. Other concerns include the potential for client exposure from pets undergoing continued radioactive decay while at home. Certain radioactive materials will be excreted in the urine and can result in contamination of the environment and personnel involved in the handling of the patient.

Measurement of Radiation

The radiation exposure is defined by the intensity of ionizing radiation that passes through a specific volume of air at a standard temperature and pressure. Exposure is measured in roentgens (R), where 1 R is equal to 2.58×10^{-4} coulombs charge/kg of air. The radiation dose can be described by the exposure in air, but that does not describe the absorbed dose in tissue. Various types of electromagnetic and particulate radiation interact with tissues differently and result in different absorbed doses. The previous unit for the radiation absorbed dose was the rad. One rad is equal to 1 erg of energy deposited within one gram of tissue. For X-rays and gamma rays the rad is equivalent to the Roentgen. The rad has been replaced by the gray (Gy) and one gray is equal to 100 rads, (1 cGy = 1 rad). A quality factor has been determined to account for the differences between particulate and electromagnetic radiation and the linear energy transfer (LET) within soft tissues. The LET is the energy deposited per track length of tissue with the units being keV/ μ m. X-rays, gamma rays and beta particles have been assigned a quality factor (QF) of 1, whereas alpha particles have a QF of 20 (protons and neutrons, depending on speed, have QF between 5 and 10). The old unit of dose equivalent is the rem (roentgen equivalent in man), where the rem = rad $\times$ QF. The current SI unit is the Sievert (Sv) = gray $\times$ QF. One Sv = 100 rems, and 1 rem = 0.01 or 1 rem = 1 mSv, and 1 mrem = 0.01 mSv.

Radiation protection in nuclear medicine is based on the ALARA principle (As Low As Reasonably Achievable). Time, distance, and shielding are all part of radiation protection for nuclear medicine personnel. One should minimize time in the pres-

ence of the nuclear medicine patient as much as reasonably achievable. One should maximize the distance (inverse square law) from the nuclear medicine source (patient) and use appropriate shielding for the radiopharmacy, shielding the syringe, etc., as appropriate when injecting patients. Lead syringe casings are available for injection of radionuclides. Lead “blankets” over a horse’s body during a bone scan while imaging the distal limbs, head, and neck will reduce exposure for personnel performing the study. Within the US, the average dose is 3.50 mSv (350 mrem) per year from natural background radiation sources (80% being radon related) and technology-based radiation (approximately 18%, with a majority of the exposure being due to medical and consumer products).

The primary US government overseeing body is the Nuclear Regulatory Commission (NRC). The NRC regulates all special nuclear material (plutonium and uranium) and by-product materials of nuclear fission. Other nuclear medicine products that are cyclotron-produced are not subject to regulations of the NRC. States that are called “agreement” states act in place of the NRC along with all radiation sources, including cyclotron-produced radionuclides. Regulations set by agreement states have to be at least as strict as the NRC, but those states have the ability to set more stringent regulations. The common regulatory programs between agreement states and the NRC include the following: workers must be informed of their rights and responsibilities, including inherent risks in handling radiation sources and the responsibility of all workers to follow the safety protocols established within Title 10 of the Code of Federal Regulations (CFR). The primary parts that impact the practicing veterinarian when using radionuclides include Part 20 (“Standards for Protection Against Radiation”) and Part 35 (“Medical Use of By-Product Material”). The FDA regulates the development, manufacturing, and safety issues related to radiopharmaceuticals. The US Department of Transportation regulates the transportation of radioactive materials. The maximal permissible dose equivalent limits for NRC requirements are listed in Table 6.1.

Personnel Dosimetry

The ideal personnel dosimeter should be able to record a response independent of the radiation energy and independent of the geometry of the dosimeter

relative to the radiation source. The ideal dosimeter should have a wide range of sensitivities (1 mrem to 1,000 rem) and should respond only to ionizing radiation. The ideal dosimeter should be able to distinguish alpha, beta, gamma, and neutron radiations and should be able to be analyzed immediately and provide a permanent record. The dosimeter should be physically light, small, rugged, easy to use, and inexpensive. There are no ideal dosimeters, but there are different types of dosimeters that will provide the necessary information depending on the situation with which one is involved.

Film badges used to be the most common type of monthly recording system for occupational workers dealing with radiation (Figure 6.1). The film emulsion has silver halide crystals (AgBr) that become exposed during the course of the month. There are three filters that are applied to the film badge; typically an open area is also present. The open area allows detection of every form of radiation except alpha and weak betas. The copper ($Z = 29$) will detect high energy betas and hard X-rays and gamma radiation. The cadmium ($Z = 48$) will allow for detection of high-energy x-rays and gamma radiation. The aluminum ($Z = 13$) will allow for the detection of X-rays and beta and gamma radiation. After the film has been processed, it is read using a densitometer so that

the amount of film darkening is proportional to the radiation exposure. The advantages of film badges are that they are sensitive to a wide range of dosages (10 mrad to 1,500 rad gamma and X-ray and 50 mrad to 1,000 rad beta). Also, the badge distinguishes between penetrating and nonpenetrating radiations, provides a permanent record, and is practical (small, lightweight, and inexpensive). The disadvantages include an energy-dependent response, some degree of geometric dependence, cannot be read immediately, and influence by environmental factors (heat and humidity). Other problems include personnel not wearing the film badge, leaving the film badge in the radiation field, or losing the film badge altogether.

Luxel and other companies have recently introduced newer body dosimeters that use optically stimulated luminescence (OSL) technology. The OSL detector is a thin strip of specifically formulated aluminum oxide (Al_2O_3) crystalline material. The detector absorbs radiation and stores the energy within the crystalline matrix. The amount of radiation exposure to the dosimeter is determined by stimulating the Al_2O_3 strip to selected frequencies of laser light. The light will cause the Al_2O_3 to luminesce with the amount of luminescence being proportional to the radiation exposure. The dosimeters give accurate reading to 1 mrem. The advantages of these dosim-

Table 6.1: Maximal Permissible Occupational and Nonoccupational Dose Equivalent Limits

Limits	Maximum Permissible Annual Dose Limits	
	mSv	Rem
Occupational		
Total effective dose equivalent	50	5
Total dose to any organ (except lens)	500	50
Dose equivalent to lens	150	15
Dose equivalent to skin/extremity	500	50
Dose to fetus/embryo	5 in 9 mo.	0.5 in 9 mo.
Nonoccupational		
Individual members of public	1/yr	0.1/yr
Unrestricted area	0.02/hr	0.002/hr

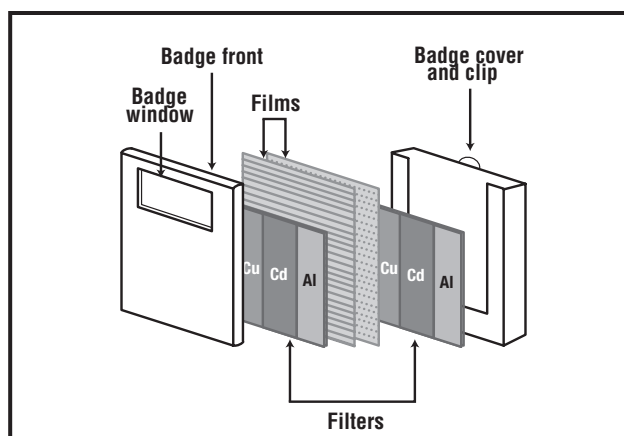


Figure 6.1: Component parts of radiation-sensitive film badge

eters is that they can be used up to 1 year prior to analysis; they are unaffected by heat, moisture, and pressure as long as the water and lighttight blister packaging is uncompromised.

The pocket ionization chamber (or pocket dosimeter) is based on a gas-filled ionization chamber where a wire element will change position on a scale as radiation ionizations occur within the chamber (Figure 6.2). The advantage is that the dosimeter can be read immediately, is reusable, is practical, and has a wide exposure range (0 to 200 mR and 0 to 500 R). The disadvantages include that particulate radiation cannot be detected, nor can low-energy photons (<20 keV) be detected and they may discharge when bumped or dropped providing a full-scale reading. Also, a permanent record is not available.

Thermoluminescent dosimeters (TLDs) are based on a lithium fluoride (LiF) crystal typically housed within a ring. As the incoming radiation interacts with the LiF atoms, the electrons move from their valence band into a conduction band that serves as a metastable electron trap. The LiF chip or crystal is then heated, and the electron moves from the electron trap back to the valence band and gives off blue light (400 nm). The amount of light given off is proportional to the amount of radiation received. The advantages include that there is a very wide dose range (<1 mR to 10^5 R). The LiF is equivalent to soft tissue, is reusable, and is practical. The disadvantages include that the LiF cannot be analyzed immediately, and no permanent record and environmental effects can influence previously recorded exposure

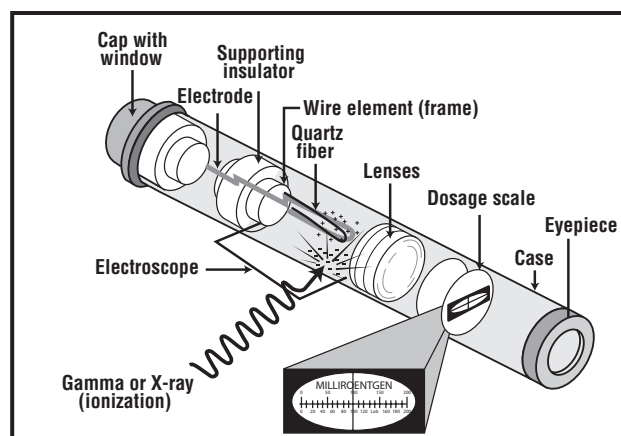


Figure 6.2: Schematic of a pocket dosimeter

The pocket dosimeter is an ionization chamber where an instantaneous reading can be made.

(humidity and heat will cause electrons to move into higher energy conduction band and into the electron trap). The LiF dosimeter is also more expensive than a film badge.

General Guidelines for Nuclear Medicine Patients

At a minimum, certain standards should be established for each individual laboratory. These should be consistent and uniform across all licenses. Basic standards, include no eating or drinking in the nuclear medicine area (radiopharmacy and active imaging area). All personnel should wear dosimetry badges and thermoluminescent dosimeters (TLD) in the form of finger rings (with the TLD part of the ring pointing toward the palm of the hand). Latex rubber gloves should be worn at all times when handling radionuclides or patients that have been injected with radionuclides. All radioactive materials that are carried in syringes for injection into a patient should be placed in leaded syringe shields. If the dose needs to be transported to another part of the hospital for injection, then the leaded shield and syringe with the radioactivity should be placed in a leaded box or container to minimize personnel exposure prior to injection. After injection of the radionuclide, the patient should be monitored using a Geiger-Müller (GM) survey meter for instantaneous dose readings at the surface of the patient (highest amount of radioactivity would be in the region of the heart for

radiotracers that do not localize to the target organ rapidly) and a second reading at 1 meter. These measurements should be recorded, and a radiation sign with this information and the type and amount of radioactivity injected should be posted on the patient's cage or stall door.

The amount of restriction placed on an individual licensee is determined by the state and the nuclear regulatory agency at the time of evaluation and establishment of the original nuclear medicine license. The factors that are necessary to take into consideration include: the radionuclide used, the type of study done, the time the patient is expected to be within the hospital after the procedure and the possible routes of excretion/contamination, release criteria for the patient, and possible public (client) exposure after the procedure. Each license determines the specific radionuclide for which the individual is licensed and the total radioactivity of that particular radionuclide that the licensee is limited to having on the premises at any given time.

The areas of controversy between individual licensees and state regulatory agencies include the release criteria for the patient and the specifics regarding the handling of the patient after the nuclear medicine study has been done. Most release criteria are determined by monitoring a patient at a specific distance with a GM survey meter. Variations include less

than 2 mR/hour at 1 foot to less than 5 mR/hour at 1 meter.

Example Licenses

At the College of Veterinary Medicine University of Tennessee, all animals are required to stay in the clinic the night following a nuclear medicine imaging procedure. An animal can usually be released to its owner the following day. At that time, animals are usually less than 0.2 mR/hour at 1 meter. All blood and urine samples should be taken before the animal is injected with the radiopharmaceutical.

A radiation safety sign must be attached to the cage or run of an animal that has been injected with a radiopharmaceutical. This sign is to remain with the animal until it is releasable. In addition to the radiation safety sign, a physical record of the radiopharmaceutical, physical half-life, physical form (liquid), and immediate postmonitoring of the patient (at the surface and 1 meter) must be posted at the animal's cage.

As most radiopharmaceuticals are excreted via the urinary tract, care should be taken to prevent this urine from contacting personnel. Gloves should be worn when changing urine-soaked papers. The papers and gloves should be placed in a separate bag and attached to the front of the cage. The fol-

Figure 6.3: Sign for cage of nuclear medicine patient during hospitalization

THIS ANIMAL HAS BEEN INJECTED WITH A RADIONUCLIDE (^{99m}Tc). CONTACT WITH THIS ANIMAL SHOULD BE KEPT TO A MINIMUM. THIS SIGN MUST BE KEPT WITH THE ANIMAL UNTIL REMOVED BY NUCLEAR MEDICINE PERSONNEL (USUALLY WITHIN 24 HOURS). URINE AND FECES MUST BE CONSIDERED RADIOACTIVE. BLOOD OR URINE SAMPLES SHOULD NOT BE COLLECTED FOR ANALYSIS UNTIL SIGNS ARE REMOVED. DISPOSABLE GLOVES MUST BE WORN WHEN CHANGING SOILED PAPERS OR WHEN HANDLING THE ANIMAL BECAUSE OF THE POTENTIAL OF URINE OR FECAL CONTAMINATION OF THE SKIN. PLACE THE SOILED PAPERS AND USED GLOVES IN A PLASTIC BAG AND ATTACH TO THE FRONT OF THE CAGE. THEY WILL BE COLLECTED THE FOLLOWING DAY. THE AMOUNT OF RADIATION IN THIS ANIMAL IS SMALL BUT CARE MUST BE TAKEN TO PREVENT CONTAMINATION OF PERSONNEL. IF YOU HAVE ANY QUESTIONS OR IN CASES OF SUSPECTED PERSONNEL CONTAMINATION, CONTACT THE RADIOLOGIST ON DUTY.

IF THE ANIMAL DIES, OR IS EUTHANIZED BEFORE THIS SIGN IS REMOVED, PLACE THE ANIMAL IN THE APPROPRIATE COOLER. ATTACH THE RADIATION SIGN AND A HOLD SIGN ON THE BAG, THEN CONTACT NUCLEAR MEDICINE PERSONNEL. ONCE THE PATIENT IS NO LONGER RADIOACTIVE, APPROPRIATE DISPOSAL OR NECROPSY CAN BE PERFORMED.

lowing day, the animal will be monitored and the waste material collected. If possible, it is suggested to keep these animals in runs or at least place them on a grate following a scan and thereby avoid these problems. If an animal is in intensive care or another location where personnel or students will have prolonged contact with it, a lead drape should be placed in front of the cage. If the animal dies before the radiation safety sign has been removed, then it should be placed in a cooler with the radiation safety sign attached to the bag. A stick on radiation sign should be placed on the body bag with this record: radiopharmaceutical given (ie, ^{99m}Tc -MDP), exposure level (actual mrem/hour at 1 m), and the time of reading.

An example of the sign that is attached to each cage or stall of a nuclear medicine patient is shown in Figure 6.3.

Release Criteria From the Society of Veterinary Nuclear Medicine

In 1989, the Society of Veterinary Nuclear Medicine was asked by the American College of Veterinary Radiology (ACVR) membership at large to come up with a standard for generic release criteria for veterinary patients. The attempt was to provide ACVR members with a guideline that could be used in requesting specific licensing with their regulatory state agencies. As the Society of Veterinary Nuclear Medicine has no regulatory powers, these release criteria are only suggested guidelines for radionuclide users relative to the use of scintigraphy in veterinary patients. The radionuclide user is obligated to conform to the regulations set by his/her respective state radiation safety division regarding the handling of radioactive materials and veterinary patients following injection with radioactive materials used for scintigraphic imaging.

Administration of Radioactive Materials

Radioactive materials may be administered in the form of liquids, gases, or aerosols for therapeutic or diagnostic purposes at a dose rate based on body weight similar to that used in human nuclear medicine. The individuals need to be trained and certified in safe health physics practices and under the direct supervision of a principle investigator with an active radiation-use license.

Confinement of Radioactive Patients

Following administration of radioactive material, patients must be housed in a designated area that can contain and/or facilitate disposal of contaminated material and has the appropriate radiation area notifications and controlled access.

The maximum exposure rate at 1 meter shall be determined immediately after administration of radioactive material. This exposure rate will be measured at a distance of 1 meter from the approximate center of the target organ(s) and shall be entered on the patient's chart. When redistribution or significant excretion of the radionuclide is anticipated, the exposure rate should be remeasured and recorded at appropriate intervals.

Exposure rate is the basis for determination of the length of time that an attendant clinician or student may spend near the patient. Clients cannot be allowed to visit patients during the period of confinement.

Contaminated excreta should be disposed through the sanitary sewer system or held for regular disposal after decay to background level.

Release of Patients to Owners and Clinical Wards

Patients may be released when all of the following criteria have been met:

- The total integrated dose that could be accumulated by any individual in close association (1 meter) with the patient for an infinite period of time is less than 100 mR. The exposure rate that will result in total accumulated dose exposures less than 100 mR can be calculated using the formula:

$$\text{Exposure rate} = 100 \text{ mR} \div [1.44 \times T_{p1/2}] \text{ or the current NCRP recommended level of exposure}$$

For the purpose of this calculation, the physical half-life of the radionuclide should be used except in those instances when the biologic half-life for the radiopharmaceutical is well established in the species of animal concerned and is very much shorter than the physical half-life.

- A minimum confinement period based on the half-life of the administered radionuclide has been satisfied. Minimum periods will be sufficient to allow at least one half-life period to occur before release and allow for excretion of radioactive urine and feces for those radiophar-

maceuticals with a significant rate of secretion. The confinement periods for most radionuclides shall be as follows:

T_{phy} Half-life	Minimum Confinement Period
<12 hr	1 physical half-life
12-24 hr	24 hr
>24 hr	48 hr

- c. The owner or agent of the patient shall be provided a detailed written document explaining the hazards and precautions relative to his/her stewardship of the patient during the period of potential exposure and environmental contamination (10 physical half-lives) if the radionuclide is of potential harm to the owner (eg: I131 therapy).

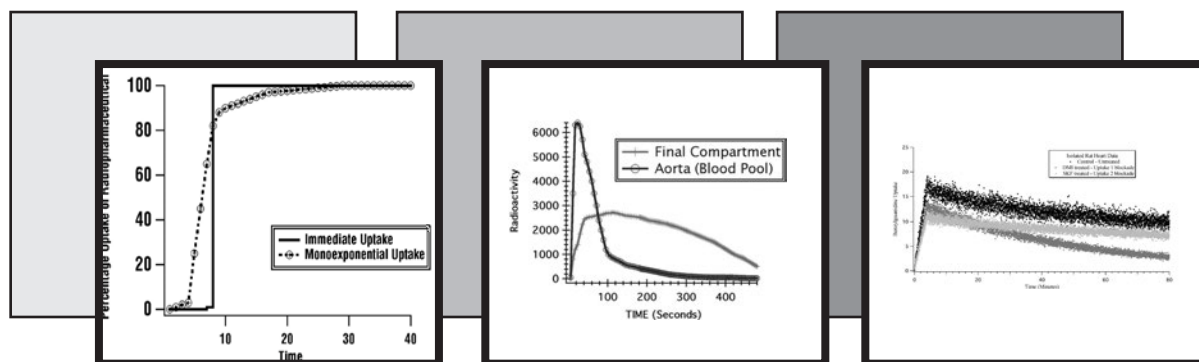
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Principles of Image Interpretation, Nuclear Medicine Counting Statistics, and an Introduction to Kinetic Modeling

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Introduction

In this chapter, the basic principles of image interpretation for nuclear medicine studies are reviewed. Counting statistics will be discussed, as nuclear medicine studies are count limited and dependent upon the Poisson statistical process of radioactive decay. Because of this, it is important to recognize abnormalities that are true abnormalities and not simply statistical noise. Finally, there is a basic introduction and review of kinetic models. This introduction should only serve as a stepping-stone for further study of radiotracers in biologic models.

Principles of Image Interpretation

The basic principles of image interpretation are dependent on the type of nuclear medicine study that the clinician is performing. The basis for interpretation is dependent on the investigator having a thorough understanding of acquisition protocols for the study, the mechanisms of localization, the knowledge of the normal appearance of the static or dynamic images related to the study, and how various disease processes will impact the radiopharmaceutical uptake and/or clearance.

Standard practice should include routine quality assurance and control programs to ensure that accurate information is obtained during acquisition and the gamma camera system is meeting or exceeding NEMA quality control specifications. This is particularly true when quantitative studies are to be done (see Chapter 4). This quality control should include the appropriate uniformity for a given study. For example, SPE[C]T studies require camera uniformities of less than 4%. Additionally, the camera should be peaked to the photopeak of the specific radionuclide being imaged. The correct collimator should be selected based on the radionuclide and the type of acquisition (high-resolution collimators are more suitable for static imaging, whereas low-energy, all-purpose, or high-sensitivity collimators are more appropriate for dynamic imaging where count sensitivity is more important than image resolution). The correct acquisition parameters should be confirmed prior to the start of a study, particularly if a long dynamic imaging sequence is going to be acquired. All aspects of the study should be reviewed starting to ensure that the patient is properly posi-

tioned, injection apparatus is in order (flush material, three-way stopcock, etc), and the correct radiopharmaceutical is being used. Because of the biologic and physical half-life of the radiotracer, if nuclear medicine studies were improperly performed, then one may be required a 24-hour or longer wait prior to re-attempting the study. For ^{99m}Tc , this requires 2 days, although a dynamic study where the initial frame is subtracted from the rest of the study could be attempted as long as the patient does not move. Studies that are based on static images are forgiving in that the radiopharmaceutical is stable in its biodistribution, and the image can be repeated.

If the study is of poor quality, the radiopharmaceutical should be tested for radiochemical impurities. Common radiochemical impurities include free pertechnetate as well as reduced colloidal $^{99m}\text{TcO}_2$. If there is excessive $^{99m}\text{TcO}_4^-$, then uptake in the thyroid, salivary glands, and gastric mucosa would be expected. If $^{99m}\text{TcO}_2$ were present as a radiochemical impurity, hepatic uptake in the dog and pulmonary uptake in the cat would be seen, as the $^{99m}\text{TcO}_2$ (macrophage uptake of the colloid).

Before evaluating the nuclear medicine study in question, one should determine whether or not the study is adequate for interpretation. Just as positioning and technique are critical factors for the routine evaluation of radiographs, positioning and technical aspects of the nuclear medicine study need to be considered. The clinician must decide if the study is of diagnostic quality so that a diagnostic impression or conclusion can be rendered. Motion correction of dynamic acquisitions may be required before time-activity curves are generated, (see Chapter 5).

The initial assessment should begin after the acquisition to determine if the study is of diagnostic quality. Just as in radiology, where a roentgen sign approach can be used for descriptive purposes, a similar approach can be used in nuclear medicine. The abnormalities in uptake patterns within structures or organs, clearance of the radiopharmaceutical from the soft tissues, and the routine excretion of the radiopharmaceutical must be noted. Each area should be evaluated for alterations in count density. The term photopenic means a lack of radiopharmaceutical in an area where it is expected to accumulate. Increased radioactivity may be true uptake or localization within an area based on altered vascular permeability or blood supply. Other descriptions of

the patterns of the radiopharmaceutical uptake would include number, size, shape, location, and margins of the lesions. If the study is a dynamic study (ie, motion), the acquisition should be reviewed in a cinematic mode to identify problems that may hinder interpretation. Often the clinician will have a sense for whether or not the study was normal or abnormal once the review of the dynamic images is finished. If the clinician is still having problems interpreting the study from this visual inspection of the data, then one should probably reassess the diagnostic quality of the study. If the clinician is having a difficult time identifying specific anatomy on the dynamic images, then a composite image is created by summing all or part of the dynamic study to form one static image. Alternatively, a static image of the patient can be obtained prior to releasing the patient back to the ward or isolation area. If either of these two techniques is not useful, then the study should be considered nondiagnostic.

After the dynamic images have been visually inspected, a composite image can be made and regions of interest drawn for direct quantification or the generation of time-activity curve data. From this data, specific quantitative values can be determined and compared with known normal values already reported in the scientific literature. The time-activity curve can provide important information from a purely qualitative inspection and should not be overlooked for the specific quantitative information that may be calculated. As previously mentioned, motion correction of the original dynamic study should be done prior to application of the regions of interest and time-activity curve generation. Each area is specific to the radiopharmaceutical that is used. The acquisition parameters and principles of interpretation are reviewed in the Scintigraphy Clinical Studies section of this book. The importance of evaluation of the image for diagnostic readability cannot be overemphasized, as nuclear medicine studies are count limited. Poor acquisition techniques can totally invalidate a study.

Counting Statistics

Because nuclear medicine studies are count limited, it is important to note where errors can occur in images and image processing just based on Poisson statistics. Counting errors can be divided into determinate and indeterminate errors. Determinate errors

include errors caused by a fault in the measurement process, such as an incorrect energy setting for the window used to count ^{99m}Tc , incorrect acquisition techniques, or increased patient-to-collimator distance. Indeterminate errors are errors due to random fluctuations in the measured counts or the random nature of the process that one is measuring. Because radionuclides decay by a random process (eg, it is impossible to tell when any one radioactive atom will undergo decay), the counting of radionuclides is inherently flawed and indeterminate errors can never be totally eliminated. The distribution of events that describes random events is called a Poisson distribution. The variance or fractional error is the probability that repeated measures will be near the mean count m , denoted $m \pm \sigma$ (σ is also called the standard deviation in normal distributed populations). For Poisson statistics, the variance can be estimated by the square root of the mean (m) so that the total count, plus or minus, the variance would be written as:

$$m \pm \sqrt{m}$$

If the total count in a study is 10,000 for a given time period, then the variance would be 100 for the same period of time. If 100 acquisitions of m are made from a static nuclear medicine procedure of the same area, 68% of these decay-corrected observations would then fall between 9,900 and 10,100 for the same imaging time period. Because the variance is the square root of the mean ($[m]^{1/2}$), it is also approximately the square root of the single measurement (x). The fractional error (%P) or the uncertainty would equal:

$$\sqrt{x}/x \text{ or } 1/\sqrt{x}$$

For an image with 100,000 counts, the fractional error (P%) would equal:

$$(1/\sqrt{100,000}) \times 100 = 0.32\%$$

The confidence intervals are important to determine whether or not a “hot” spot or a cold defect in a nuclear medicine image is an indeterminate error (eg, random statistical fluctuations) or true increased or decreased radiopharmaceutical uptake. Nuclear medicine usually follows a generally accepted rule

at least twice the standard deviation of a measurement is within indeterminate error (95% probability that is within Poisson statistical limits of mean), and anything outside that range is considered abnormal radiopharmaceutical accumulation. These formulas for counting statistics are summarized in Tables 7.1 and 7.2 along with the rules for addition, subtraction, multiplication, and division when using numbers associated with Poisson statistics.

If the count density is 853 counts per pixel then the σ value would be 29.2 counts. The 95% confidence intervals would then range between 796 and 910 counts. In nuclear medicine, as counts involve random or indeterminate error, it is necessary to estimate the uncertainty of the results and evaluate the possibility of error propagation. There are various effects of mathematical operations that must be taken into account when adding, subtracting, mul-

tiplying, or dividing independent counts associated with image acquisition. Whenever two independent counts are added or subtracted, their variances are additive. If the gross counts are 10,000 and the background counts are 100, then the net counts expressed as the:

$$\text{mean} \pm \sigma, \text{ where } (10,000 - 100) \pm \sqrt{(10,000 + 100)}$$

or $9,900 \pm 100.5$. The fractional error for the net counts is $100 \times (100.5/9,900) = 1.02\%$. For multiplication and division, the x and the variance or fractional error can be divided or multiplied by the constant respectively. In dealing with counts per minute (rates) or counts per pixel (density) per unit of time, it is possible to introduce the time or pixel into the equation at any point recognizing that the variance and the error of a count rate will be smallest

Table 7.1: Propagation of Error Formulas for Mathematical Manipulations of Counting Statistics That Follow Poisson Distribution*

Operation	Poisson Operation
Multiply a constant (C)	$\sigma = C \sqrt{N}$
Addition	$\sigma = \sqrt{(N+M)}$
Subtraction	$\sigma = \sqrt{(N+M)}$
Multiplication	$\sigma = \sqrt{[(1/N)+(1/M)]}$
Division	$\sigma = \sqrt{[(1/N)+(1/M)]}$

*N = the number of counts and σ represents the variance. Errors are additive.

Table 7.2: Commonly Used Formulas for Counting Poisson Statistics

Condition	Formula
Variance or uncertainty associated with N counts	$\sigma_N = \sqrt{N}$
Fractional uncertainty or the precision associated with N counts	$P(\%) = 100\% \times [\sqrt{N} / N]$ Or $P(\%) = 100\% \div \sqrt{N}$
Counts (N) necessary to obtain a certain level of precision [P(%)]	$N = 10000/P^2(\%)$
Uncertainty associated with count rate R determined over time t	$S_R = \sqrt{R/t}$ where $R = N/t$
Precision (P) associated with count rate (R) multiplied by time (t)	$P(\%) = 100\% \times [1/\sqrt{R \times t}]$

the longer the time counted.

A clinical example is an equine bone scan with a focal area of what is perceived as increased uptake in the proximal palmar aspect of metacarpal bone III. This area looks slightly different from the surrounding bone and looks different compared with the opposite limb. The previously described principle can be used to determine if this is truly increased ^{99m}Tc -MDP uptake in this region. If the proximal third metacarpal bone has a count density of 100 counts per pixel and the adjacent area of increased MDP uptake is 120 counts per pixel, then the error term for both measurements is:

$$\sqrt{100 + 120} = 14.8$$

At two standard deviations the count variation would be ± 29.6 counts per pixel (or 70.4 to 129.6). The measured difference is not outside the expected variation so that one could not confidently say that the change is physiologically significant. If one could record for increased time without motion being a problem (or record as a dynamic and motion correct) so that the proximal aspect of Mc III is 400 counts per pixel and the area of increased MDP uptake is 500 counts per pixel. The error term or total image variance is:

$$\sqrt{400 + 500} = \sqrt{900} = 30 \text{ cts/pixel}$$

The observed difference is more than three standard deviations beyond the expected value and is likely not secondary to Poisson noise.

Evaluation of Radiopharmaceutical Uptake and Clearance Kinetics

Compartmental Models in Nuclear Medicine

One of the advantages of nuclear medicine is that it can provide basic physiologic information about an organ or system. This includes the calculation of individual or global renal glomerular filtration using ^{99m}Tc -DTPA. Another example is calculating the hepatic extraction fraction of ^{99m}Tc -mebrofenin as a quantifiable method for evaluating hepatic function. The ability to model the uptake, distribution, and/or clearance of specific radiopharmaceuticals relative to an individual organ or body system is one

of the unique aspects of nuclear medicine (planar, SPE[CT], or PET scintigraphy). The purpose of this section is to review basic concepts of tracer kinetic modeling related to radiopharmaceuticals and the potential spaces of biological distribution. As the term implies, the discussion covers the dynamic (kinetic) distribution of a radiotracer/nuclide within an area of interest called the "compartment." One can try to mathematically explain the behavior of the radiotracer moving into, staying within, and/or leaving the compartment of interest.

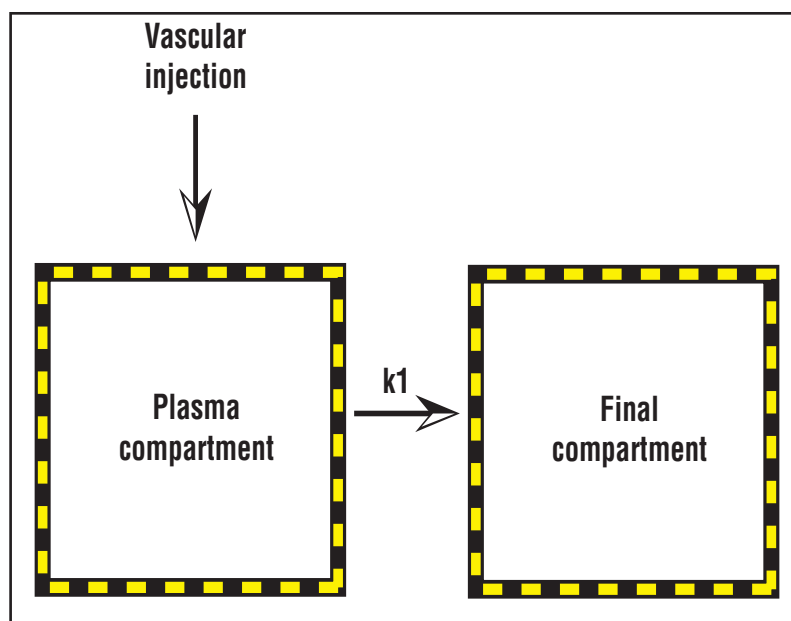
Radiopharmaceuticals As Tracers

Various radiopharmaceuticals are used to evaluate basic physiologic processes within the body. The actual uptake mechanisms and distribution of the radiopharmaceutical are based on biologic behavior, chemical characteristics of the radionuclide used, availability of the radionuclide or pharmaceutical to the target organ (specific pool) or physiologic process in question, and the pharmaceutical properties. In vivo imaging is defined ultimately by a combination of all of these factors. The ideal radiopharmaceutical would have ideal imaging characteristics (short physical half-life, no particulate emission, decay with gamma emissions suited for detection by the gamma camera, and not alter the biodistribution of the process to be imaged) as well as provide a high fraction of the injected dose within the target organ or body compartment so the signal-to-noise ratio is high. The fundamental static information provided by the radiopharmaceutical distribution within the organ of interest is that there is either too great a quantity (hot spot) or too little a quantity (cold spot or photopenic area) seen during the study. Two forms of radiotracers are currently available. The first is a free ion (cation or anion) that will localize based on the chemistry of the radionuclide (chemical factors include the atomic radius, valence and elemental position on the periodic chart). The second form of a radiopharmaceutical is the radionuclide that has been chemically bonded to a pharmaceutical. The radiopharmaceutical is a stable complex that is bound by covalent or ionic bonds depending on the nuclide and pharmaceutical. The radiopharmaceutical will then localize based on the biochemistry of the molecule that it is tracing.

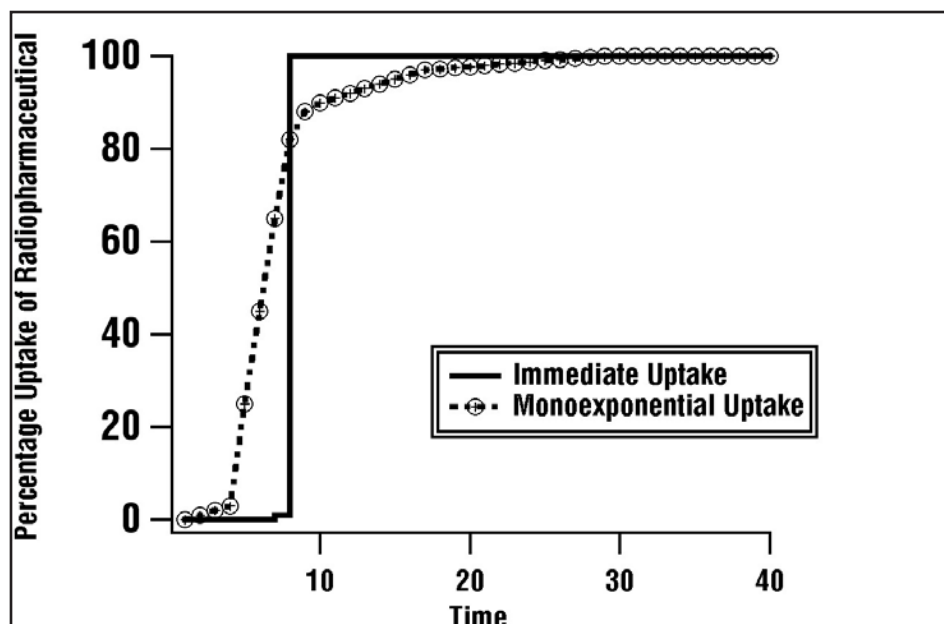
The basic mechanism of localization needs to be understood if the radiopharmaceutical in question

Figure 7.1:**(A) Simple diagram of the injection of a vascular tracer that immediately distributes itself into the plasma compartment**

It is assumed that the tracer is not protein or cell bound within the blood and is actively taken up into the final target compartment over time.

**(B) Time-activity curve whereby a radiotracer is injected into a closed compartment and the first pass extraction is 100%**

A second curve represents a simple compartmental model and time-activity curve (exponential buildup without leaving the final compartment). This is an example of a two-compartment model (plasma and the final compartment with a single radiotracer injection).



is to be modeled. Initial experimental data using specific radiopharmaceuticals will take advantage of list mode acquisitions so that the data can be manipulated in any of a number of ways to come up with the best way for evaluating the radiopharmaceutical as it enters, resides, and leaves a specific compartment (area of interest).

Basis of Kinetic Modeling

The basic concepts of region of interest drawing, understanding time-activity curve (TAC) generation, background subtraction, cross talk, radioactive decay, and attenuation correction are reviewed in Chapter 5. These basic concepts are critical to understanding radionuclide kinetics within the animal.¹⁻⁵ The distribution of a given radiopharmaceutical within the body is a dynamic process. Initial distribution of the radiotracer to the organ/compartment is dependent on cardiac output for delivery and regional blood supply to the target organ(s). Whenever kinetic models are to be evaluated, certain assumptions are made in order to understand how a radiopharmaceutical is delivered to an organ. There are complex interactions of the radiopharmaceutical within the organ and many possible explanations of how the radiopharmaceutical is bound within the organ, broken down, or redistributes into the original delivery compartment and/or is eliminated or metabolized by the animal. An ideal tracer is totally delivered in one pass to an organ or system via the bloodstream or entry point and is stuck within the organ/system without leaving the compartment or being metabolized by the cells that make up the particular compartment (Figure 7.1). The clearance of the tracer, if monitored from the outside using scintigraphy, would then be dependent on the decay of the radionuclide and not any transport mechanisms or metabolism of the tracer. As a starting point, a kinetic model can be defined as a mathematical description of a process or a variety of biochemical processes under investigation that will determine the biodistribution of a radiopharmaceutical. The purpose of a kinetic model is to expand the clinician's ability to describe and better understand the underlying process(es) from a clinical standpoint and then see if these descriptions change with a specific disease or as a general consequence of a variety of diseases.

A tracer is then any substance that follows a physi-

ologic or biochemical process.^{1,2} The requirements of the tracer are that the behavior of the tracer should be identical to the endogenous substance or process being traced so that the tracer enters the process like the molecule in question but does not alter the physiologic process in question. As the word implies, the quantity or mass of the tracer is so small that it does not alter the underlying physiologic process or impact rates of any chemical reactions that are being evaluated (actual concept of a tracer mass being substantially smaller and not competing with the compound being traced). The specific activity of the tracer should be sufficiently high to allow for plasma sampling and/or imaging without violating the first two tracer requirements. The final tracer requirement is that any isotopic effect (isotope of the compound tracing used, such as radioiodine) should be negligible. If the first two requirements are violated, then the tracer is called an indicator and most radioactive compounds used in nuclear medicine are in reality indicators.

Each potential space, organ, tissue, etc., that can contain a radiopharmaceutical is defined as a compartment. A more formal definition of a compartment is a volume or space within which the tracer rapidly accumulates and becomes uniformly distributed.^{1,5} The actual number of compartments, their interrelationships, organization, and basic definition is derived from knowledge of the known physiologic and biochemical facts about the metabolic uptake or excretion process. A compartment can be as simple as the blood pool, but as complex as a variable number of specific receptor populations found in several cell types of a given organ.

Mathematical models are attempts at quantification of the uptake and/or clearance of a given radiopharmaceutical into and out of a specific compartment. These models attempt to reflect the understanding of how a normal physiologic process can be described through a series of uptake or clearance values called "rate constants." Again another layer of assumptions is placed on the experimental design. The first assumption is that it is possible to quantify a given physiological process accurately and precisely in a normal steady state. Secondly, it is assumed that a disease process will alter this steady state and that the difference between normal and abnormal can be identified based on differences in uptake and clear-

ance values (rate constants or k) determined during administration of the particular radiopharmaceutical being used.

Compartments can be thought as being closed or open. A closed compartment is one where the tracer will enter but cannot escape. An open compartment implies that the tracer can move into the compartment and can also move out of the compartment. If the tracer is injected into a closed compartment, there will be conservation of mass of the tracer within the compartment, once the tracer has distributed itself throughout the compartment. The volume of distribution or distribution volume (Vol_d) is defined as the total radioactivity [A (mCi)] divided by the concentration of the tracer (radioactivity/mL) at steady state within a specific compartment. The assumptions are that one has injected the tracer into a closed compartment, and the sample obtained to determine the concentration of the tracer in the compartment has been taken after the system is in equilibrium. Steady state can be defined as either the concentration of a substance or the evaluation of a given process/flux of a substance into and out of the compartment so that the Vol_d does not change over time. Measurable quantities include the total tissue radiotracer accumulation as a function of time, peak uptake of the radiotracer at a specific time point, models that describe the uptake pattern of the radiotracer, and finally clearance models of the radiotracer as it is metabolized or leaves the compartment of interest (while correcting for decay) as a function of time.

The input function can be defined as the radioactivity concentration versus time after injection into the vascular space (typically the intravenous space as it is most readily accessible). The vascular compartment provides the input stage to the model as the radiotracer is delivered to the tissues by way of the circulatory system. As all biologic systems have multiple variables that impact the circulatory system (cardiac output, blood volume, blood flow, systemic vascular resistance, and blood pressure), there can be wide variations in the delivery of the radiotracer. This has to be taken into account when determining uptake kinetics of the radiotracer within the compartment/organ of interest. Changes in the radioactivity or concentration of the radiotracer within the systemic circulation are evaluated to determine the validity of the input function. Input function can be determined from blood collected from a peripheral

artery (metatarsal and femoral arteries are commonly used in dogs and cats) simultaneously with imaging. Alternatively, a time-activity curve can be generated for a large arterial vessel if the vessel is within the region being imaged. The input function to an organ can be altered by the magnitude or time course of the radiotracer delivery to the organ of interest. Venous blood samples can be used for evaluating the input function if the extraction of the radiotracer is low on any given "pass" through the capillary bed of the tissue/organ that is being evaluated.

Mass balance is used to describe compartmental models where there is a conservation of mass of the radiotracer being used within the compartment being explored (steady state). If there is a mass balance within a compartment, then the accumulated radiotracer within the compartment would equal the concentration of the radiotracer entering the compartment over a given time period minus the efflux of the radiotracer out of the compartment in question. When a compartment is said to be in steady state, one of two things is occurring. First, the influx of radiotracer is equal to the efflux of radiotracer and there is no further or new accumulation of radiotracer in the defined compartment. Second, the influx and efflux mechanisms may have stopped, again, resulting in no accumulation of the radiotracer over time.

The simplest of the compartmental models is a one-compartment or single-compartment model. In this case, the radiotracer is injected into an afferent input relative to the organ of interest and there is 100% delivery and uptake of the radiotracer. If the compartment (organ) is closed, then there would be only one rate constant (k_1) describing the rate of uptake of the radiotracer (mCi or μ Ci) per unit of time (sec/min/hr). The rate constant (k) has the units of inverse time (per sec or sec^{-1}) and describes the rate of accumulation of the radiotracer into the compartment per unit of time. In this case the rate constant would approach 1 as all of the radiotracer is delivered and taken up by the compartment in a single pass (Figure 7.1). A display of the time-activity curve of the radiotracer into the organ of interest is evaluated and could be described as being linear, linear-quadratic, polynomial, logarithmic, or exponential in shape (Figure 7.1). By fitting the time-activity curve with a curve-fitting or line-function program, one could determine this initial input uptake rate constant (k_1). In a single compartment model, it is assumed that

the tracer may leave the vascular pool or the final compartment and never reenter. This, of course, is an oversimplification and cannot adequately explain influx and efflux of tracers into and out of various compartments.

A type of kinetic model that is used to describe a tracer that can leave and return to various compartments is called "multicompartmental kinetics," (Figure 7.2).

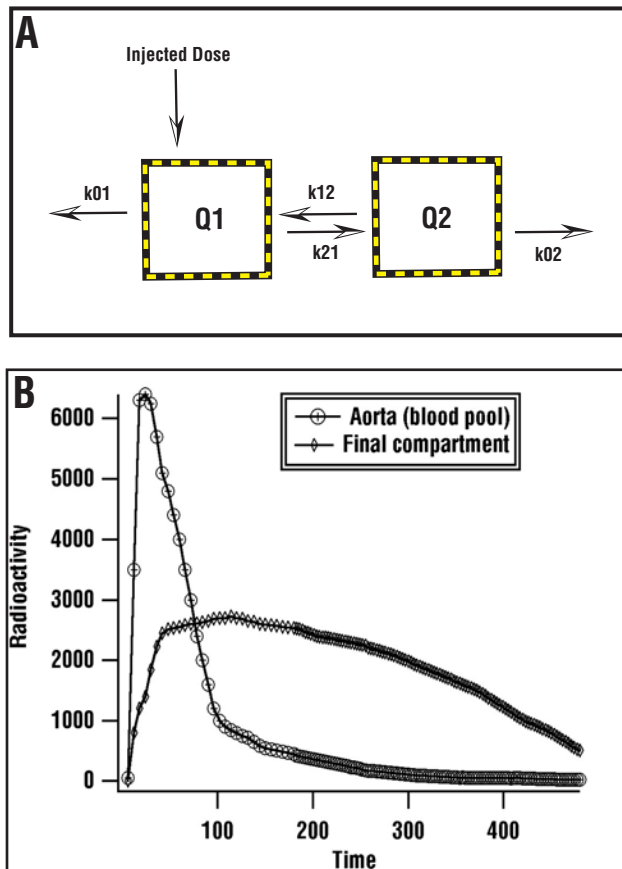


Figure 7.2: Two-compartment model (Q_1 and Q_2) where there is efflux out of the final compartments (k_{20} and k_{21}) in question so that the blood pool (k_{12} and k_{01}) and the final compartment ultimately lose tracer to a final excretion route. After decay correction, there is a loss of tracer over time from the total system.

A Schematic of the described scenario. B Decay-corrected, time activity data from the blood pool, and final compartment showing this concept of eventual loss of the radiotracer from both compartments (through metabolism or excretion).

The simplest of the multicompartmental models is the two-compartment model. The mathematical complexity increases (it seems exponentially!) as the number of compartments increases for consideration when evaluating tracer influx and efflux patterns. In the two-compartment model, the first compartment is the vascular space into which the radiopharmaceutical is injected. The second compartment is the final organ or tissue into which the tracer moves. The flux of tracer from the blood pool into this second or final compartment can be described by the following equation:

$$F = Q \times k_{\text{blood compartment}}$$

where F is the flux (radioactivity/unit of time), Q is the size of the final compartment, and k is the rate constant from the blood pool to the final compartment or the fraction of the radioactivity entering per unit of time. Two differential equations can be written to describe the specific activity (SA) of the radiotracer within the blood pool (Q_1) and the final organ or tissue compartment (Q_2).

$$d[\text{SAQ1}]/dt = [\text{SAQ1}] (k_{01} + k_{21}) + [\text{SAQ2}] (k_{12})$$

AND

$$d[\text{SAQ2}]/dt = [\text{SAQ2}] (k_{02} + k_{12}) + [\text{SAQ1}] (k_{21})$$

The 0 implies that there is an outside disposal of the tracer from which no tracer can reenter either compartment, once the tracer goes there (Figure 7.2). The solution for these differential equations involves using a nonlinear, least squares, curve-fitting program (ie, Igor Pro, Wavemetrics, Inc., Lake Oswego, Oregon).

As the number of compartments in the mathematical model increases, so does the complexity for solving the mathematical models that describe the rate constants for each possible direction a radiotracer can accumulate within a compartment and move between compartments or a number of possible ways the radiotracer may be handled within a given compartment (metabolized versus uptake and storage within a given cell). Limitations in the dynamic frame rates can reduce the temporal resolution of planar scintigraphy if the computer system does not have list mode capability. Similar temporal resolution limits are also found with PET imaging. SPE[C]T imaging is even more temporally limited

because of the time required to rotate the detector(s) around the patient. Because of the time limit with SPE[C]T, kinetic modeling for input and clearance rates cannot be determined. In planar scintigraphy, evaluation of a time-activity curve from an ROI of a particular organ is the result of summation of multiple compartments (two-dimensional flattening of a three-dimensional animal); and, therefore, clearance rate constants cannot be unambiguously determined. Because of the low count density information inherent to nuclear medicine, noise and partial volume effects will also hinder accurate assessment of specific rate constants.

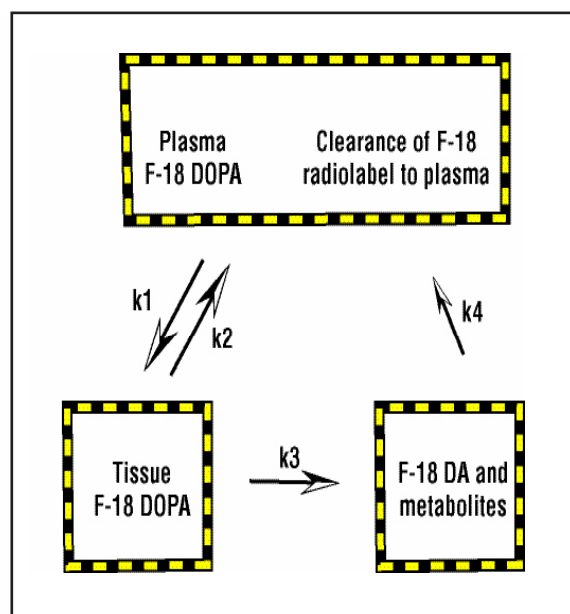
In addition, there are model-independent methods for evaluating several of the kinetic parameters while making minimal assumptions. If the interest is in how the radiotracer leaves the compartment, then the same curve-fitting programs could be used to determine the best-fit description of the change in concentration of the radiotracer over time (decreasing amounts of radiotracer over time, again taking into account decay and background correction). Commonly, linear or nonlinear (mono-exponential and bi-exponential) mathematical fits are used to describe the uptake or clearance of the time-activity data from the radiotracer (specific to a region of interest). For the clearance of any radiotracer over the course of time, it is assumed that the rate at which a radiotracer leaves a compartment is proportional to the amount of radiotracer within the compartment of interest. If this is true, then first-order differential equations can be used to describe the clearance from the compartment. Although one could argue that the function used for this purpose is a mathematical model; others would argue that the functions used are merely a numerical tool and not meant to represent the inner workings of the entire tracer model. In the examples described, next, both compartmental models and model-independent methods have been used.

^{18}F -fluorodeoxyglucose (^{18}F -FDG) is a metabolic analog that is used to determine areas of absent, low, normal and high metabolic activity (see Chapter 3). ^{18}F -FDG will be actively taken up at the cell membrane via a series of glucose-transport proteins called GLUT 1 to 6. The ^{18}F -FDG then enters the glycolysis cycle; however, the ^{18}F -FDG is converted immediately into an inert substance that does not continue after the first enzymatic interaction. Hexokinase is

the first enzyme of the glycolytic cycle and phosphorylates the ^{18}F -FDG into ^{18}F -2-deoxyglucose-6-phosphate. Due to the strict structural requirements of the enzyme, glucose phosphate isomerase, the ^{18}F -FDG-6-P cannot be metabolized any further and is trapped in the cell. Areas or organs with increased concentrations of ^{18}F -FDG are assumed to be hyper-metabolic, reflecting a high demand for glucose metabolism and ATP synthesis. The ^{18}F -FDG then directly reflects the hexokinase enzymatic reaction and thereby glycolysis if in steady state. In this case, as the radiotracer is trapped in the cell, a standardized uptake ratio has been derived that quantitates

Figure 7.3: ^{18}F -fluoro-DOPA kinetic model of uptake and metabolism within the basal ganglia (nucleus ambiguous and striatum nigrum) in the human brain

Each $k(i)$ represents a rate constant describing the exchange rate from one compartment to the next either by diffusion, active transport, or metabolism. The rate constant k_1 represents the active transport of the ^{18}F -DOPA from the plasma across the blood-brain barrier into the basal ganglia. The rate constant k_2 represents any back diffusion of the ^{18}F -DOPA out of the basal ganglia back into the plasma. The rate constant k_3 represents the enzymatic conversion of ^{18}F -DOPA into its metabolic product (^{18}F -dopamine [DA]) and the rate constant k_4 represents any loss of radioactivity from ^{18}F being cleaved from either the ^{18}F -DOPA or ^{18}F -DA and diffusing back into the plasma.



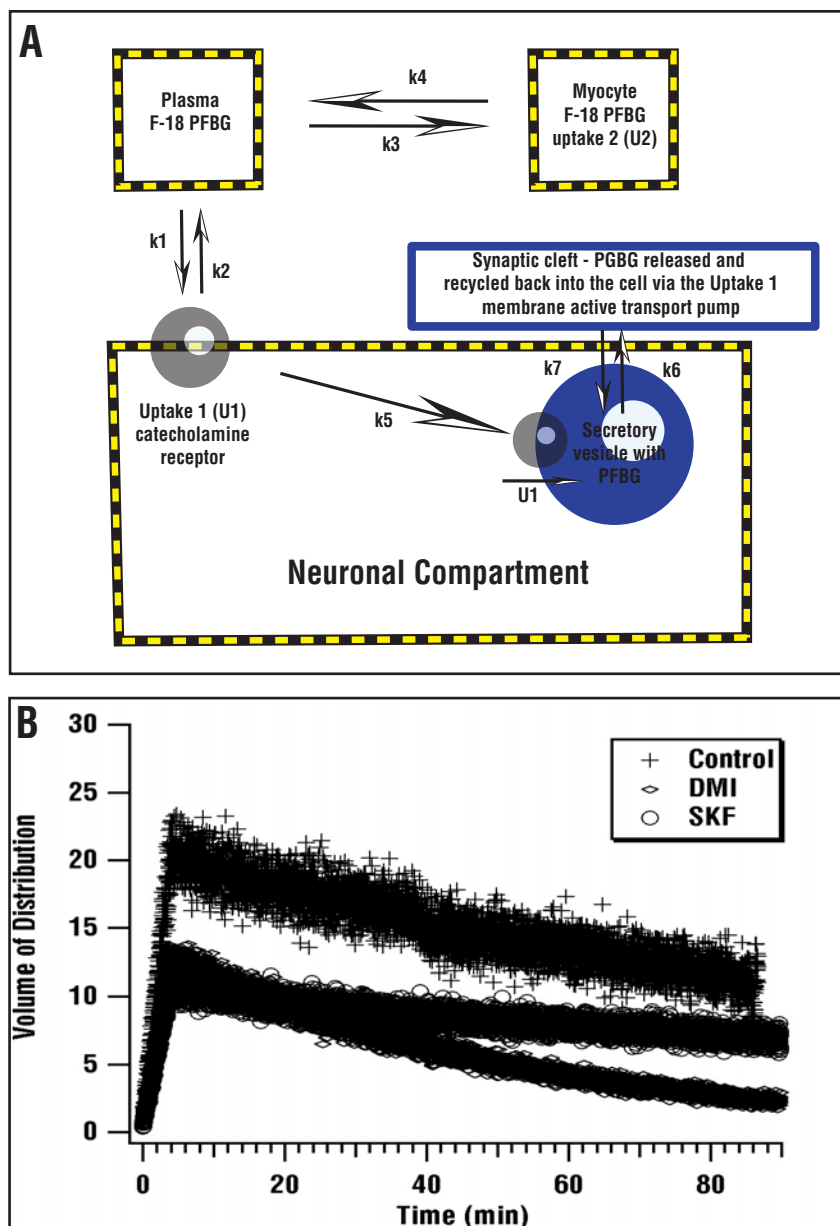


Figure 7.4: ^{18}F -PFBG model and time-activity data

A, Schematic representation of possible ^{18}F -PFBG uptake mechanisms in the isolated rat heart. The ^{18}F -PFBG is taken up by uptake-1 (neuronal) and uptake-2 (nonneuronal) mechanisms. Within the synaptic terminal, the ^{18}F -PFBG is actively transported into the secretory granules. Within the granule, the ^{18}F -PFBG is not metabolized. The granule can be released and the ^{18}F -PFBG enters the synaptic gap/cleft between the neuronal terminal and the effector organ. Reuptake of the ^{18}F -PFBG is possible at this point back into the neuronal terminal with a recycling into the secretory granule.

B, Time-activity curve data from ^{18}F -PFBG isolated rat heart data where no uptake blockers (control), uptake-1 blockers (DMI), and uptake-2 blockers (SKF) have been administered prior to administration of the ^{18}F -PFBG into the perfusion solution. Using this type of blocking experiment, the rate constants for individual compartments can be explored.

the ^{18}F -FDG uptake within the tissue normalized to the injected dose and patient's body weight.

A more complex model includes the evaluation of dopamine metabolism and the use of ^{18}F -DOPA (Figure 7.2). L-tyrosine is converted into L-dihydroxy-phenylalanine by the enzyme tyrosine hydroxylase.^{6,7} This enzyme is located in the cytosol of chromaffin cells of the adrenal medulla, sympathetic nerve terminals, and in specific cells found within the substantia nigra and ventral tegmental area of the central nervous system. A second cytosolic enzyme, the amino acid decarboxylase, converts L-dopa to dopamine in the adrenal medulla and the central nervous system tissues described. In the adrenal medulla, the dopamine is actively transported into secretory granules (via a catecholamine- H^+ exchanger called VMAT1) where conversion to norepinephrine takes place via dopamine β -hydroxylase. The norepinephrine is then actively transported into the cytosol where conversion to epinephrine takes place via the enzyme, phenylethanolamine-N-methyltransferase (PNMT). The epinephrine is then actively transported via the same catecholamine- H^+ exchanger (VMAT1) pump back into the secretory granule where epinephrine and norepinephrine are stored until release.

^{18}F -DOPA is used to evaluate the targets within the central nervous system. ^{18}F -DOPA is injected intravenously and targets the presynaptic dopaminergic function. ^{18}F -L-DOPA is transported across the blood-brain barrier (along with other amino acids) and is decarboxylated in the presynaptic dopaminergic neuron terminal. It has been shown in humans that there are abnormal accumulations of the ^{18}F -DOPA in the nigrostriatal projections and basal ganglia in Parkinson's disease, (Figure 7.3). The compartments involved in this radiotracer's fate within the body include initial distribution into the plasma (vascular space) and entrance into the blood-brain barrier, with active uptake into the specific region of the telencephalon, including the basal ganglia. The ^{18}F -DOPA is then converted to ^{18}F -dopamine (DA) that is used as a specific neurotransmitter within this area. The model is complicated by the fact that the ^{18}F -DA can be further metabolized (into 3-O-methyl-6-fluoro-L-DOPA) or the radiolabel ^{18}F bond cleaved and the free ^{18}F released back into the plasma. The metabolized compound can exhibit redistribution within the

brain in a nonspecific manner, thereby complicating the possible modeling of dopamine kinetics.⁸

Another complex, multicompartmental model, would be the use of ^{18}F -parafluorobenzyl guanidine (^{18}F -PFBG) for the evaluation of normal sympathetic uptake, the adrenal medulla, and identification of neural crest cell tumors. A complex series of uptake mechanisms and various scenarios for distribution of the radiotracer exist within the myocardium (Figure 7.4). When evaluated externally using PET or planar dynamic imaging (^{123}I -MIBG), there are a number of compartments that are complexly linked with a large number of potential rate constants. In certain animal species, such as the dog and rat, the ^{18}F -PFBG is taken up by the sympathetic neurons (uptake 1) and by the myocytes of the myocardium (uptake 2). There are specific binding receptors that bind the ^{18}F -PFBG in the extracellular space and move the ^{18}F -PFBG into the sympathetic neuron or the myocyte. Typically, once inside the neuron, the ^{18}F -PFBG will be actively transported into the secretory granules as L-dopamine is (presumably by the same VMAT1 receptor). Once inside the secretory granule the ^{18}F -PFBG is not broken down but can be secreted into the synaptic cleft, where the ^{18}F -PFBG is taken back up and actively recycled within the secretory vesicle.⁴ Additionally, there is a backward rate constant of the ^{18}F -PFBG over time from the myocyte. This multicompartmental model with many possible compartments that is a complicated process is not easily modeled using several rate constants.

Summary

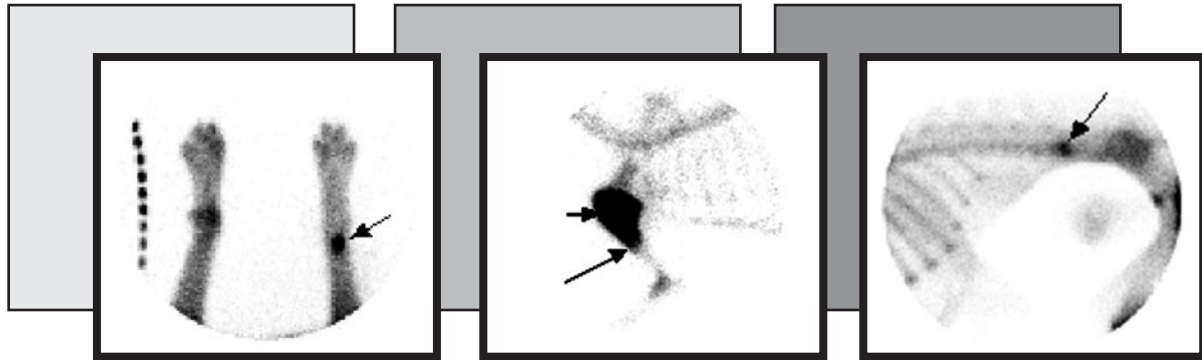
Principles of radiotracer interpretation are based upon the ability to acquire static or dynamic images of a technical quality that are not severely count limited and are appropriate according to the radiotracer and physiologic process being imaged. A basic approach to the review of static and dynamic image data sets should be systematic and abnormalities described based on expected normal biodistribution patterns for animals. Further refinement of dynamic data sets can take place so that radiotracer distribution and kinetics can be evaluated from time-activity curve data. Kinetic modeling results in the production of rate constants that can then be used to evaluate the biochemical process for dysfunction.

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Small Animal Skeletal Scintigraphy

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Introduction

Skeletal scintigraphy has been utilized as a diagnostic tool in veterinary medicine since the 1970s, primarily in equine orthopedic practice. Characterization of scintigraphic abnormalities includes the extent, pattern, and anatomic origin of any abnormal areas of increased or decreased uptake of the skeletal radiopharmaceutical ^{99m}Tc -methylene diphosphonate (^{99m}Tc -MDP) or ^{99m}Tc -oxidronate (^{99m}Tc -HDP). These scintigraphic abnormalities in concert with signalment, history, physical examination, and radiographic findings can increase the specificity; and, in some cases, a definitive diagnosis can then be made.

Skeletal scintigraphic imaging of small animals has the following advantages when compared with equine skeletal scintigraphy: ease of patient positioning, faster total scan time, fewer retakes due to patient motion, ability to do a true whole-body bone scan, use of standard (unmodified) gamma camera equipment, and lower administered dose (thereby decreased personnel exposure). Most small animals require tranquilization for the procedure, and some may require general anesthesia. Small animal images can be acquired with the gamma camera head placed underneath a 3/8-inch to 1/2-inch plexiglas table with the camera head against the bottom surface of the table. Care should be taken to ensure that the camera face is touching or placed as close as possible to the underside of the imaging table and that the camera face is parallel to the table top. By imaging from under the animal, positioning is easier and the patient feels less threatened than it would if the camera were placed above it. Dorsal and ventral dynamic or static images are easily obtained when dogs and cats are placed in lateral recumbency on the table with the ventral or dorsal aspect against the camera face (perpendicular to the imaging table). Using a large field of view gamma camera, a whole-body bone scan of a large dog can be obtained in 30 to 60 minutes.

Skeletal Physiology

Although it is beyond the scope of this book to review all of the essential elements and complex hormonal and cellular interactions of normal bone metabolism, a brief overview of bone anatomy and physiology is warranted. Anatomically, long bones

can be divided into major parts depending upon the age of the animal. In immature animals, the long bone is composed of the epiphyses that are the articular ends of the bone (covered by hyaline cartilage), the physis (center of longitudinal growth via the process of endochondral ossification, where new bone is formed at the metaphyseal border of the physis), the metaphysis (area of active bone remodeling), and the diaphysis. The blood supply to long bones is typically via small periosteal vessels and a single vessel or multiple large nutrient vessels that enters into the bone marrow within the diaphysis. In small animals, the physis forms a division between the blood supply of the diaphysis and metaphysis (nutrient vessel) and the epiphysis/physis (epiphyseal and synovial vessels). The nutrient supply to the articular (hyaline) cartilage is supplied by a plasma filtrate modified by the synovial cells lining the joint space. In large animals, there are perforating vessels that cross the physis from the metaphysis into the epiphysis. In adult small animals, the physis cartilage model completely disappears and the metaphysis becomes contiguous with the epiphysis.

Remodeling of all bones is a continuous process according to the stresses placed on the bones (Wolff's law). There are two different types of bone that include cancellous and compact or cortical bone.¹ Cancellous bone is found on the inside of cortical bone and tends to be less concentrated in the diaphysis, being found predominantly in the epiphyseal regions of adult long bones. The diaphysis of long bones in the immature animal contains active cellular elements responsible for the formation of blood cell precursors, whereas the diaphysis of long bones in adults predominantly contains fat. Cortical or compact bone is made up of fundamental bone units called osteons in which central canals called haversian canals are surrounded by a number of osteocytes.¹ These osteocytes are buried within lamellar layers of a mineralized organic matrix that provides strength and rigidity to bone. The osteocytes are in communication with other osteocytes and surface osteoblasts via canaliculi and gap junction connections between cytoplasmic projections.¹ Within the haversian canals, perforating blood vessels from the nutrient artery and vein, travel to the osteocytes providing appropriate nutrients. The surface osteoblasts come from superficial progenitor or osteogenic cells that will differentiate into osteoblasts upon appropriate stimulation. The differentiated osteoblast

produces the organic, protein bone matrix called osteoid. The osteoid is not a single compound but is a complex helical arrangement of many collagen (90% of which is Type I) fibrils that are interconnected. This Type I collagen triple helix is made up of two alpha-1 monomers and one alpha-2 monomer that is secreted by the osteoblast into the surrounding interstitial space.¹ These collagen fibers cross link within the triple helix and between collagen fibers resulting in a well-ordered meshwork that provides the sites for binding of the inorganic matrix. The inorganic matrix is predominantly made up of the hydroxyapatite crystal, with the hydroxyapatite crystal matrix aligned lengthwise with the long axis of the collagen fiber.

Several other important proteins that are necessary for the mineralization process are secreted by the osteoblasts. These include osteocalcin and osteonectin.¹ Osteocalcin is synthesized by osteoblasts at sites of new bone formation that have undergone a Vitamin K-dependent posttranslational modification. Once modified, osteocalcin will avidly bind calcium and hydroxyapatite. It has been suggested that osteocalcin may be responsible for the initiation of the nucleation process of bone mineralization at the hydroxyapatite crystal surface.¹ Osteonectin also binds hydroxyapatite and has been shown in vitro to facilitate mineralization of collagen fibers. Osteoblasts also directly promote inorganic matrix formation (nucleation). This is accomplished by the osteoblast releasing secretory vacuoles that have accumulated intracellular calcium and phosphate. An osteoblast is under the control of many hormones and local factors, including activated vitamin D and parathormone. These hormones will cause the osteoblast to produce macrophage-colony-stimulating factor (M-CSF) that will induce osteoclastic precursors to differentiate and form osteoclasts, the cells responsible for bone resorption. Glucocorticoids will promote an imbalance between bone production and resorption, with a promotion of bone loss through protein factors (osteoprotegerin ligand and osteoprotegerin) that are produced by the osteoblast. These protein factors also play a role in formation of new osteoclasts and their subsequent activation.¹

Radiopharmaceuticals and Mechanism of Localization

Strontium-89 and fluorine-18 were initially developed as bone-seeking radiopharmaceuticals but had poor Anger scintillation camera imaging characteristics. Development focused on phosphate analogs and included radiopharmaceuticals that were classified according to their phosphate linkages. The polyphosphates (P-O-P), imidophosphates (P-N-P), pyrophosphates (P-P) and finally the diphosphonates (P-C-P) were produced. The polyphosphates were hydrolyzed by intraskeletal alkaline phosphatase resulting in poor image quality with low target to background differentiation. The diphosphonate bond (P-C-P) resists alkaline phosphatase breakdown and has been the radiopharmaceutical of choice. Currently, ^{99m}Tc -methylene diphosphonate (MDP) and ^{99m}Tc -disodium oxidronate (HDP) are used, and either radiopharmaceutical produces high-quality images. ^{99m}Tc -HDP is cleared more rapidly from the extracellular fluid space by the kidneys than ^{99m}Tc -MDP is. Bone-phase images using ^{99m}Tc -HDP can be obtained 1 to 2 hours after intravenous injection versus waiting 2 to 3 hours for the ^{99m}Tc -MDP. These pharmaceuticals are sold in kit form and are easily formulated using a fresh eluate of sodium ^{99m}Tc -pertechnetate. Within the MDP kit there is stannous chloride that will reduce the sodium ^{99m}Tc -pertechnetate (VII) to ^{99m}Tc -dioxide ($^{99m}\text{TcO}_2$ [IV]). The MDP or HDP will form coordinate bonds with any chelating agent, such as the metal $^{99m}\text{TcO}_2$. Inadvertent injection of air (oxygen) into the MDP vial along with the sodium ^{99m}Tc -pertechnetate will result poorly soluble oxides that are phagocytized by the liver and spleen. Oxidative degradation of the ^{99m}Tc -MDP chelate will produce $^{99m}\text{TcO}_4^-$, resulting in thyroid, salivary gland, and gastric uptake.

Plasma protein binding of the ^{99m}Tc -MDP does occur, but does not preclude rapid urinary excretion with 40% of the dose being excreted by 2 hours and 60% to 70% of the total dose being excreted in the urine after 24 hours in humans.² After intravenous injection, the ^{99m}Tc -MDP rapidly diffuses into the extracellular fluid compartment, and bone binding occurs exponentially over time with a near maximum bone uptake being estimated at 60 minutes postinjection.³

The dynamic interaction between the clearance of the radiopharmaceutical from the soft tissues and the uptake of the radiopharmaceutical within the bone is a dynamic process and dependent upon many factors including: normal renal activity, normal calcium and phosphorus turnover, and age of the patient. Due to the presence of high background radioactivity in the soft tissues, a longer delay is allowed so as to take advantage of maximal target to background differentiation at the time for obtaining bone phase images. The maximum target-to-background ratio (highest activity in the bone and lowest activity in the soft tissues) occurs at 6 hours post-injection.³ A compromise of 3 hours has been used as the standard bone-phase-imaging time due to the potential trade-off of decreased photon flux secondary to radioactive decay. If one waited to image at 6 hours, then actual acquisition times would be impractical for obtaining adequate count statistics.

The exact mechanism of uptake for the ^{99m}Tc -MDP in bone is incompletely understood. It has been shown that bone uptake is dependent upon adequate delivery of the ^{99m}Tc -MDP to the bone (blood flow) and the extraction efficiency of the ^{99m}Tc -MDP (presumed osteoblastic activity). The first factor is adequate blood flow so that, once delivered, skeletal uptake is not a linear function of perfusion and, in fact, does not increase after a doubling of flow rates to a given bone.² Perfusion to cancellous bone is 5 to 13 times greater than to cortical bone which only partially explains relatively greater uptake at the epiphyseal end of bones in adults when compared to the mid diaphysis where there is more cortical bone and less cancellous bone. Bone is made up of three compartments that include the inorganic matrix (comprising hydroxyapatite crystals $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$ and amorphous calcium phosphate), the organic matrix (composed of collagen produced by osteoblasts) and different cell populations (including osteocytes, osteoblasts, osteoclasts, and other bone marrow precursor cells). Experimental studies have shown that uptake of ^{47}Ca and ^{32}P radionuclides correlates to the rate of mineralization in bone grafts, while ^{99m}Tc -MDP uptake correlates only with the early mineralization phase of bone graft incorporation. A large body of experimental evidence supports the binding of the ^{99m}Tc -MDP via chemisorption to the exposed surface of the hydroxyapatite crystal. Because there is an abundance of proteins that

normally line the surface of the inorganic matrix, relatively little is exposed for ^{99m}Tc -MDP binding in the normal adult bone. In an immature animal, or when active osteogenesis is taking place, there is a larger amount of exposed hydroxyapatite crystal; and thereby there will be more available for ^{99m}Tc -MDP binding. This is supported by in vitro work where the binding of ^{99m}Tc -MDP to the inorganic hydroxyapatite crystal is 40x greater than that of ^{99m}Tc -MDP binding to organic bone matrix. Microradiographic studies have shown that maximal binding of the ^{99m}Tc -MDP occurs within the calcified cartilage at the ends of the metaphyseal vascular loops in long bones. These areas are the sites that correspond to new mineral deposition as shown by tetracycline uptake studies.⁵ Also, using ^3H -proline as a marker for new collagen formation, these binding sites did not correspond to the areas of newly formed organic bone matrix.⁵ It has also been shown that immature bone has a larger hydroxyapatite crystal surface area per gram when compared with the crystal size of mature cortical bone. Diphosphonate uptake has been shown to be impacted by other substances, such as parathormone, vitamin D, and glucocorticoids.⁶ Recent studies have shown that not only does the ^{99m}Tc -MDP undergo chemisorption onto the surface of the hydroxyapatite crystal but also is incorporated into the crystalline structure of the hydroxyapatite.⁷

There is additional evidence that suggests that there is dissociation between the MDP tracer and the $^{99m}\text{TcO}_2$ within bone.⁸ In this study, it was shown that $^{99m}\text{TcO}_2$ dissociated from the radiolabeled ^{32}P -MDP and preferentially bound to the organic phase (collagen) of the bone matrix, whereas the tracer, ^{32}P -MDP was selectively bound to the inorganic phase (hydroxyapatite crystal). This study suggests that increased ^{99m}Tc -MDP binding during bone healing reflects the increased osteogenic activity related to the formation of new osteoid matrix (organic phase) and not just the mineralization process with hydroxyapatite crystal formation.⁸ This study also provided some evidence for the dissociation of the ^{99m}Tc -MDP within the bone and the MDP acting only as a delivery vehicle.⁹⁻¹¹ Uptake of the ^{99m}Tc -MDP is directly proportional to osteoblastic activity and can be affected by decreased perfusion and regional sympathetic tone.⁹⁻¹²

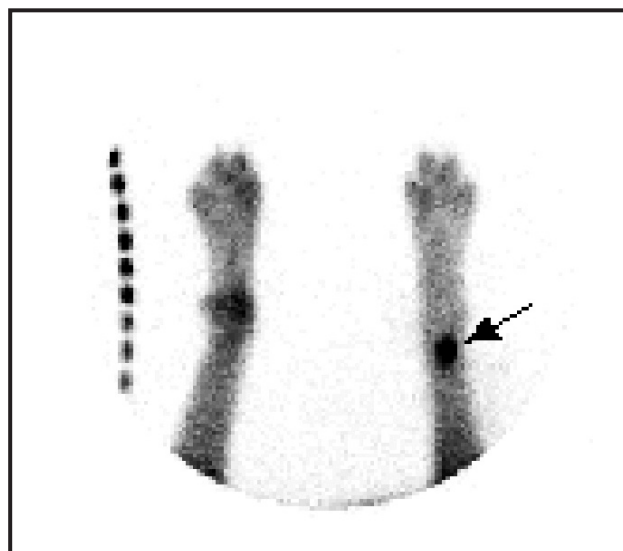
Patient Preparation/Imaging Considerations

Patient preparation prior to scanning is not needed, other than standard tranquilization or anesthesia precautions. Common imaging parameters for small animal skeletal scintigraphy are summarized in Table 8.1. Radiopharmaceutical doses range from approximately 185 to 1,110 MBq (5 mCi to 30 mCi), depending on the animal's size (see Table 8.2). The ^{99m}Tc -MDP is administered intravenously through a preplaced catheter. The catheter can be flushed prior to and after the dose is given using heparinized sterile saline. If some of the ^{99m}Tc -MDP is injected perivascularly, then a hot spot at the injection site is seen on subsequent imaging (Figure 8.1). Regional lymph node uptake is seen on bone phase images as a result of a perivascular injection of the radiopharmaceutical. Because injection-site hot spots are relatively common, it is recommended not to inject the radiopharmaceutical into the limb with the suspected lameness.

Care should be taken to minimize external contamination of the animal by urine, as soft tissue clearance is by renal excretion. If imaging of the pelvic region is of interest, then an attempt to empty the urinary bladder should be made just prior to imaging. This is

Figure 8.1: Radiopharmaceutical extravasation at the injection site

The focal “hot spot” associated with the distal antebrachium is due to extravasation of a small amount of the radiopharmaceutical at the injection site.



easiest in male dogs where a urinary catheter can be passed and the urinary bladder manually evacuated. The urine should be safely disposed of as radioactive waste according to licensing requirements. Emptying of the urinary bladder should be done carefully to minimize contamination in the surrounding area, including the animal's haircoat. Examination gloves, laboratory coats, and radiation monitoring devices (film badges and thermoluminescent dosimeter finger rings) should be worn by all personnel involved in the handling and imaging of the patient. The ALARA (as low as reasonably achievable) concept should be strictly enforced.

A low-energy, all-purpose, parallel-hole collimator is used for imaging. A high-resolution, low-energy, parallel-hole collimator can also be used; but acquisition times must be increased by 20% to 30% as the number of photons reaching the camera face are decreased due to the increased collimator height. The gamma-camera pulse height analyzer should be peaked to 140 keV with a 20% window centered on the photopeak. A pinhole collimator can be helpful in acquiring high-resolution images of small parts, such as a coxofemoral, elbow, tarsal or carpal joint or the sesamoid bones associated with the metacarpo- or metatarsophalangeal joints. If a pinhole collimator is used, then the number of acquired counts will need to be decreased as the acquisition time becomes prohibitive for high-count-density images. Typically, pinhole images should contain 100,000 counts as a compromise between count statistics and imaging time.

All static images should be acquired on a count basis. Generally speaking, the more counts that can be acquired, the higher the image quality, as long as motion is not an issue or can be corrected using appropriate acquisition techniques and software processing. Total counts for static image acquisitions have been recommended and are different for various body parts. Acquisition images of different body parts are based on total counts and not on preset time, (Table 8.3). If any of these images are “zoomed” prior to acquisition, the counts required need to be increased to obtain similar image quality. During acquisition, the animal should not be allowed to move. Tranquilization using hydroxymorphone should be avoided, as dogs pant excessively with this sedative. Some movement associated with respiration cannot be avoided; however, panting artifact can be minimized by manually holding the animal's

Table 8.1: Common Imaging Parameters Used in Small Animal Skeletal Scintigraphy

Animal preparation	Placement of an intravenous catheter if 3-phase imaging is to be performed. Be sure patient is well hydrated.
Radiopharmaceutical	^{99m}Tc -methylene diphosphonate (^{99m}Tc -MDP); ^{99m}Tc -hydroxymethylene diphosphonate (^{99m}Tc -HMDP).
Dosage	See Table 8.2.
Acquisition parameters	The acquisition parameters are specific to the various phases of the scintigraphic bone study. For the vascular phase, place both the area of interest and the contralateral site in the same field of view.
Mode	Dynamic (vascular phase imaging); static frame mode images (soft tissue and bone phase images).
Matrix size	$128 \times 128 \times 16[8]$ (dynamic); $256 \times 256 \times 16$ (static).
Collimator	Low-energy, all-purpose or low-energy, high-resolution.
Time to image	Depends on phase of the skeletal scintigraphy to be imaged. The vascular phase is initiated simultaneously with intravenous injection of the ^{99m}Tc -MDP. Static images during the soft tissue phase are acquired 3 to 15 minutes after administration. For bone phase images, acquisition is started 3 hours after administration.
Positioning	Lateral recumbency with the camera positioned under the table.
Views	Lateral and dorsal images of the areas of interest. Dorsal and oblique images of the head, vertebrae, and/or pelvis as indicated.

Table 8.2: Dosages of ^{99m}Tc -MDP or ^{99m}Tc -HDP Used for Skeletal Scintigraphy in Small Animals

	Dose in MBq	Dose in mCi
Small dogs and cats	185	5
Medium breed dogs	370-555	10-15
Large breed dogs	740-925	20-25
Giant breed dogs	1,110	30

muzzle closed, unless the animal struggles as a result. Positioning of the animal to image a particular body part can be critical in obtaining a high quality scan that is free of artifact. Recommendations to aid in patient positioning are listed in Table 8.4.

There are two methods that allow comparison of ^{99m}Tc -MDP uptake for opposite anatomic areas of interest (eg, right compared with the left elbow joint). The easiest method for comparing contralateral limbs is to place the areas of interest of both limbs (right

and left carpal joints) in the middle of the gamma camera within the same field of view. Care must be taken to ensure that both limbs are positioned the same distance from the camera face and not rotated relative to each other. Both limbs should be equidistant from the camera face or, ideally, in contact with the camera face. The second method for comparison of contralateral areas of anatomy is to image the right and left sides separately. The right or left side is imaged for a preset number of counts, and the amount of time required to obtain the desired number of total counts is recorded. The contralateral limb is then imaged for the same amount of time it took to acquire the first image. To use this method, it is important that the two images obtained appear as mirror images with the same centering and coverage of the limb or body part by the camera face.

Principles of Interpretation

Without experience, the normal bone scan in small animals can be difficult to interpret. Skeletally immature animals have focal-intense ^{99m}Tc -MDP areas of uptake in physeal/metaphyseal regions of long bones and at costochondral junctions (Figure 8.2). Normal areas of increased skeletal uptake in all (immature and mature) small animals include the thicker subchondral epiphyses, temporomandibular joints, ventral skull, the first cervical vertebrae (on

a lateral image if the patient is truly lateral during acquisition), caudoventral maxillary region and costochondral junctions (Figure 8.3). Normal areas of soft tissue accumulation include the kidney and the urinary bladder. Renal radioactivity is variable depending on renal function, presence of hypercalcemia, various diseases of the kidneys, and the patient undergoing current chemotherapy. If radioactivity in the urinary bladder is marked and cannot be shielded, evacuation prior to image acquisition is recommended.

Nonskeletal ^{99m}Tc -MDP uptake may be seen in calcinosis cutis, pulmonary mineralization (pulmonary alveolar mineralization, hyperadrenocorticism), renal infarction with dystrophic mineralization, acute rhabdomyolysis, the regional lymph node following extravasation of the dose,¹³ thyroid uptake of free pertechnetate, hepatic uptake secondary to oxidation of the ^{99m}Tc -MDP, and a $^{99m}\text{TcO}_2$ colloid or dystrophic mineralization of soft tissues.² ^{99m}Tc -MDP uptake has also been reported in breast tissue of lactating women¹⁴⁻¹⁶ and the uterus of pregnant women.¹⁷ Reasons for poor image quality secondary to decreased skeletal uptake of ^{99m}Tc -MDP includes: decreased cardiac output, a soft tissue mass overlying the area of interest, generalized anasarca, renal failure, and old age (normal skeletal metabolic rates are reduced).

Table 8.3: Recommendations for Count-Based Acquisitions for Specific Body Parts in Small Animal Skeletal Scintigraphy

Anatomic Section	Total Counts to Acquire
Thorax and thoracic spine	750,000
Pelvis*	500,000
Skull and cervical spine	350,000
Lumbar spine*	350,000
Cubital or stifle joints	200,000
Distal extremity (carpus and manus; tarsus and pes)	100,000

*Assumes the urinary bladder is empty or adequately shielded. The proximal thoracic and pelvic limb regions can be imaged for total counts similar to those for the thorax and pelvis, respectively.

Table 8.4: Positioning Recommendations for Small Animal Skeletal Scintigraphy

Anatomic Section	Recommendations
Dorsal skull (or ventral), spine, or pelvis	Place animal in radiolucent (V) trough, extend legs, and ensure symmetrical placement.
Lateral skull	Extend neck, rotate head axially so that eyes are perpendicular to tabletop, and pull thoracic limbs caudally.
Lateral Cervical spine	Apply traction to neck, rotate head axially as for skull; pull thoracic limbs caudally.
Lateral shoulder, elbow, antebrachium or manus	Extend neck; place shoulder to be imaged down with the ipsilateral thoracic limb extended and pulled cranially. Pull contralateral thoracic limb caudally. Adjust the field of view distally to acquire the distal limb and extremity.
Lateral thorax or thoracic spine	Pull thoracic limbs cranially.
Lateral lumbar spine	Evacuate (or shield) urinary bladder; pull pelvic limbs caudally.
Lateral pelvis	Evacuate (or shield) urinary bladder; pull pelvic limbs caudally, rotate pelvis axially until ilia are superimposed.
Lateral femur, stifle, crus, tarsus or pes	Evacuate (or shield) urinary bladder, place stifle to be imaged down, pull pelvic limb to be imaged caudally placing the stifle in center of the camera. Abduct contralateral stifle out of field of view. Adjust the field of view distally to acquire the distal limb and extremity.
Distal limbs	For a palmar or plantar view, place both limbs next to each other in same field of view and center and rotate each limb until the two are symmetric.
	For a lateral view, extend the limb to be imaged and abduct the contralateral limb away from the camera face. Place a lead shield on the medial side of the limb imaged to prevent contamination of the image from the contralateral limb.

Table 8.5: Indications for Small Animal Scintigraphy

Evaluate primary or metastatic bone disease.
Evaluate for septic arthritis or osteomyelitis.
Evaluate bone and soft tissue viability after traumatic injury.
Evaluation of occult lameness (radiographs normal or equivocal change).
Identification of soft tissue inflammation.
Identification of viability of limb sparing or salvage procedures.
Evaluate for stress fractures.

Clinical Skeletal Scintigraphy

The indications for small animal skeletal scintigraphy in small animals and the expected imaging results are summarized in Tables 8.5 and 8.6. These include evaluation for primary and metastatic disease, septic arthritis, osteomyelitis, prosthetic implant loosening or infection, soft tissue and bone viability, occult lameness, and fracture healing. Because of the increased sensitivity to early bone turnover, ^{99m}Tc -MDP scintigraphy may help to localize subtle lesions that are not seen on routine radiographs.

Neoplastic Disease

Skeletal scintigraphy is one of the most common nuclear medicine procedures done in human medicine. In humans, the most common indication is the evaluation of possible or extent of known metastatic bone disease.¹⁸ Bone scanning has been shown to be a sensitive indicator for the detection of skeletal metastasis.^{19,20} However, recent human studies have

shown that metastases to the bone marrow may result in changes in signal intensity on magnetic resonance images (MRI), particularly T2 weighted images, prior to an increased ^{99m}Tc -MDP uptake.¹⁸ In veterinary medicine, overall rate of occurrence of skeletal metastasis is not known, but considered low (<10%).²¹ Bone metastasis has been documented in prostatic, pulmonary, transitional cell, thyroid and mammary gland carcinomas as well as malignant histiocytosis and primary bone tumors (osteosarcoma).^{21,22} Skeletal scintigraphy has been shown to be 30% to 50% more sensitive for the detection of metastatic bone disease than radiographs in humans.²³ Because of this, skeletal scintigraphy may document undetected metastatic sites prior to skeletal pain.²² By allowing earlier detection of metastatic bone disease, one can alter treatment options according to the tumor type and scintigraphic findings. Several patterns of metastatic bone disease have been described. The most common abnormal uptake pattern includes variably sized, multifocal (polyostotic), intense hot spots that are randomly distributed throughout the skeleton.²⁴ The axial skeleton is most commonly affected, including the vertebral bodies,

Figure 8.2: Normal bone phase images from skeletally immature dog

Intense focal uptake is seen in the region of the physis and metaphysis, conforming to the shape of the physis as viewed radiographically. Note the location of the proximal radial physis that overlies the area of the medial coronoid process. This should not be confused with a fragmented medial coronoid process (right lateral images are the images with the dog facing toward the right and the left lateral image are the images with the dog facing toward the left).

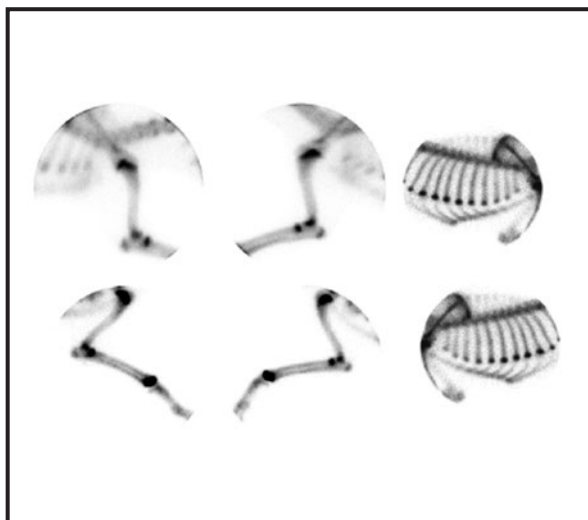
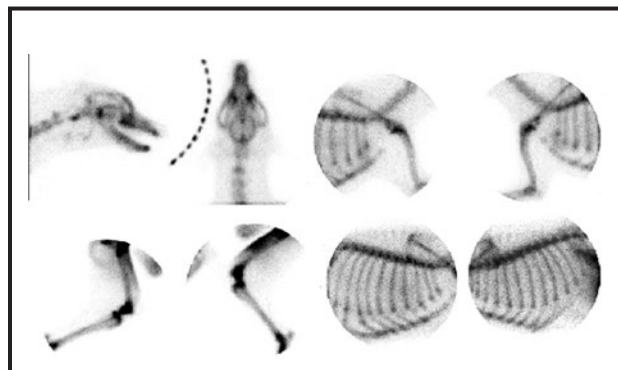


Figure 8.3: Normal bone scan in an adult dog

Right lateral, left lateral and dorsal images acquired 3 hours post ^{99m}Tc -MDP administration. When compared with the immature canine bone scan in Figure 8.2, there are increased soft tissue (background) counts. In older dogs with renal compromise, the target-to-background ratio is diminished so that the bone uptake does not appear as distinct. Note the location of normal areas of increased ^{99m}Tc -MDP uptake compared with the remaining skeletal structures, which include the atlas (end-on transverse processes), occiput, temporomandibular joints, epiphyseal subchondral bone regions, caudoventral maxilla, and costochondral junctions.



ribs, skull, and pelvis followed by appendicular skeletal uptake where the proximal limbs are more likely to be affected (Figure 8.4).²⁵ In the skull, the metastatic lesions are usually associated with suture lines. Abnormal ^{99m}Tc -MDP uptake in the ribs secondary to metastatic disease is randomly distributed, whereas increased ^{99m}Tc -MDP uptake at the same level on adjacent ribs is most often due to previous trauma. Normal areas of increased uptake can be seen at the costochondral junctions and may need to be differentiated from metastatic disease by using follow-up radiographs.

If the appendicular skeleton is involved, metastatic lesions are usually found in the diaphysis, in the region of the nutrient foramen. False-negative bone scans are uncommon but can occur due to the fact that up to 5% of bone metastasis shows no significant ^{99m}Tc -MDP uptake as alterations in regional osteogenesis or blood flow have not taken place.²⁶ A large study of multiple myelomas in veterinary patients has not been done. Multiple myelomas can have a normal or abnormal pattern of ^{99m}Tc -MDP uptake. As skeletal scintigraphy is a sensitive test, but not specific to any disease process, abnormal areas of increased uptake should be differentiated from benign bone lesions that may have similar focal ^{99m}Tc -MDP uptake. These would include osteophyte and enthesiophyte formation, bone islands, bone infarcts, spondylosis deformans, panosteitis, or

chronic fractures. These lesions can usually be differentiated based on the location of uptake (metaphyseal, diaphyseal, or within a joint space), the clinical history, signalment, the physical examination, and pertinent radiographic abnormalities.

A persistent problem in both human and veterinary medicine is that of a solitary focus of increased uptake in a patient known to have a primary tumor elsewhere. Although there is not a similar type study in veterinary medicine, Tumah reported only 10% of solitary rib lesions were due to metastatic disease in a group of patients with known breast cancer.²⁷ In these cases, radiographic correlation is essential; and demonstration of benign radiographic features can sometimes answer the question definitively. However, histologic confirmation may still be required.

Survey radiographs are usually the first imaging modality for the evaluation of dogs and cats with primary bone tumors, such as osteosarcoma, chondrosarcoma, and fibrosarcoma. The skeletal scintigraphic appearance of primary bone tumors includes a typical metaphyseal location with intense ^{99m}Tc -MDP uptake. Some tumors may have photopenic centers or areas of heterogeneous uptake consistent with areas of necrosis (Figure 8.5).^{28,29} Skeletal scintigraphy is used in these dogs to rule out the presence of metastatic lesions prior to amputation,

Table 8.6: Phases of Bone Scan with Expected Findings for Specific Diseases

Disease	Vascular Phase*	Soft Tissue Phase*	Bone Phase*
Cellulitis	+	++	—
Vascular damage and compromise	absent	absent	absent
Septic arthritis	++	++	+
Osteomyelitis	++	++	+++
Fracture	+/-	+	++
Chronic degenerative joint disease	—	—	+
Bone tumor	+	+	+++

Increased ^{99m}Tc -MDP uptake, where + = mild uptake; ++ = moderate uptake; +++ = intense uptake; - = a normal ^{99m}Tc -MDP pattern and distribution; and absent = no ^{99m}Tc -MDP uptake.

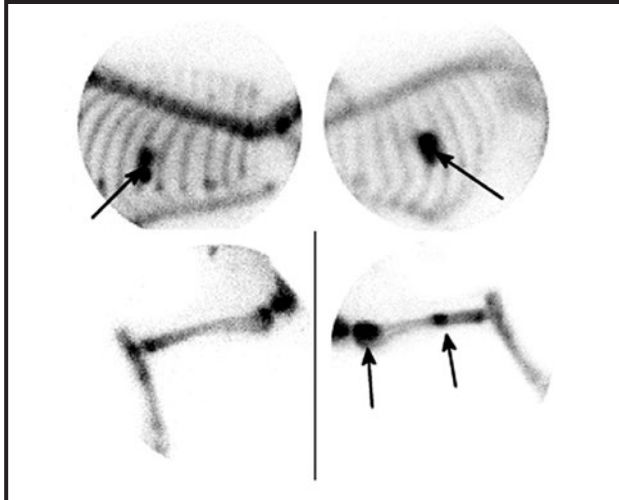


Figure 8.4: Skeletal metastases

Multifocal, intense ^{99m}Tc -MDP uptake is seen in multiple ribs, the proximal metaphyseal and mid-diaphyseal region of the left tibia (arrows). The lateral image of the right crus is normal and is provided for comparison.

chemotherapy, radiation therapy, or limb-sparing techniques. MRI has proven to be superior to radiography, computed tomography, and scintigraphy in evaluating the extent and degree of invasiveness of primary or metastatic bone tumors.³⁰⁻³² Skeletal scintigraphy will overestimate the extent of primary bone tumors due to bone reactivity at the margins of the tumor and bloom of the increased ^{99m}Tc -MDP uptake (Figure 8.6).²⁸ In the case of bloom, the marked increase in ^{99m}Tc -MDP uptake is larger than the actual tumor dimensions within the bone. Pulmonary metastasis may demonstrate a faint area of increased ^{99m}Tc -MDP uptake on scintigraphic images of the thorax, and areas of soft tissue mineralization secondary to either metastatic or dystrophic mineralization may also be seen as areas of ^{99m}Tc -MDP uptake on the scintigraphic examination (Figure 8.7 and Figure 8.8).

Infection

In skeletally mature small animals, acute hematogenous osteomyelitis is rare, where septic arthritis and discospondylitis are more common. Hematogenous osteomyelitis is most commonly seen in immature small animals and appears as an intense area of increased linear cortical uptake within 24 to 48

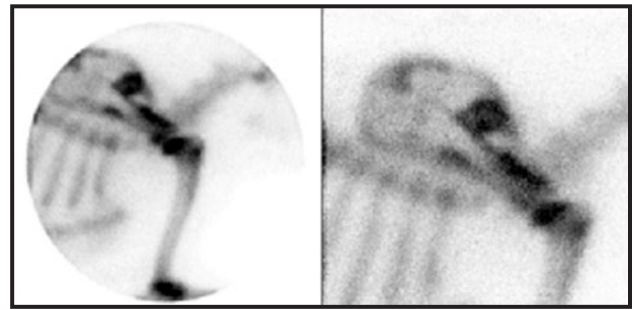


Figure 8.5: Primary bone tumor, right scapula

An irregular area of focal, intense heterogeneous ^{99m}Tc -MDP uptake is seen along the dorsal margin of the spine of the right scapula with abnormal areas of ^{99m}Tc -MDP uptake noted at various locations in the supraspinous fossa. The lesion contains a photopenic center, consistent with a central area of necrosis. The histologic diagnosis was osteosarcoma.

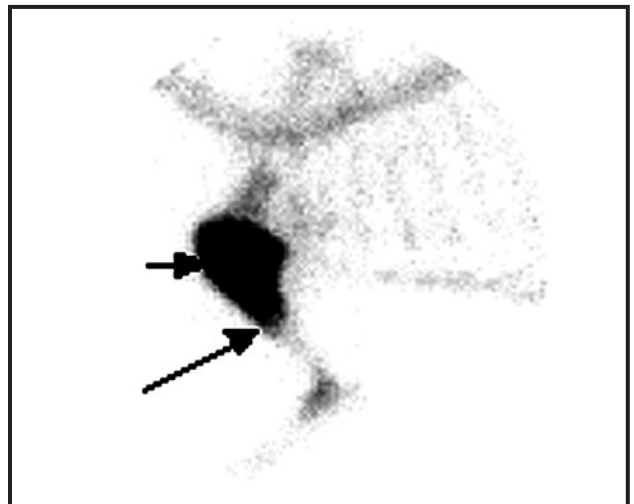


Figure 8.6: Primary bone tumor, left humerus

There is a large homogeneous area of intense ^{99m}Tc -MDP uptake in the proximal left humeral metaphysis (small arrow). Note that the lesion does not appear to cross the scapulohumeral joint space and appears to extend to the mid-diaphyseal region (bloom effect, long arrow). The distal area of increased ^{99m}Tc -MDP uptake may also represent reactive bone between the neoplasm and normal bone. The histologic diagnosis was osteosarcoma.

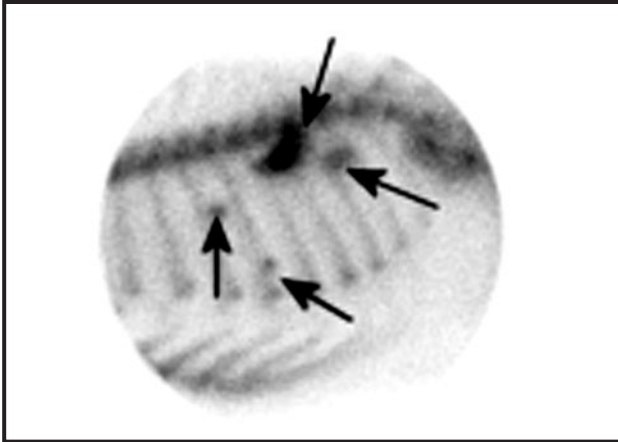


Figure 8.7: Pulmonary metastatic nodules

There are areas of abnormal ^{99m}Tc -MDP uptake noted between the ribs (arrows). The degree of ^{99m}Tc -MDP uptake within these areas varies (mild to marked intensity). Differentiation from rib lesions on the opposite side of the thorax (shine-through) is done by evaluating the specific sites noted on the original image. In this dog, the uptake was within pulmonary nodules associated with metastatic osteosarcoma.

hours, whereas radiographs are usually not positive for 10 days after the onset of clinical signs in adult humans.³³⁻³⁵ ^{99m}Tc -MDP uptake has been shown to persist for weeks to months after the infection has resolved.²⁹ Because of this, skeletal scintigraphy is not helpful in determining the presence of active disease, although a negative scan usually excludes active infection. Focal areas of ^{99m}Tc -MDP uptake on bone phase images will be seen in some cases of septic arthritis (Figure 8.9), septic physisitis, and discospondylitis (Figure 8.10) prior to any radiographic changes.^{36,37}

Occult Lameness Evaluation

Occult lameness can be defined as a persistent, subtle, undiagnosed lameness that cannot be localized based on physical or orthopedic examination. If anatomic localization is possible, radiographs may be normal or inconclusive. Causes for an occult canine lameness include fragmented medial coronoid processes, partial tear of the cranial cruciate ligament, meniscal injury, stress fractures, and fractures of the metacarpophalangeal or metatarsophalangeal sesamoid bones (Figure 8.11). Both bone-phase and three-phase skeletal scintigraphy may be useful in



Figure 8.8: Accumulation of ^{99m}Tc -MDP in soft tissues

Dorsal image of thorax from a dog obtained 3 hours after injection of ^{99m}Tc -MDP. There is abnormal soft tissue ^{99m}Tc -MDP accumulation with a marked increase in renal parenchymal ^{99m}Tc -MDP uptake that is bilateral and symmetrical in appearance. In addition, there is a generalized ^{99m}Tc -MDP uptake pattern in the lungs where a photopenic area is noted, centrally indicative of the cardiac silhouette. Causes of metastatic or dystrophic mineralization should be considered for both the pulmonary and renal ^{99m}Tc -MDP uptake.

helping to localize areas of osteoblastic activity or abnormal blood flow. However, a positive scintigraphic abnormality does not equate with a definitive cause of lameness.

Panosteitis

Panosteitis appears on bone scans as intense linear uptake, within the medullary cavity of long-bone diaphyses (Figure 8.12). Positive abnormalities on skeletal scintigraphy can be helpful to diagnose panosteitis in dogs with equivocal radiographic changes.

Fragmentation of the Medial Coronoid Process and Canine Elbow Dysplasia

Radiography is the primary imaging modality used to assess fragmentation of the medial coronoid process (elbow dysplasia). Radiographs, however, can be inconclusive early in the disease, as many of the abnormalities that are seen are associated with secondary degenerative changes of the elbow joint.³⁸⁻⁴⁰ Computed tomography (CT) has been shown to have excellent sensitivity in the diagnosis of fragmentation of the medial coronoid process.³⁹ Skeletal scinti-

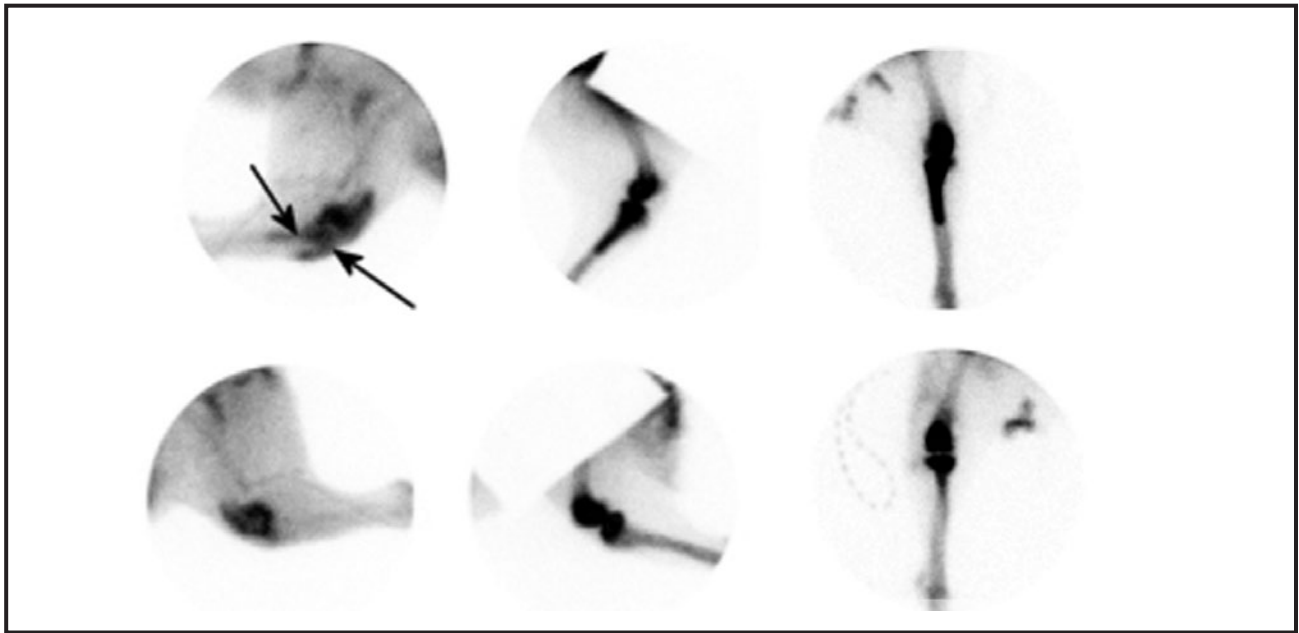


Figure 8.9: Osteomyelitis and septic arthritis

Soft tissue phase and bone phase static images of the right (top row of images) and left (bottom row of images) stifle joints. On the soft tissue phase images, there is marked soft tissue and early bone ^{99m}Tc -MDP uptake seen in the proximal metaphyseal/diaphyseal regions of the right tibia and within the right stifle joint (arrows). On the bone phase images there is intense ^{99m}Tc -MDP uptake of the distal metaphyseal/epiphyseal regions of the femurs and proximal metaphyseal regions of the tibias (right greater than left). *Staphylococcus aureus* was cultured from the synovial fluid of both stifle joints. There is also increased ^{99m}Tc -MDP uptake in the soft tissues cranial to the left stifle.

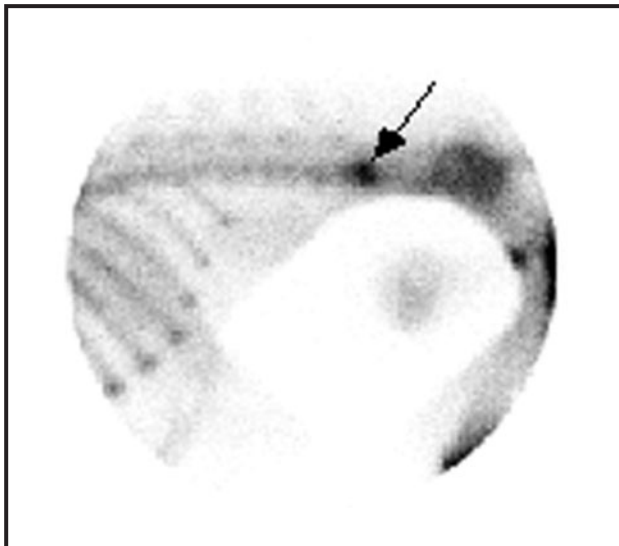


Figure 8.10: Discospondylitis

A left lateral bone phase image of the lumbar spine shows marked focal intense ^{99m}Tc -MDP uptake at the vertebral end plates of L5-6.

graphic findings that are suggestive of a fragmented medial coronoid process are dependent on the dog's age. In immature dogs (6 to 12 months old), the medial coronoid process overlies the proximal radial physis on the lateral view (Figure 8.2). An area of intense ^{99m}Tc -MDP uptake in this region may be due to either fragmented medial coronoid disease and/or the ^{99m}Tc -MDP uptake in the proximal radial physis. Comparison of the amount and pattern of uptake with the opposite limb can be helpful in diagnosing a unilateral fragmented medial coronoid process if the radiographs are normal. Focal intense uptake associated with the proximal radial physis should be symmetrical. Asymmetrical uptake between the right and left elbow joints would suggest a possible diagnosis of fragmented medial coronoid process. Frequently, however, fragmented coronoid processes are bilateral; and delineation on scintigraphy may not be possible. In skeletally mature animals, the amount of ^{99m}Tc -MDP uptake by the radial head/medial coronoid process region should be similar to or less than the distal humeral condyle in the lateral projection. Focal increased uptake by the region of

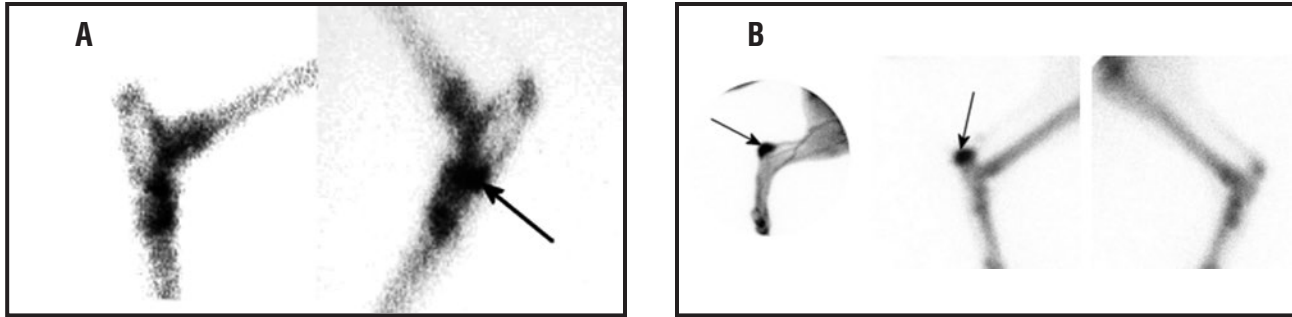


Figure 8.11: A, Avulsion fracture, insertion of the tarsal plantar ligament, left tarsus

A focal area of intense ^{99m}Tc -MDP uptake corresponding to the insertion site of the tarsal plantar ligament along the plantar aspect of the left fourth tarsal bone (arrow).

B, Enthesopathy and syndesmitis, common calcaneal tendon insertion, right tuber calcaneus

Soft tissue and bone phase images show focal, marked ^{99m}Tc -MDP uptake in the region of the right tuber calcaneus (arrows). The bone phase image of the left crus is also available for comparison.

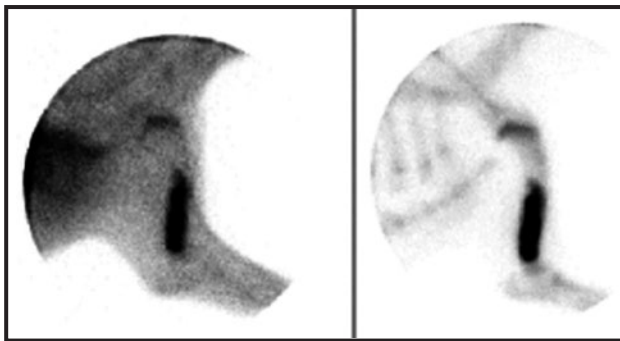


Figure 8.12: Canine panosteitis

Right lateral soft tissue and bone phase images of the brachium and proximal right thoracic limb. The soft tissue image obtained at 5 minutes after ^{99m}Tc -MDP injection shows early ^{99m}Tc -MDP in the humeral diaphysis. This does not represent abnormal soft tissue accumulation of the ^{99m}Tc -MDP. On the bone phase image, there is marked focal intense ^{99m}Tc -MDP uptake in a linear pattern in the mid-diaphyseal region of the right humerus.

the medial coronoid process that is greater than that seen by the distal humeral condyle is consistent with fragmented medial coronoid disease (Figure 8.13).⁴¹ In both young and older animals, caudal images, or images obtained using a pinhole collimator may be helpful for differentiating ^{99m}Tc -MDP uptake by the radial head versus abnormal ^{99m}Tc -MDP uptake in the medial coronoid process.

Stifle Injuries

Three-phase bone scans may also be helpful in localizing inflammatory and bone remodeling changes that can be seen in dogs with a ligamentous injury (Figure 8.14).⁴² The soft tissue phase images may be useful to differentiate acute inflammatory synovitis from chronic joint effusion without concurrent inflammation. In the normal canine stifle, there is a distinct photopenic area seen within the cranial aspect of the stifle joint that corresponds with the shape and location of the infrapatellar fat pad. In dogs with an active synovitis, there is increased ^{99m}Tc -MDP uptake noted in this area. This same uptake pattern is not seen in dogs with chronic effusion or joint capsule thickening. The role of skeletal scintigraphy for the evaluation of stifle joints after acute cranial cruciate ligament injury has not been documented.

Stress Fractures

Stress fractures result from repetitive, prolonged muscular action on bone that is not accustomed to such stress. Typical clinical signs include mild to marked lameness, bone pain, and minimal soft tissue swelling. In dogs, stress fractures are seen in athletic and working breeds and most commonly occur within the diaphyseal portions of long bones, particularly the tibia (Figure 8.15). Skeletal scintigraphy has proven to be highly sensitive in the early detection of stress-related bone disease, often documenting increased ^{99m}Tc -MDP uptake prior to the presence

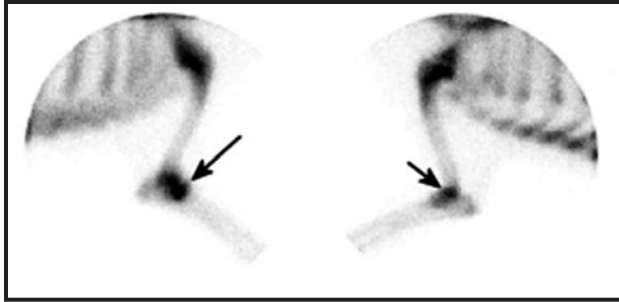


Figure 8.13: Fragmentation of the medial coronoid process

Right (left) lateral and left (right) lateral static bone-phase images of the proximal thoracic limbs. There is focal intense ^{99m}Tc -MDP uptake seen in the region of the right medial coronoid process (long arrow), greater than that seen by the adjacent right distal humeral condyle. Comparison with the contralateral normal left elbow shows a normal amount of ^{99m}Tc -MDP uptake associated with the distal humeral condyle (short arrow), which is greater than the degree of ^{99m}Tc -MDP uptake seen in the area of the medial coronoid process (proximal ulna and radius).

of radiographic abnormalities.⁴³⁻⁴⁵ Specific sites of predilection for the development of stress fractures in racing greyhounds have been reported. These include the pelvis (dorsal acetabulum), tibia, and tarsus.^{46,47}

Multipartite Sesamoids Versus Acute or Chronic Sesamoid Fracture(s)

In humans, the incidence of bipartite sesamoid bones at the metatarsophalangeal joint is approximately 10% to 33%. Although the incidence in small animals is not known, rottweilers, greyhounds, doberman pinschers and labrador retrievers may have a higher incidence of multipartite sesamoids.^{40,41} These multipartite sesamoids are the abaxial sesamoids (numbers II and VII) associated with the second and fifth metacarpophalangeal or metatarsophalangeal joints. These sesamoids are associated with the tendon of insertion of the interosseous muscle. Skeletal scintigraphy may help differentiate multipartite sesamoid bones from fractures. Multipartite sesamoids will not have abnormal ^{99m}Tc -MDP uptake, whereas recently fractured sesamoid bones should have marked focal ^{99m}Tc -MDP uptake (Figure 8.16).

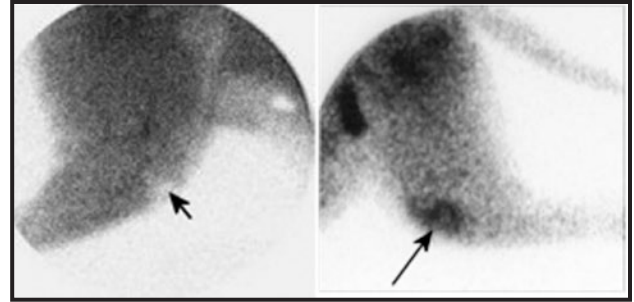


Figure 8.14: Partial tear, left cranial cruciate ligament

Right lateral (left) and left lateral static soft-tissue image of the stifle and proximal pelvic limbs. There is regional increased uptake seen within the left stifle joint (long arrow) on soft tissue phase images. The normal right stifle shows the typical photopenic triangle that corresponds to the infrapatellar fat pad (short arrow). This indicates an active synovitis. In this dog, this was attributed to partial tear of the cranial cruciate ligament.

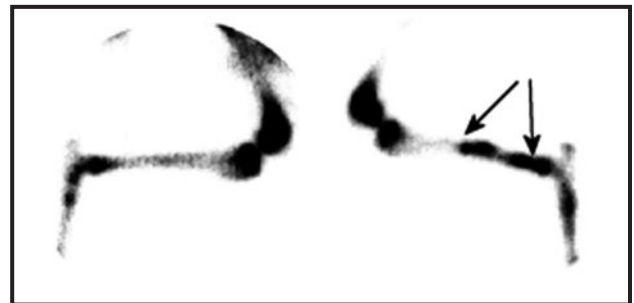


Figure 8.15: Stress fractures, left tibia

Right lateral (left) and left lateral (right) static bone-phase images of the distal pelvic limbs. There are focal areas of intense ^{99m}Tc -MDP uptake in the mid to distal diaphyseal region of the left tibia (arrows). There are normal areas of focal uptake in the metaphyseal regions in this young animal. Without clinical and radiographic correlation, the area of diaphyseal ^{99m}Tc -MDP uptake might also represent panosteitis; osteomyelitis; or, less likely metastatic bone lesions due to the age of the dog.

Acute Fractures/Fracture Healing

Evaluation of acute fractures and fracture healing can also be performed using skeletal scintigraphy. Bone phase images are sensitive for the identification of fractures. Pathologic fractures, malignant transfor-

mation, acute traumatic injuries, and healed fractures may show the same degree of increased ^{99m}Tc -MDP uptake, emphasizing the lack of specificity of skeletal scintigraphy. It has been reported in humans that bone phase images are positive at 24 hours in 80% of patients; by 72 hours 95% of patients will have increased ^{99m}Tc -MDP uptake, and by 7 days 98% of the fractures will have increased ^{99m}Tc -MDP uptake.⁴⁸ It has also been shown that 90% of patients with a previous fracture are negative on bone phase images at 2 years after radiographic healing.¹² Skeletal scintigraphy may be helpful for evaluating nonunion fractures and the relative blood supply to a nonunion fracture or traumatic injury. Focal intense uptake at fracture ends most likely indicates viable tissue and possible fracture union. Absent ^{99m}Tc -MDP uptake at fracture ends would be indicative of a non-union.⁴⁹

Avascular Necrosis

Avascular necrosis of the femoral head (Legg-Calve-Perthes disease) has a unique appearance depending on the time point after the initial vascular event when the dog is imaged. Within 12 to 48 hours after vascular disruption, a focal photopenic area can be identified within the femoral head (may need to use a pin-

hole collimator). This is followed by a rim of focal ^{99m}Tc -MDP uptake, with moderate intensity around a central photopenic core within the femoral head at 1 to 3 weeks after the initial event. As revascularization and remodeling occur, the central photopenic area will have a similar ^{99m}Tc -MDP uptake pattern to the remainder (periphery) of the femoral head.⁵⁰

Three-Phase Skeletal Scintigraphy

Multiphase skeletal scintigraphy can be helpful in differentiating active septic from nonseptic conditions.⁵¹ The three-phase bone scan (Table 8.6) consists of an initial vascular phase that is acquired as a dynamic study (2 sec/frame for 30 frames) for the evaluation of blood flow to an anatomic area (Figure 8.17). The dynamic acquisition is started just prior to the ^{99m}Tc -MDP injection. The ^{99m}Tc -MDP injection should be made in a limb that is not in the field of view of the gamma camera and should be injected in bolus fashion (within 2 seconds) through a pre-placed intravenous catheter followed by saline flush. The use of an extension set and three-way stopcock is preferred. Because of the dynamic acquisition, the arterial phase is limited to the area of interest. Postprocessing of the dynamic data set may include smoothing and reformatting operations (see Chapter 5) best viewed using a cine loop from the processing computer work station. The dynamic data set is reframed to 3 to 4 seconds per frame so that a higher total count density will allow easier visualization and distinction between the arterial and venous blood pool phases.

The second phase of imaging is called the soft-tissue or blood-pool phase. Static images are acquired of the anatomic areas of interest. These images include four images that are initiated 3 to 5 minutes postinjection of the ^{99m}Tc -MDP. Images are acquired for 300,000 to 500,000 counts of the anatomic region of interest and the contralateral area used for comparison (Figure 8.18). Because the radiopharmaceutical distribution is rapidly changing, four static images are acquired where the area of interest is imaged first; then the animal is repositioned and two static images of the contralateral area are obtained. Finally, the animal is repositioned to the original affected region and the last image obtained. Interpreting the soft tissue phase involves both a direct comparison of the images between the affected and contralateral

Figure 8.16: Fractured sesamoid bone, fourth digit of the right thoracic limb

Ventral bone-phase, static images of the right and left distal thoracic limbs. There is focal, intense ^{99m}Tc -MDP uptake at the right fourth metacarpophalangeal joint (arrow) consistent with fracture of one of the palmar sesamoids of the interosseous muscle.



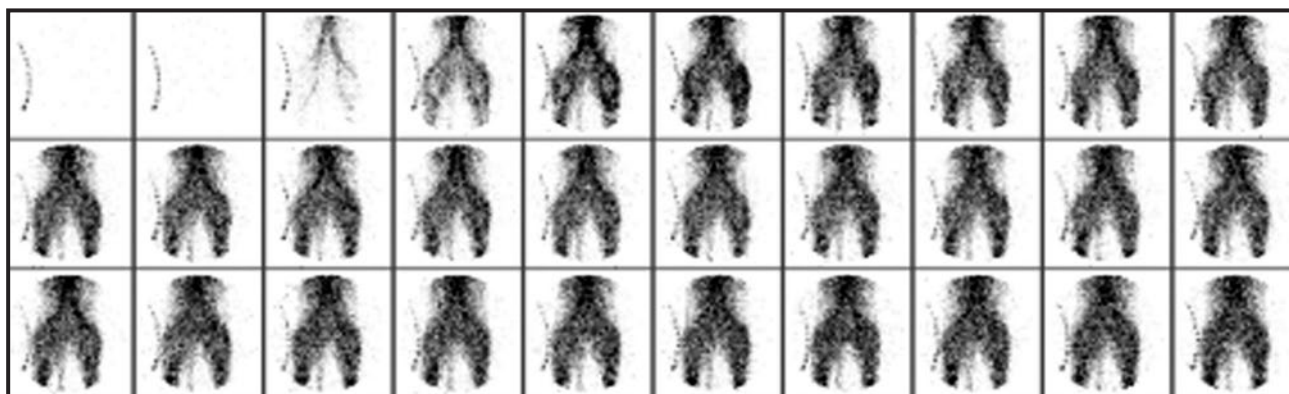


Figure 8.17: Normal dynamic, vascular-phase images

Dorsal images of the pelvis obtained at 2 sec/frame immediately following injection of a bolus of ^{99m}Tc -MDP. On frame 3 (numbered from right to left starting in the left upper corner), the caudal abdominal aorta, and external and internal iliac arteries are seen. Symmetrical distribution of the ^{99m}Tc -MDP is seen during the arterial and venous phases of the vascular study. After it is in the tissue capillaries, the ^{99m}Tc -MDP rapidly distributes to the extracellular interstitial fluid space. An external, radioactive marker has been placed along the left coxal joint and proximal left pelvic limb.

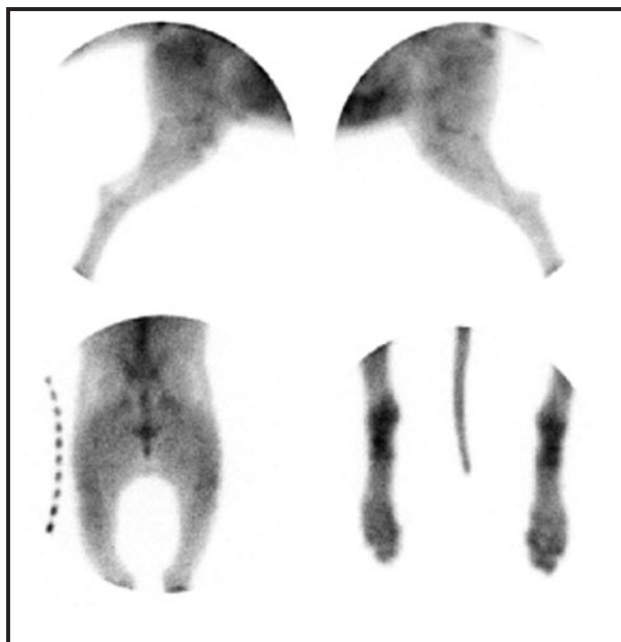


Figure 8.18: Normal soft-tissue phase images

Static right lateral and left lateral soft tissue phase images of the pelvic limbs. A dorsal image of the pelvis (left is on the side of the image with the external radioactive marker). Plantar image of the distal pelvic limbs obtained starting at 5 minutes after ^{99m}Tc -MDP injection. By the last image acquisition (lower right hand corner); early bone uptake is seen.

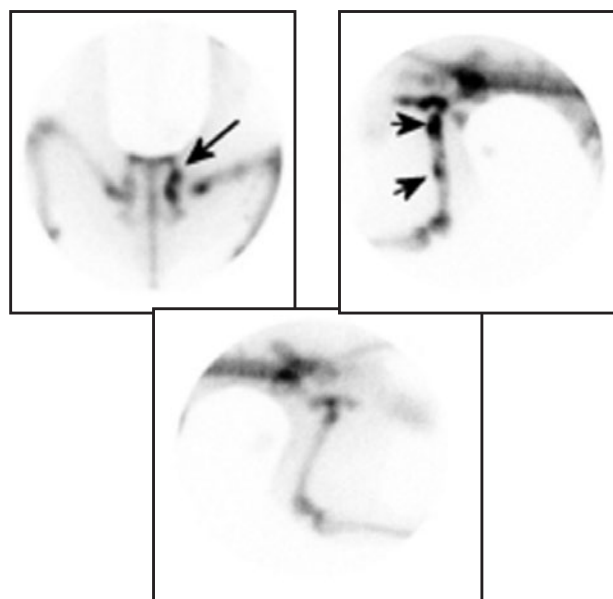


Figure 8.19: Loose acetabular and femoral prostheses

Static bone-phase images document focal areas of intense ^{99m}Tc -MDP uptake along the caudal cortex of the right femoral mid-diaphysis (small arrows, right lateral image), corresponding to the level of the distal aspect of the femoral stem. Additional areas of increased ^{99m}Tc -MDP activity are present in the caudal cortex of the proximal femur (small arrows) and acetabular rim (long arrow, "frog-leg" ventral image).

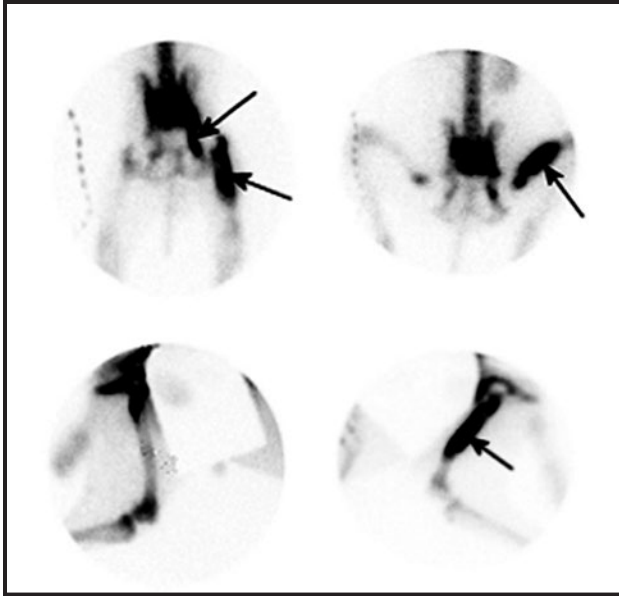


Figure 8.20: Septic total hip arthroplasty

Static bone-phase images including an extended leg and "frog-leg" ventral image of the pelvis. Lateral static images of the right and left femur are also available. There is marked ^{99m}Tc -MDP uptake associated with the entire portion of the left femoral and acetabular prosthetic implants (arrows).

sides. This way, temporal changes can be appreciated, particularly in the radiopharmaceutical distribution in the affected limb. Early bone uptake will normally be seen by the last soft-tissue phase images.

Phase three of the skeletal scintigraphic study represents the static bone-phase images that are obtained at 3 to 4 hours after ^{99m}Tc -MDP administration. The static images obtained should include the areas of interest and the contralateral side. A matrix size of $256 \times 256 \times 16$ is recommended for both the soft-tissue and bone-phase images. Delayed phase 24-hour images can also be obtained, although this is rarely done due to poor photon flux (decay of the ^{99m}Tc -MDP) and lack of proven advantages for acquiring this image.

Three-phase skeletal scintigraphy can be helpful to differentiate noninflammatory and inflammatory diseases, identifying a loosened or septic total hip arthroplasty. The typical appearance of a loosened femoral component includes a normal vascular and blood pool phase with focal increased activity of moderate intensity seen at the level of the distal tip

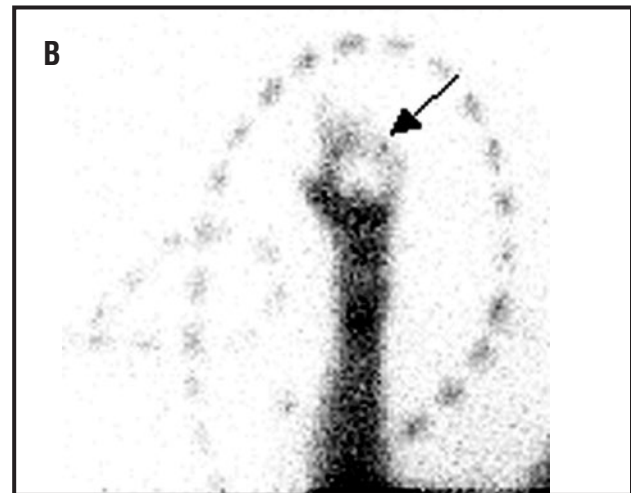
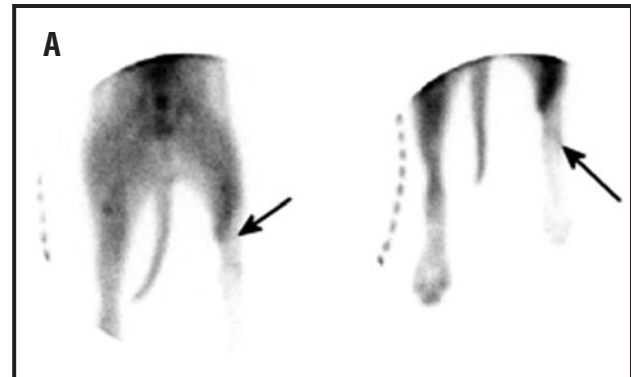


Figure 8.21: A, Perfusion Defect, Distal Left Pelvic Limb

This dog had been previously hit by a car and had a chronic malunion of the left tibia. On soft-tissue phase ventral images, there is little to no perfusion of the affected limb distal to the area of fracture (arrows). The second soft tissue phase plantar image was obtained immediately after the first image. There is early increase in ^{99m}Tc -MDP uptake at the level of the tibial malunion fracture.

B, Perfusion Defect, Distal Left Thoracic Limb

This dog had previously received a crushing injury to the metacarpal region resulting in decreased ^{99m}Tc -MDP perfusion to the digits during the vascular phase. This soft tissue phase image was obtained 5 minutes after ^{99m}Tc -MDP injection. A circular, flexible ^{57}Co marker has been placed around the distal limb.

of the femoral stem, usually in the mid-diaphyseal region on the bone phase images. Loosening of the acetabular component is seen as a curvilinear area of focal, moderately intense ^{99m}Tc -MDP uptake along the acetabulum on bone phase images and normal soft tissue phase images (Figure 8.19). Sepsis of the prosthetic (acetabular or femoral) should be considered when there is moderate to marked ^{99m}Tc -MDP uptake on all three phases of the bone scan associated with either the acetabular or femoral implants (Figure 8.20).⁵²

Three-phase skeletal scintigraphy is also helpful to assess tissue viability secondary to trauma, gunshot injury, and frostbite (Figure 8.21).^{53,54} Decreased or absent perfusion on the vascular, soft tissue and bone phase images may indicate nonviable tissue. It has been recommended to repeat the study in 24 to 48 hours to determine if any reperfusion is present. If there is no change, then the limb should be presumed to be nonviable, thereby necessitating amputation. Decreased perfusion but normal uptake on the bone phase images indicates some degree of vascular integrity and tissue viability.

Summary

Skeletal scintigraphy is a useful imaging tool for evaluating dogs and cats with lameness as well as small animals with primary or secondary bone tumors. An excellent-quality study is required to ensure that each phase of the scintigram can be evaluated and interpreted. Working knowledge of normal anatomy, physiology, pathology, and orthopedic disorders in dogs and cats is necessary when interpreting skeletal scintigraphy. Interpretation is based on successful identification of abnormal areas of increased or decreased ^{99m}Tc -MDP patterns that deviate from the expected norm for the age of the patient. Future areas of investigation include imaging bone tumors with novel radiopharmaceuticals and evaluating these radiopharmaceuticals for prognostic potential in predicting response to therapy, patient outcomes, time to remission, and survival data.

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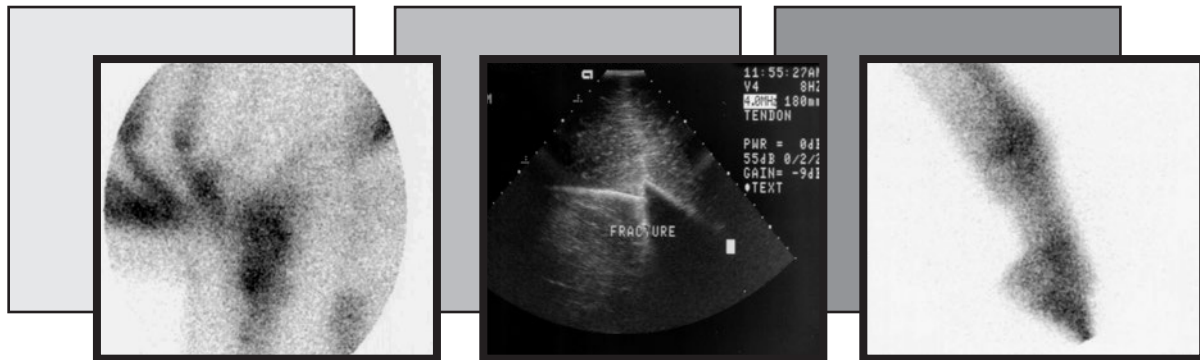
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Equine Skeletal Scintigraphy

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Introduction

Skeletal scintigraphy has been used in equine imaging for over 30 years and is now a well-established technique.^{1,2} Most veterinary schools and many private practices have gamma cameras for nuclear imaging, and equine skeletal scintigraphy forms the majority of scintigraphic studies at these hospitals. Equine athletes are frequently pushed to their physiologic and biomechanical limits, and musculoskeletal injuries are common. The excellent sensitivity of scintigraphy in detecting lesions with increased bone turnover is ideally suited to the horse where large physical size limits radiographic and ultrasonographic studies. The indications for equine scintigraphy are summarized in Table 9.1.

Technique

An indwelling external jugular, intravenous catheter is used to deliver the radiopharmaceutical as this largely eliminates the possibility of perivascular injection. The catheter can also be used for administering sedatives prior to the imaging procedures. The feet may be wrapped before injecting the radiopharmaceutical dose. The distal limb wraps can

then be removed at the stall at the time of delayed bone phase imaging. This procedure reduces urine contamination of the foot and is essential if a lesion is suspected in that area. If a nuclear angiogram or soft tissue phase study is to be obtained the horse is injected in the imaging room; if not the injection is performed in the stall. If the pelvis is to be imaged, furosemide may be injected intravenously at a dose of 150 mg per 500 kg body weight 1 hour prior to imaging. This will reduce the quantity of radiopharmaceutical in the urinary bladder thereby improving the quality of pelvic and femoral images. Sedation is frequently necessary and a blindfold may also be employed. Overzealous use of sedative drugs may render the patient ataxic and cause significant motion artifact. Pieces of leaded rubber or leaded portable boards are useful for shielding body parts that are to be excluded from the image. Positioning aids, such as a plastic shelf to support the horse's head, reduce the necessity for manual restraint thereby decreasing personnel exposure.³ The common imaging parameters used in equine scintigraphy are summarized in Tables 9.2 and 9.3.

Table 9.1: Indications for Equine Bone Scintigraphy*

Lameness that cannot be localized (even with local anesthesia).
Lameness localized by local anesthesia but radiographic or ultrasonographic lesions are not seen.
Multiple limb lameness.
Lameness that cannot be ameliorated by local anesthesia or lameness originating from the proximal limb.
Abnormal gait with no evidence of neurologic disease.
Suspected spinal pain.
Suspected pelvic fractures.
Suspected fracture without radiographic change, ie, before radiographic evidence of bone resorption in nondisplaced fractures.
Assess viability of distal limb and extremity following tourniquet-type injuries.
Suspected osteomyelitis, septic arthritis, or septic physitis (young foals).
Suspected acute rhabdomyolysis.

*Dyson SJ, Pilsworth RC, Twardock AR and Martinelli MJ, eds. *Equine Scintigraphy*. Suffolk, UK: *Eq Vet J*, 2003.

Table 9.2: Common Imaging Parameters for Equine Scintigraphy

Horse preparation	Placement of a jugular intravenous catheter. Be sure patient is well hydrated. Remove all horse-shoes. After initial soft tissue or vascular phase images of the distal extremity, boots and wraps can be applied to the distal extremities to prevent urine contamination of the external skin and hoof surfaces while in the stall waiting for delayed phase imaging. The boots and wraps are then removed at the stall just prior to transport to the imaging area for the bone phase.
Radiopharmaceutical	^{99m}Tc -methylene diphosphonate (^{99m}Tc -MDP); ^{99m}Tc -hydroxymethylene diphosphonate (^{99m}Tc -HMDP).
Dosage	7-11 MBq/kg (0.2-0.3 mCi/kg) or approximately 3.5 to 5.5 GBq by intravenous injection.
Acquisition parameters	The acquisition parameters are specific to the various phases of the scintigraphic bone study. For the vascular phase, a dorsal image of the thoracic limbs is typically attempted so that the area of interest and the contralateral arterial blood flow can be evaluated. The vascular phase is initiated simultaneous with intravenous injection of the radiopharmaceutical.
Mode	Static frame mode images (dynamic images can be obtained and motion corrected so that a single composite image is viewed as the single static image if the computer program has an automated motion correction algorithm).
Matrix size	256 × 256 × 16 for soft tissue and bone phase; 128 × 128 × 16 for vascular phase.
Collimator	Low-energy, all-purpose or low-energy, high-resolution.
Time to image	Depends on the phase of the skeletal scintigraphy to be imaged. For the nuclear angiogram (vascular phase), the dynamic acquisition is started simultaneous with injection of the radiopharmaceutical. Static images during the soft tissue phase are acquired 3 to 15 minutes postradiopharmaceutical administration. For bone phase images, acquisition is started 2 to 3 hours after radiopharmaceutical administration.
Positioning	Horse is standing.
Views	Lateral and dorsal images of the areas of interest are obtained. Dorsal and oblique images can be obtained of the head, vertebrae, and/or pelvis as indicated.

Radiation Safety

All personnel involved in scintigraphy should be wearing dosimetry badges. The nuclear medicine laboratory, scan room and holding stalls must all be clearly marked with the radiation hazard trefoil sign. The three conventional ALARA (as low as reasonably achievable) factors (time, distance, and shielding) are applicable in equine nuclear medicine. Contact time with the radioactive patient should be limited to the shortest possible duration. This means completing the scan as quickly and efficiently as possible. The radioactive patient and any other radioactive material should always be handled with latex gloves. These gloves have no ability to attenuate radiation but

prevent skin contamination and thus minimize the duration of exposure and prevent ingestion of any radionuclide. Food or beverages should not be permitted in the nuclear medicine area. A major source of radioactive exposure is from urinary excretion which contaminates bedding and the horse's stall.⁴ Personnel should enter the stall only when necessary and for as little time as possible. Protective plastic overboots should be worn to prevent spreading contamination around the hospital. The contaminated stall should not be cleaned until background radiation levels have been reached (10 physical half-lives or 60 hours is using ^{99m}Tc). The number of personnel involved during the scintigraphic procedure should

Table 9.3: Imaging Phases of Equine Scintigraphy

Phase	Frame Mode	Matrix Size	Time from Injection	Stop Parameters
Vascular phase	Dynamic	128 × 128 × 16	Simultaneous	1 sec/frame for 120 sec
Soft tissue phase	Static	256 × 256 × 16	Begin 5 minutes after injection	60 sec/image*
Bone phase	Static	256 × 256 × 16	Image between 90 minutes for HDMP and 3 hours for MDP	60 sec/image*

*For static frame mode acquisitions, one should determine whether one will use a time limited or count limited acquisition setup. For a time limited acquisition, typically 60 seconds is used generically for all images of the horse. Distal extremity images should be reviewed prior to releasing the horse so that if the counts are less than 75,000, the images can be repeated for longer time periods (if possible and motion is not an issue). If the static acquisition is to be terminated based on a set number of counts, or count limited (75,000 to 300,000 counts), the time for each image should be recorded. In order to compare the symmetry of radiopharmaceutical uptake for the contralateral areas, the contralateral images are then acquired for the same time that it took to acquire the original count limited images. Therefore, images will be count limited for a given body part or area and then the contralateral body part image will be acquired for the same time. Due to low count rates, images of the distal extremities are often acquired for relatively small numbers of total counts (75,000) to reduce artifacts secondary to motion. Images of the proximal limb and axial skeleton should be acquired for at least 150,000 counts to minimize image noise and improve target-to-background contrast.

be kept to the smallest number possible to safely manage the horse. A large field-of-view camera reduces the number of images required to survey the skeleton thereby reducing personnel exposure times. Lead rubber aprons, such as are worn for radiology procedures, are not usually employed but can provide some limited protection. Lead shields should always be used for syringes containing radiopharmaceuticals, and the syringe should be kept in a leaded box until needed. Once injected, the radioactive syringe should be returned to the box, as a significant proportion of the dose may remain within the syringe. There should be a shower facility nearby in case of major personnel contamination. These measures are suggestions for safe practice; but as radiation safety regulations vary considerably, the local regulatory authority should be consulted.

The Scintigraphic Examination

The study may be divided into three phases, and images may be obtained at any or all phases depending upon the clinical question(s) to be answered.⁵ The vascular phase or nuclear angiogram lasts for the first 1 to 2 minutes following intravenous injection of the radiopharmaceutical. In this phase, the radio-

pharmaceutical is distributed throughout the intravascular space or blood pool. This is followed by diffusion of the radiopharmaceutical into the extracellular fluid (interstitial) space, and equilibrium is rapidly reached. At this point, soft tissue phase static images can be obtained. The soft tissue phase lasts approximately 5 to 10 minutes after injection of the radiopharmaceutical. Early skeletal uptake can be seen on soft tissue phase images if the osteoblastic activity is sufficient for immediate binding to take place. By the end of the soft tissue phase, skeletal binding of the ^{99m}Tc-diphosphonate will be noticeable on any image obtained. Depending upon the speed of skeletal binding of the radiopharmaceutical and the efficiency of the kidneys in clearing residual radiopharmaceutical, the horse may be brought back to the camera room for imaging the bone phase. Typically, this is within 2 to 3 hours after injection of the ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP). Bone phase images may be acquired between 1 and 2 hours postinjection for ^{99m}Tc-HDP. In this phase, the radiopharmaceutical is bound to the exposed crystalline, inorganic matrix (hydroxyapatite crystal or amorphous crystalline phase) of bone (see Chapter 8 for complete details on binding). In skeletally immature animals, bone uptake is generally quicker and,

regardless of the radiolabeled diphosphonate used, the bone phase images may be obtained at 2 hours.

Image Acquisition

The acquisition parameters used in scintigraphic imaging are summarized in Table 9.1 and briefly reviewed here. Dynamic images are obtained at the time of intravenous injection of the radiopharmaceutical for the vascular phase or the nuclear angiogram. The dynamic acquisition consists of 120 frames, obtained at the rate of 1 second per frame (total imaging time 120 seconds). A $128 \times 128 \times 16$ matrix is used, and the image is usually acquired as a dorsal image so that the contralateral limb can be compared with the affected limb. The soft tissue and bone phase images are acquired as static frame mode images using a $256 \times 256 \times 16$ matrix. The images are usually acquired in a time-limited manner with 60 seconds being standard. Acquisitions can also be count limited (75,000 counts for the distal extremity up to 300,000 counts for the pelvis and axial skeleton).

To compare the symmetry of ^{99m}Tc -MDP accumulation between contralateral limbs, images must be obtained for the same amount of time, or the time required to acquire a fixed number of counts must be compared. If the images are count limited for a specific body part, then the same time is used to acquire the image from the contralateral body part. Due to low count rates, images of the distal part of the limbs are often acquired for relatively small numbers of counts (50,000 to 75,000) to reduce motion artifacts. Images of the proximal limb and axial skeleton should be acquired for at least 150,000 counts to minimize image noise and improve image contrast.

Normal Scintigraphic Appearance

Nuclear Angiogram/Vascular Phase

If possible, simultaneous images of paired body parts should be obtained, such as dorsal images of both metacarpophalangeal joints. The first few frames should demonstrate rapid distal travel of the radiopharmaceutical within the arterial vessels. Progressive ^{99m}Tc -MDP distribution corresponds with the major veins of the area being imaged. Within a few minutes, there should be rapid equilibrium into

the extracellular space and uniform distribution of the ^{99m}Tc -MDP in the soft tissues, so that the soft tissue phase of the bone scan can be obtained.

Soft Tissue Phase

During the soft tissue phase, there should be uniform symmetrical distribution of the radiopharmaceutical in the soft tissues. Initially, the bone will appear photopenic but skeletal uptake begins immediately and by the end of acquiring all of the soft tissue images, bone uptake is typically already apparent. In young horses and horses with active bone lesions, there may be immediate bone uptake equal to or greater than the soft tissues by 5 to 10 minutes post-injection. ^{99m}Tc -MDP kinetics and biodistribution is not in a steady state but is a dynamic process. Because of this, the appearance of the soft tissues and bone changes rapidly over the first 30 minutes. A diffusion gradient is established whereby ^{99m}Tc -MDP diffuses back into the vascular space as it is eliminated by the kidneys via glomerular filtration. It is recommended to acquire an immediate image of the limb (area of interest), turn the horse 180° and acquire two static images of the same region of the contralateral limb. After these two images are acquired, the horse is turned back to its original position and the original area of interest is re-imaged. This sequence allows the reviewer to gain a sense of the dynamic changes that are taking place.

Bone Phase

By 2 to 3 hours post- ^{99m}Tc -MDP injection, most of the circulating radiopharmaceutical has been excreted by the kidneys, unless the horse is in renal failure. The ^{99m}Tc -MDP left within the body is bound to the inorganic matrix of bone with some mild persistence of soft tissue activity that is most noticeable when imaging the axial skeleton. The appearance of the skeletal uptake pattern will vary with the age of the horse.^{6,7} Skeletally immature horses have intense ^{99m}Tc -MDP uptake in their physes and adjacent metaphyses, which may obscure any uptake present in the rest of the bone (Figure 9.1[A]). Viewing these images with an exponential gray scale (see Chapter 5) may help bring out the other bony structures. Mature horses will have a more uniform distribution of uptake. The long-bone epiphyses and metaphyses are the primary location of ^{99m}Tc -MDP uptake, especially the regions of distal condyles (Figure 9.1[B]).

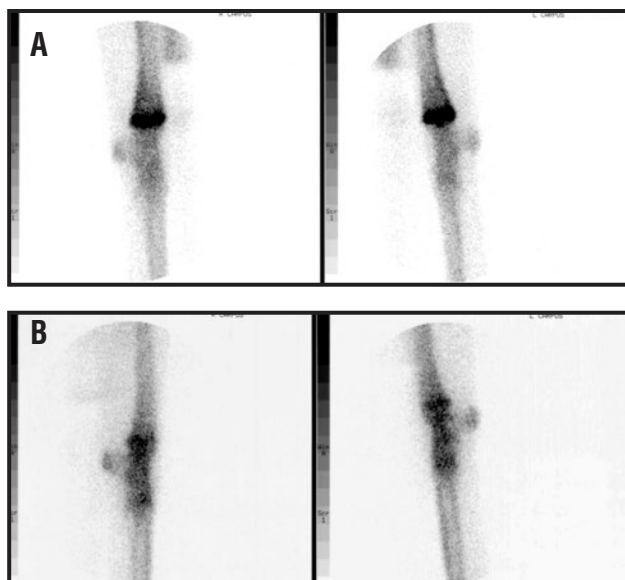


Figure 9.1: A, Lateral images of the distal antebrachium and carpus of a normal 2-year old thoroughbred

There is intense ^{99m}Tc -MDP uptake in both right and left distal radial physes. Note the incomplete lead shielding of the opposite thoracic limb proximally.

B, Lateral images of the distal antebrachium and carpus of a 4-year old thoroughbred

Note the diffuse ^{99m}Tc -MDP uptake in the region of the antebrachial carpal joint. The physal ^{99m}Tc -MDP radioactivity is no longer evident, indicative of physal closure and lack of active metaphyseal growth.

The degree of interposed soft tissue also affects the apparent uptake. The half-value layer for the photons of ^{99m}Tc (140 keV) in soft tissue is 5 centimeters, meaning there is 50% attenuation of the photons by just 5 centimeters of soft tissue. This artificially causes the superficial bony structures to appear to have more ^{99m}Tc -MDP uptake than deeper skeletal structures that have a similar degree of ^{99m}Tc -MDP uptake. Also, significant areas of increased ^{99m}Tc -MDP uptake within the deep bony structures (pelvis) may be overlooked due to the soft tissue attenuation.

Principles of Interpretation: Abnormalities of Each Phase of

Skeletal Scintigraphy

Vascular Phase

Absence of blood flow or compromised blood flow causes a complete failure of or a reduction in the delivery of the radiopharmaceutical to the distal limb. This may happen with tourniquet or snare type injuries, severe lacerations, or arterial thrombosis.⁸⁻¹⁰ Even if there is no appreciable blood flow during the vascular phase, soft tissue phase and bone phase images should be obtained to see if there has been development of any collateral circulation. Reduced blood flow to the distal limbs has been seen in some horses as an unexplained event without a satisfactory clinical explanation. These changes may persist into the bone phase images, as ^{99m}Tc -MDP delivery to a region must take place prior to being available for binding to the inorganic bone matrix. This phenomenon has been associated with cold weather or prolonged periods of rest before scintigraphy. Examinations are usually repeated within 24 to 48 hours. This phenomenon has been hypothesized to be related to arterial vasospasm or sympathetic innervation of the arterial blood supply to the distal extremities but has not been experimentally proven or disproven. Increased vascular delivery of the radiopharmaceutical may be seen in acute traumatic or inflammatory lesions with associated hyperemia.

Soft Tissue Phase

Increased ^{99m}Tc -MDP accumulation in soft tissues usually occurs as a result of regional soft tissue inflammation. Inflammatory lesions increase the overall blood perfusion, vascular permeability, and local tissue edema resulting in increased delivery and leakage of the radiopharmaceutical into the soft tissues. Such accumulations may be relatively subtle, so that close comparison with the contralateral limb is essential for lesion recognition. Again, early bone uptake may occur with metabolically active lesions and is expected in immature horses. Therefore, the period of time elapsed between injection and obtaining images should not be prolonged beyond 5 minutes to initiate acquisitions of the soft tissue phase. If early bone uptake is considered to be a potential, the vascular and soft tissue can be recorded using a different radiopharmaceutical, such as ^{99m}Tc -DTPA or ^{99m}Tc -mebrofenin. Both of these radiopharmaceuticals are rapidly excreted, and persistent soft tissue localization is not an issue so that a bone scan could

be performed on the same day or within 24 hours of the vascular and soft tissue studies.

Bone Phase

Abnormal uptake during the bone phase may be classified or described in a number of ways. The intensity of the uptake should be characterized as mild, moderate, or severe. Likewise, the extent of ^{99m}Tc -MDP uptake should be assessed and classified as diffuse, multifocal, or focal. The geographic pattern of uptake should then be described as this may help determine the type of lesion. For example, linear patterns of uptake may be associated with remodeling of the cortex of a bone or with increased bone turnover along a fracture line. Location of the abnormality is equally important, as abnormalities will occur in very localized, specific anatomic sites of a particular bone. Skeletal scintigraphy is a sensitive technique for the detection of bone remodeling due to any cause. Increased bone radiopharmaceutical uptake is a nonspecific change but familiarity with the age, history, and use of the horse and a working knowledge of the typical locations of common lesions are very helpful in refining the differential diagnosis or rendering a specific diagnosis.⁷

Abnormalities in Equine Skeletal Scintigraphy

Stress Fractures

Stress fractures and stress remodeling are common injuries in equine athletes.¹¹ Moderate to severe focal ^{99m}Tc -MDP accumulation characterizes this type of lesion. The intensity of the uptake depends upon the duration and severity of the injury. The term stress fracture should be reserved for cases in which there is radiographic correlation with evidence of a linear cortical defect and periosteal or endosteal callus formation. By contrast, stress remodeling lesions are characterized by pain and increased radiopharmaceutical accumulation with or without periosteal and endosteal new bone formation but with no visible fracture line on radiographs. It has been hypothesized that stress remodeling lesions that demonstrate pain and increased ^{99m}Tc -MDP accumulation are the result of radiographically invisible microfractures in the bone. However, experimental models in rabbits and dogs have shown scintigraphic and radiographic changes as described previously without gross or

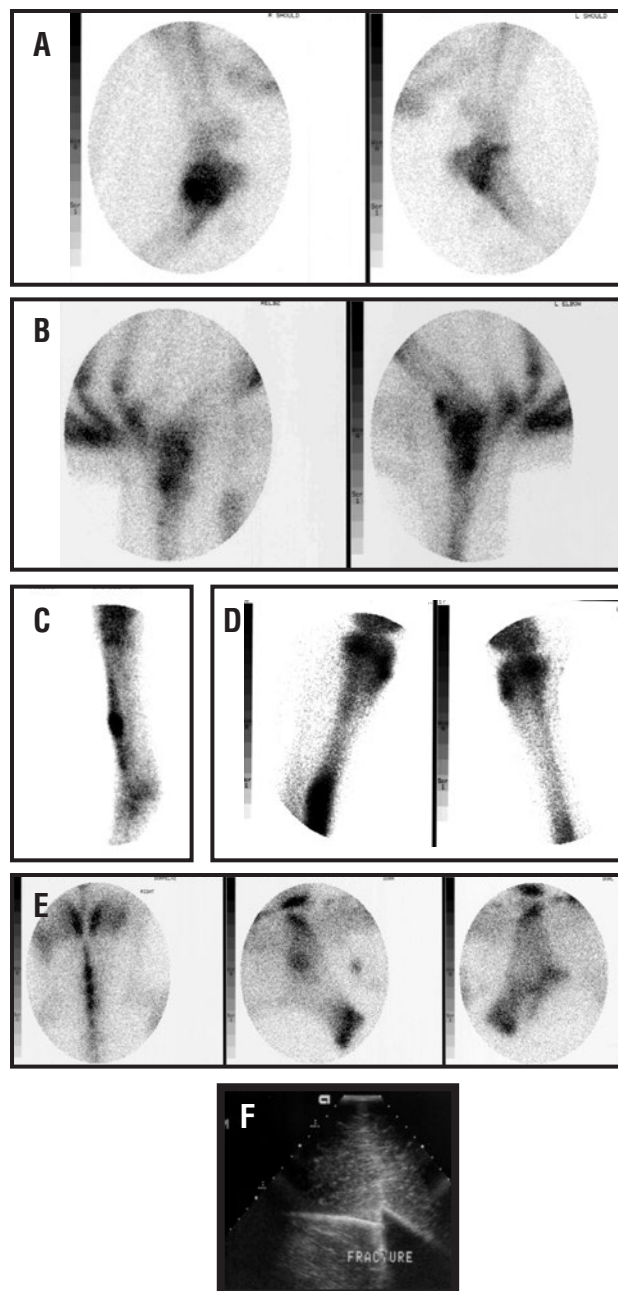


Figure 9.2: Stress fractures in thoroughbred racehorses

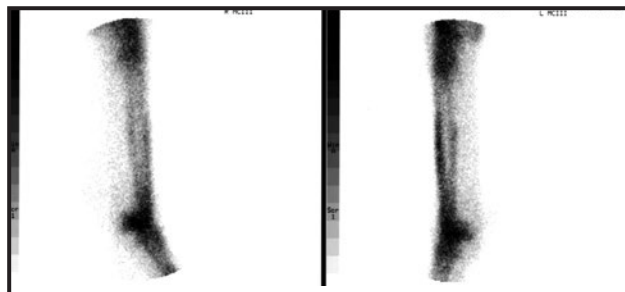
A, Stress fracture in the caudoproximal aspect of the right humerus; the left is normal. **B**, Stress fracture of the left distal humerus; the right humerus is normal. **C**, Stress fracture of the dorsal cortex of the mid portion of the left third metacarpus. **D**, Right distal and caudal tibial stress fracture; the normal left tibia is shown for comparison. **E**, Bilateral iliac wing stress fractures seen on dorsolateral oblique and dorsal views of the pelvis. **F**, Transverse ultrasound image of the iliac wing showing a sharp step defect in the bone surface with overriding of the fracture fragments.

histologic evidence of fractures.^{12,13} Common sites for stress fractures in Thoroughbreds include the caudal border of the neck of the scapula, caudolateral proximal humerus, craniomedial distal humerus, mid-diaphysis of the radius, palmaroproximal metacarpus, dorsomedial mid-metacarpus, proximolateral tibia, caudolateral distal tibia, and iliac wing (Figure 9.2).¹⁴⁻¹⁸ In standardbreds, tibial stress fractures have been reported to occur more commonly in the mid-diaphysis than the proximal and distal positions seen in thoroughbreds.^{19,20}

In jumping and eventing horses, a specific site of focal, severe, increased ^{99m}Tc-MDP accumulation is the dorsal cortex of the proximal phalanx.^{21,22} This is not accompanied by any radiographic evidence of a fracture or any periosteal or endosteal callus formation. If a similar pattern of uptake were seen in a racing thoroughbred, then it would be suggestive of an incomplete sagittal fracture of the proximal phalanx. Show jumping and event horses can develop focal areas of increased thoracic vertebral spinous process uptake.²² Standardbred trotters have a tendency to have increased uptake in the area of the third carpal bone, proximal sesamoid bones and the metatarso-phalangeal joints.¹⁹ Thoroughbreds in training most commonly have areas of increased uptake at the palmar distal aspect of the third metacarpal bone, dorsal cortex of the third metacarpal bone, palmaroproximal metacarpal bone, third carpal bone, and tarsus (Figure 9.3).^{7,23,24}

Figure 9.3: Lateral images of the metacarpal regions of a 3-year old thoroughbred

There is mild to moderate diffuse uptake in the dorsal cortex and moderate focal uptake in the palmar distal aspect of both third metacarpal bones.



Occult Fracture Detection

Scintigraphy is particularly useful in evaluating the severely lame horse when a fracture is suspected but cannot be identified radiographically. This is often the case with incomplete or recent nondisplaced fractures when insufficient time has elapsed to allow osteoclastic resorption at the fracture line. Increased radiopharmaceutical accumulation is seen with most fractures within 24 to 48 hours of injury, whereas it may take 7 to 10 days for a fracture line to be visualized on radiographs. Common clinical scenarios where this occurs include distal phalangeal fractures, incomplete fractures of the palmar aspect of the distal condyle of the third metacarpus, and fractures of the cuboidal tarsal bones.^{25,26}

Scintigraphy is also valuable in detecting skeletal lesions that are obscured by the sheer size of the horse. Pelvic fractures may be diagnosed radiographically but usually require general anesthesia, and recovery may result in significant exacerbation of fracture displacement and a possible complicating degree of comminution. Stress fractures of the iliac wing adjacent to the sacroiliac joint are encountered in racing thoroughbreds and are sometimes difficult to diagnose clinically.¹⁵ Dorsolateral oblique views of this area usually reveal increased radiopharmaceutical accumulation (Figure 9.2E).²⁷ Sacroiliac injuries, stress fractures of the spinous processes and complete fractures of the pelvis may also be diagnosed by scintigraphy.^{28,29} Accumulation of urine containing a radiopharmaceutical can obscure such lesions, and diuretics may be employed to encourage micturition. If there is any suspicion of a pelvic or sacral injury, then the images should be repeated after the horse has voided and the amount of radioactivity within the urinary bladder has decreased. It should also be kept in mind that the large muscle mass around the pelvis will attenuate the photons originating from a deep lesion (half-value layer = 5 centimeters of soft tissue). In contrast, muscle wastage may create the appearance of diffusely increased uptake in one hemi-pelvis. In addition, the camera will be away from the lesion, thereby causing significant blurring of the image. Therefore, pelvic lesions are not always impressive, and careful scrutiny of the area is required to avoid overlooking any lesions.²⁷

Osteoarthritis/Osteoarthrosis

Degenerative joint disease, either as a primary entity or secondary to another process, is a common cause of lameness in horses. Once the physes have closed, the uptake pattern around joints is the area of greatest intensity of ^{99m}Tc -MDP uptake in the limb of the horse. Degenerative joint disease results in increased accumulation of radiopharmaceutical involving the subchondral bone of the affected joint (Figure 9.4). Increased radiopharmaceutical accumulation can occur before radiographic evidence of osteoarthrosis. There is usually mild to moderate diffusely increased

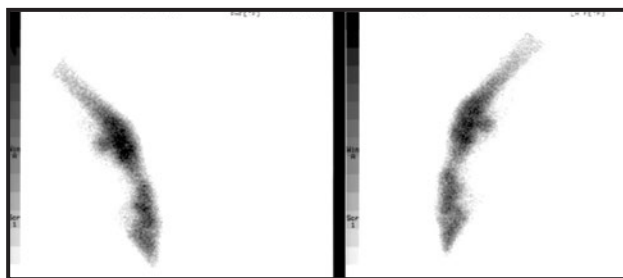


Figure 9.4: Lateral images of both pelvic limb distal extremities

There is moderate diffuse uptake in both metatarsophalangeal joints consistent with degenerative joint disease.

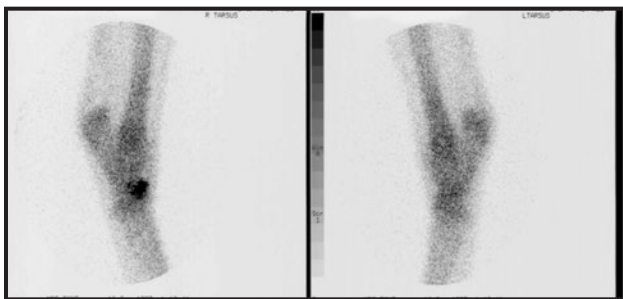


Figure 9.5: Lateral images of the right and left tarsi

There is an intense focal area ^{99m}Tc -MDP uptake at the dorsal aspect of the distal row of the right and left tarsal bones. Possible differentials for this focal hot spot include a slab fracture of the central tarsal bone or active degenerative joint disease in the distal intertarsal joint. Radiographs confirmed degenerative joint disease with multifocal lucencies and subchondral bone sclerosis along the distal articular surface of the central tarsal bone and the proximal articular surface of the third tarsal bone.

uptake in a joint with osteoarthrosis. Focal uptake within a joint would suggest either a chip fracture or pathology affecting an isolated joint compartment. Severely increased uptake is unusual with osteoarthrosis and suggests either an articular fracture or septic arthritis. An exception to this is degenerative disease of the intertarsal and tarsometatarsal joints where radiopharmaceutical uptake is sometimes very intense (Figure 9.5). The intensity of uptake in the tarsus does not always correlate with the severity of the radiographic changes or the degree of clinical lameness. These lesions are characterized by a linear pattern of uptake that follows the plane of the proximal or distal intertarsal joints. Older horses, with well-developed radiographic evidence of osteoarthrosis (and ankylosis), can have no significant scintigraphic uptake in the affected tarsal joint.

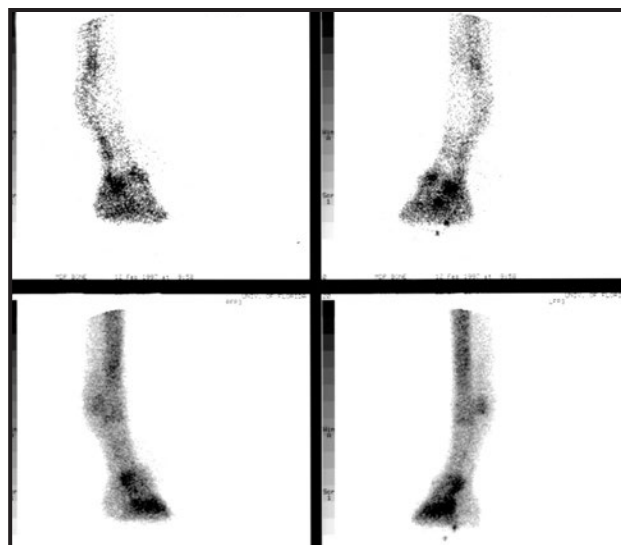
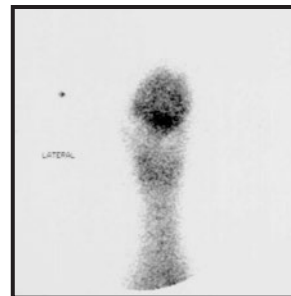


Figure 9.6:

A, Soft tissue phase and bone phase lateral images of the thoracic distal extremity document moderate radiopharmaceutical accumulation in the area of the distal sesamoid (navicular) bone and bursa. **B**, A palmar view of the right thoracic distal extremity (marker is lateral) documents a moderate linear area of ^{99m}Tc -MDP uptake in the area of the distal sesamoid (navicular) bone consistent with abnormal navicular bone remodeling and navicular syndrome.



Navicular Syndrome and Navicular Bursitis

Navicular syndrome is a common cause of lameness in middle-aged and older horses. The diagnosis of this syndrome is difficult as pain originating from the distal sesamoid (navicular) bone, navicular bursa, and the deep flexor tendon may not be accompanied by specific radiographic changes. When evaluating the distal phalanx and distal sesamoid bone, both lateral and palmar/plantar projections of the distal extremity should be obtained (Figure 9.6). On the lateral projection, radiopharmaceutical uptake in mineralized collateral cartilages may be mistaken for distal sesamoid bone uptake. The use of the palmar/plantar view eliminates this source of error. At some clinics, a second small field-of-view gamma camera set in the floor is used to acquire palmar or plantar views. Increased uptake may be seen in the region of the distal sesamoid bone, the soft tissue phase, and/or bone phase images.³⁰ Combined soft tissue and bone phase imaging are considered complementary to radiography and clinical data for the diagnosis of navicular syndrome.

Equine Skull Scintigraphic Imaging

Diagnosis of conditions affecting the equine skull can be challenging. The complex nature of the bone and soft tissue anatomy with multiple overlapping shadows on radiographs can obscure a lesion or cause the radiographic conclusion to be ambiguous. General anesthesia may be required to obtain good-quality radiographs or cross-sectional imaging (computed tomography or magnetic resonance imaging). Such lesions as otitis media and dental-associated sinusitis have an osseous component and are amenable to scintigraphic examination. Scintigraphy has the advantage of not requiring anesthesia and allowing the entire skull to be surveyed quickly.³¹ Chief among the disadvantages of scintigraphy is the relatively poor anatomic resolution that is worsened by motion and the increased distance of the horse's head from the camera. A plastic shelf fitted to the camera on which the horse's head can be rested is very helpful in reducing motion and minimizing camera-patient distance.³ Although the teeth are composed largely of calcium hydroxyapatite crystal, they do not accumulate any radiopharmaceutical and appear as photopenic structures outlined by the alveolar bone (Figure 9.7). Scintigraphy has been found to have excellent sensitivity but only moderate specificity in detecting dental disease.³² The speci-



Figure 9.7: Normal lateral scintigraphic image of the skull

Notice the normal focal uptake in the area of the temporomandibular joint and the moderate uptake in the alveolar bone outlining the photopenic teeth.

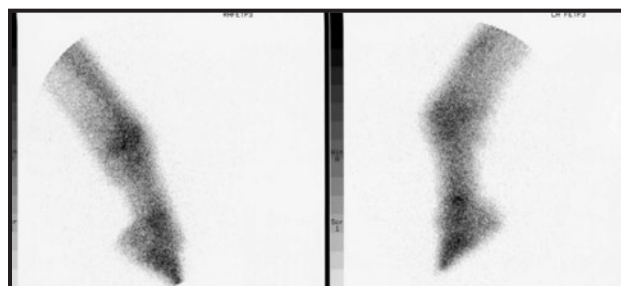


Figure 9.8: A bone phase image obtained 3 hours after injection shows almost equal degrees of skeletal and soft tissue ^{99m}Tc-MDP uptake

This is consistent with poor skeletal binding of the ^{99m}Tc-MDP. See text for details.

ficacy can be improved by combining scintigraphic and radiographic findings.

Abnormal Soft Tissue Uptake of ^{99m}Tc-MDP and Poor Bone Uptake

Persistent soft tissue uptake or poor bone uptake in

the distal limb is a sporadic problem encountered in equine skeletal scintigraphy. One or more limbs are affected, usually from the level of the carpus or tarsus and distal (Figure 9.8). The severity of the problem is variable ranging from mild persistent soft tissue activity with fair bone uptake to cases where the soft tissue activity is severalfold greater than the skeletal uptake. The problem occurs more frequently in middle-aged and older horses but can be seen in horses of all ages. It has been suggested that it may be associated with cold weather and may also be linked to prolonged periods of rest before scintigraphy. Such measures as applying leg wraps; housing the patient in a warm stall; walking the horse vigorously before injection; and the use of peripheral vasodilator agents, such as acepromazine, have been employed in an attempt to reduce the occurrence of this problem. In the authors' experience, these measures do not work reliably but certainly do no harm. If the study is repeated within 1 to 2 days, the appearance may either be the same or bone uptake may be improved. Poor bone uptake of radiopharmaceutical has been attributed to low-output cardiac disease, edema, renal failure, and old age in humans.³³ Although increasing age is associated with an increased incidence in horses, none of the other factors seem to apply. The precise cause of this problem remains to be determined, but owners should be warned of the possibility of obtaining a nondiagnostic study, especially during the colder months.

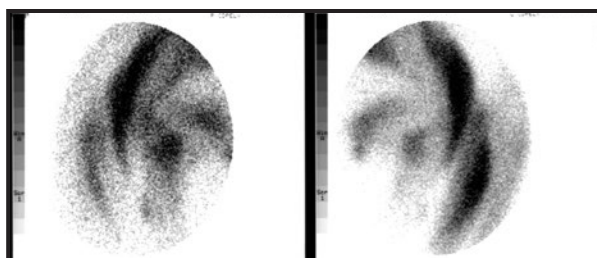


Figure 9.9: Lateral images of the caudal thigh and hip region obtained during the bone phase

The fusiform areas of moderately to severely increased uptake represent radiopharmaceutical accumulation in the caudal thigh muscles due to rhabdomyolysis. The image on the right is the left gluteal region, and the image on the left is the right gluteal region.

Although the ^{99m}Tc -labeled diphosphonates are primarily targeted at bone, uptake in soft tissues may be observed.^{33,34} This may occur in cases of dystrophic or metastatic mineralization or areas of calcium salt deposits because of active muscle necrosis and muscle damage. The most common cause of soft tissue uptake in horses is rhabdomyolysis (Figure 9.9).^{11,35,36} It has been shown that the radiopharmaceutical uptake in rhabdomyolysis is the result of binding with calcium salts secondary to the muscle necrosis, rather than secondary to an increased volume of extracellular fluid.³⁶ Depending on the extent of the muscle damage these horses have a variable presentation, from mild to crippling lameness. Scintigraphy may be useful in obtaining a diagnosis and assessing the severity and extent of the muscle damage.

There will always be a focal amount of residual ^{99m}Tc -MDP at the site of the intravenous catheter. If perivascular injection occurs, an ill-defined focus of radiopharmaceutical will be observed in the area. This may diffuse along the fascial planes, and local lymph node uptake may be seen during bone phase imaging.

Miscellaneous Orthopedic Diseases

Although scintigraphy is considered a sensitive imaging modality for the diagnosis of skeletal disease, there are some lesions that do not demonstrate increased radiopharmaceutical uptake. Lesions of osteochondrosis, osteochondritis dissecans, or subchondral osseous cystlike lesions are commonly seen on radiographs of the affected joint, without scintigraphic evidence of increased radiopharmaceutical uptake in the equine athlete.³⁷ In the authors' experience, this occurs in approximately 50% of such lesions, whereas in the remaining 50% the increased uptake more likely is secondary to the presence of osteoarthritis rather than the primary lesion. It is uncertain why these lesions fail to result in increased radiopharmaceutical uptake. Possible explanations include the absence of increased bone turnover in quiescent or chronic lesions or where the lesion is characterized by failure of endochondral ossification and neither a fissure or an osteochondral fragment is evident. Purely osteoclastic lesions may also fail to accumulate abnormal quantities of radiopharmaceutical. Avascular lesions, such as sequestra or bone infarcts fail to accumulate any radiopharmaceutical due to the lack of blood supply and are usually seen

as photopenic regions or sites. The authors have also observed a small number of axial and appendicular skeletal fractures, which showed no evidence of increased radiopharmaceutical accumulation. All of these fractures were at least several days old and none subsequently progressed to sequestrum formation. Serial radiographs of a saucer cortical fracture of Mc III in one horse documented delayed healing over a period of 9 months accompanied by minimal abnormal radiopharmaceutical accumulation at the fracture site. Also, abnormal areas of increased radiopharmaceutical uptake may not be seen in pelvic fractures. Although it is unlikely, a fracture cannot be completely excluded based on a negative scintigraphic examination.

Influence of Nerve and Intra-articular Blocks on Skeletal Scintigraphy

Horses undergoing skeletal scintigraphic evaluation have usually been subjected to a clinical lameness examination that includes perineural or intra-articular injection of local anesthetic drugs. These injections may have some effect on the appearance of the soft tissue phase depending upon when they were performed. Focal uptake on soft tissue phase images may be seen for up to 17 days following the local injection of 2% lidocaine solution.³⁸ Similar soft tissue phase uptake has been identified with intra-articular injections of local anesthetic agents.³⁹ Neither intra-articular nor perineural injection in the distal limb of lidocaine, mepivacaine or bupivacaine were reported to have any effect on bone phase images.^{38,40} Focal radiopharmaceutical accumulations on bone phase images have been reported with perineural injections in the proximal limb, such as the ulnar or median nerves.⁴¹ The authors have seen occasional clinical cases with focal bone phase uptake in the area of recent perineural injection in the metacarpus or metatarsus. This may be the result of inadvertent injury to the periosteum when injecting difficult patients. The clinician interpreting the images must be aware of what types and the sites of any anesthetic injections prior to the scintigraphic study, to avoid misinterpretation of associated changes expected on the soft tissue and bone phase images.

Image Postprocessing

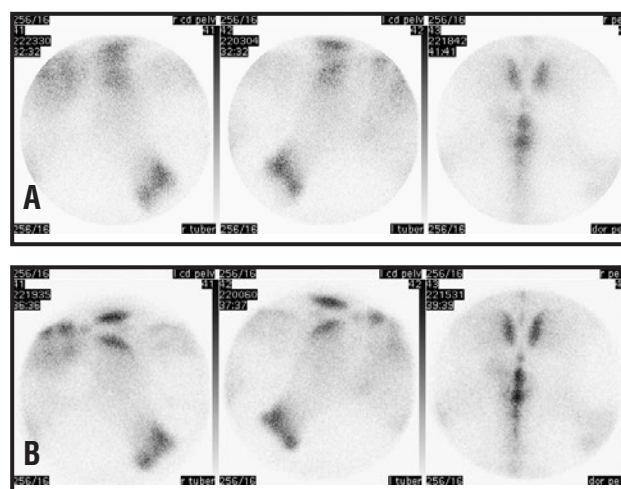
Computer manipulation of the image data may improve diagnostic accuracy. Movement either by

the patient or of the gamma camera gantry will result in blurring of the image, thereby reducing image sharpness and lesion contrast. Excessive movement also increases the time required to obtain a diagnostic study. Images may be obtained as a dynamic sequence and motion corrected to overcome this problem. Motion correction can be done by manually realigning each frame of the acquisition or using automated motion correction software. Most systems require inclusion of a radioactive marker in the image for automatic correction; however, the system currently in use at the University of Florida will correct for motion without the inclusion of a marker object. The software scans the frames for recognizable landmarks and can correct for motion in the X-axis and Y-axis. The resulting image is significantly sharper than an uncorrected summed dynamic acquisition equating to a conventional static acquisition (Figure 9.10). This has reduced the time required to complete a scan and significantly improved image quality.

Digital filtering may also improve image quality and lesion detection. Scintigraphic images contain relatively small amounts of data in comparison to radiographic or ultrasonographic images. Image quality can be improved by increasing the amount of data in each image. This may be achieved by increas-

Figure 9.10: Dorsolateral oblique and dorsal images of the pelvis.

A, A composite or summed image of a 60-second dynamic study acquired at 1 frame per second. **B**, The same acquisition as in 9.10A after motion correction has been applied. Notice the improved definition of the tuber sacrale and tuber coxae.



ing the injected dose of radiopharmaceutical, but the increase may result in an unacceptable increase in personnel exposure. Alternatively, one can increase the acquisition time for images; but that might exacerbate problems associated with motion and prolongs the overall time to complete the entire study.

The images could also be subjected to a filtering process that enhances the visibility of low-contrast lesions. This technique has been shown to improve detection of a phantom lesion in low count density image.⁴² However, it has also resulted in an increase in false positive diagnoses, especially at higher count densities. The application of digital filters has been validated in human nuclear medicine, but their utility in clinical veterinary scintigraphy is yet to be proven.

Combined Modality Imaging

Scintigraphy is a sensitive but nonspecific technique. Any scintigraphic abnormality should be evaluated using radiographs, ultrasound, or in conjunction with cross-sectional imaging (computed tomography or magnetic resonance imaging) to refine the differential diagnosis. Radiography is relatively insensitive to skeletal remodeling changes but provides excellent anatomic resolution. Radiographs should be evaluated for lesions, such as chip or fissure fractures, endosteal and periosteal new bone formation, and osteoarthritis. Radiography may be more helpful than scintigraphy in evaluating fracture repair, as increased ^{99m}Tc -MDP accumulation persists for prolonged periods after radiographic evidence of complete healing. Scintigraphy can be helpful in targeting a radiographic study to a specific joint or anatomic region. An intense focal uptake in the distal tarsus is strongly suggestive of a central or third tarsal bone fracture. With this evidence, there is greater justification in performing an exhaustive radiographic study with additional oblique radiographic projections to

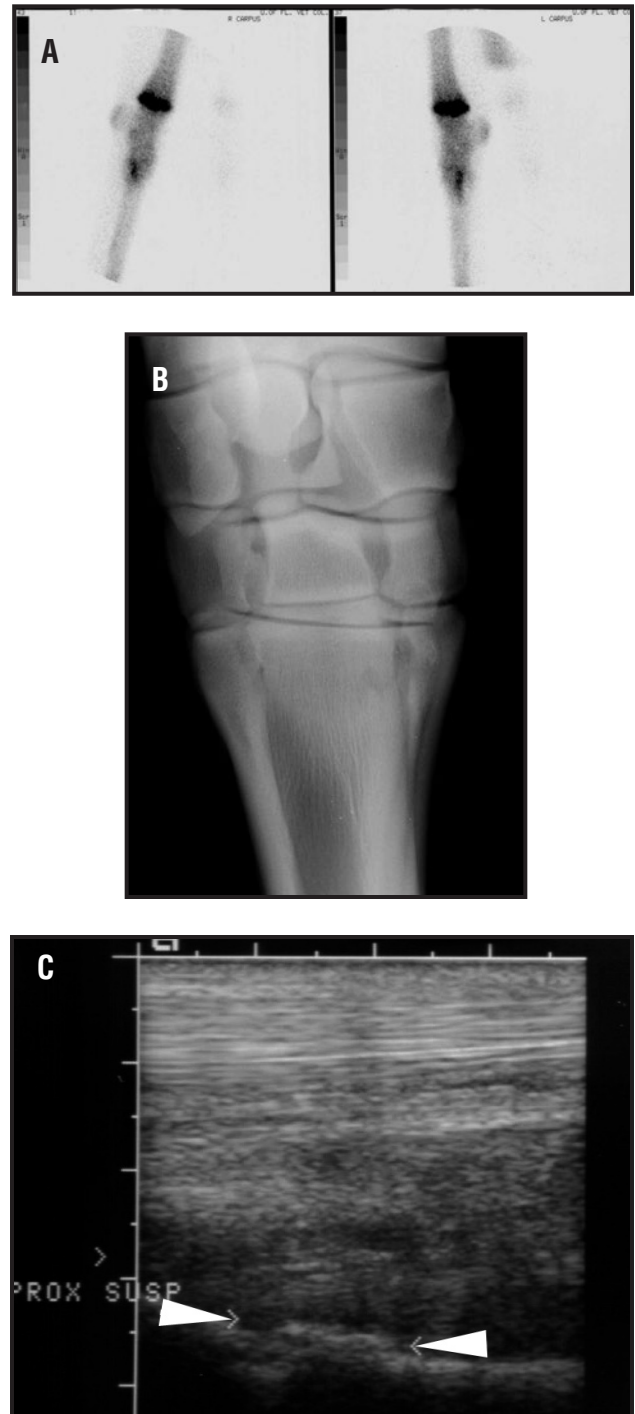


Figure 9.11: Lateral images of the carpus and proximal metacarpus of a 2-year old thoroughbred

A, There is focal increased uptake at the proximal palmar aspect of the metacarpus in both limbs. The intense uptake in the distal radial physes overshadows these lesions. **B**, Dorsopalmar radiograph of the carpus and proximal metacarpus. There is moderate sclerosis of the proximal medial aspect of the third metacarpal bone. A crescent-shaped lucent area and corresponding fragment can be seen within the sclerotic area. **C**, Longitudinal ultrasound image at the origin of the suspensory ligament. The ligament is severely enlarged, hypoechoic, and has a severely disrupted fiber pattern. An avulsed fragment of bone is also apparent (arrowheads).

identify a fracture line. If the radiographs fail to do so, then repeat radiographic examination should be done in 7 to 10 days. At this time, osteoclastic resorption may be large enough that a fracture line can be clearly visualized. Ultrasonography is a very useful tool in equine orthopedic disease. It may be used to confirm the presence of a fracture of the iliac wing quickly and easily (Figure 9.2F). It is also useful to evaluate increased radiopharmaceutical accumulation at the site of origin or insertion of soft tissue structures. A focal increased uptake in the palmar proximal third metacarpal bone may be the result of a stress fracture or stress remodeling and/or avulsion fracture of the origin of the suspensory ligament (Figure 9.11). Radiographs may confirm the presence of endosteal new bone and may identify a fracture fragment. Ultrasound may be used to evaluate the suspensory ligament for alterations in size, echogenicity, and fiber pattern and may identify small bone avulsions better than radiographs in certain horses. Increased radiopharmaceutical accumulation in the proximal sesamoid bones may be caused by a suspensory branch desmitis. In such cases, ultrasound should be used to evaluate the branches of the suspensory ligament and can also be used to image the abaxial surface of the proximal sesamoid bones for any contour or margin abnormalities.

Summary

In summary, equine skeletal scintigraphy has become a mainstay in the lameness evaluation of working, event and racing horses. The use of scintigraphy should not replace a thorough adequate physical examination and lameness evaluation. One can find a number of lesions on skeletal scintigraphy that must then be interpreted in light of the known history and other pertinent findings obtained prior to the nuclear medicine study. Follow-up radiographs are beneficial for the complete evaluation of abnormalities seen on scintigraphic studies. It is incumbent on the clinician to be familiar with common sites of scintigraphic abnormalities seen in specific types and breeds of performance horses.⁴³ The use of follow up scintigraphy for the evaluation of progression or regression of lesions after therapy or prolonged periods of rest can also serve to provide important clinical information.

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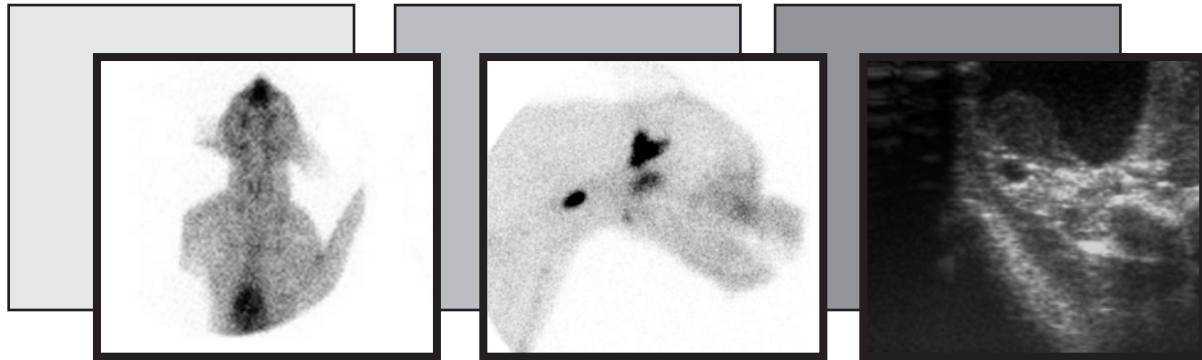
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Thyroid Scintigraphy

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Introduction

Thyroid scintigraphy provides both functional and anatomic information that cannot be determined using any other single diagnostic procedure. Indications for thyroid scintigraphy are listed in Table 10.1. Thyroid scintigraphy is most often used to evaluate for hyperthyroidism in cats. Hyperthyroidism is the most common endocrine disease in middle aged and geriatric cats.^{1,2} The clinical signs are attributed to elevations in thyroxin (T_4) and triiodothyronine (T_3) concentrations.³⁻⁵ The most common cause of this disorder is adenomatous hyperplasia or hyperfunctioning thyroid adenoma(s).⁴ Thyroid carcinoma will also result in hyperthyroidism but the incidence is less than 3% of all hyperthyroid cats.^{2,6,7} The diagnosis of hyperthyroidism, is typically based on the history, clinical signs, physical finding of an enlarged thyroid, and elevated T_4 concentrations. However, clinical signs may be confused with other diseases and diseased thyroid lobes may not be palpably enlarged, or they may be located within the thoracic inlet making them inaccessible on physical exam. Because of day-to-day fluctuations in serum

T_4 concentrations the diagnosis is difficult in some cases.^{4,8-10} Confirmation of hyperthyroidism may require a full thyroid hormone panel including T_3 suppression test or thyroid scintigraphy.¹¹⁻¹³

Mechanism of Localization and Elimination

Radioiodine

Ingested iodine (I_2) is converted to iodide (I^-) in the upper intestine and is very rapidly absorbed into the blood. Ninety percent of administered iodine is absorbed within 60 minutes.¹⁴ Iodide is distributed in the blood as an extracellular ion similar to chloride. Follicular thyroid cells remove or trap up to 20% of the circulating iodide by an active transport mechanism.¹⁵ Thyroid uptake is regulated by the thyroid-stimulating hormone (TSH) and is dependent on oxidative phosphorylation.¹⁶ Iodide is trapped in the thyroid by a mechanism is referred to as the iodide pump. This process can result in an iodide concentration within the thyroid gland that is

Table 10.1: INDICATIONS FOR THYROID SCINTIGRAPHY

Evaluation of the functional status of the thyroid gland (hyperthyroidism, euthyroidism, or hypothyroidism).
Determination if a cervical mass is of thyroid or nonthyroid origin.
Differentiation of unilateral and bilateral thyroid disease; this is especially important for surgical treatment.
Detection and localization of ectopic thyroid tissue.
Detection of functional metastatic lesions.
Differentiation between malignant and benign thyroid disease.
Determination of thyroid gland size for radiation therapy calculations.
Differentiation of functional and nonfunctional thyroid tumors in dogs.
Evaluation of the efficiency of therapy.
Evaluation for residual tissue following thyroidectomy.
Evaluation of dogs for hypothyroidism.
Differentiation between hypothyroidism and euthyroid sick syndrome.
Differentiation between primary, secondary, and tertiary hypothyroidism.
Differentiation between thyroid dysgenesis and inherited iodination defects.

30 times the plasma concentration in a normal thyroid gland and up 300 to 500 times plasma concentrations in diseased thyroid glands.¹⁵ Iodide trapping can be competitively blocked by large quantities of monovalent anions, such as pertechnetate (TcO_4^-), perchlorate (ClO_4^-) or thiocyanate (SCN^-).¹⁴ In the thyroid, iodide is oxidized to iodine by thyroid peroxidase and then bound to the amino acid tyrosine to form moniodotyrosine and diiodotyrosine. Two molecules of diiodotyrosine are coupled to form tetraiodothyronine or thyroxine (T_4). Alternately, one molecule of moniodotyrosine couples with one molecule of diiodotyrosine to form triiodothyronine (T_3) that represents about one-fifth of the stored hormone.¹⁵ These hormones are then incorporated by direct linkage with the protein, thyroglobulin, in a process called organification. Thyroglobulin is produced by the thyroid cells and secreted directly into the colloid of the thyroid follicle. The body will handle radioactive iodine exactly like nonradioactive iodine. Radioiodine is continuously concentrated in the thyroid gland during the 24 hour period after administration, providing high thyroid uptake. Radioiodide is rapidly absorbed after intravenous, subcutaneous, oral, or rectal administration.

Circulating iodide is also trapped by the salivary glands, gastric mucosa, choroid plexus of the brain, placenta, ciliary body of the eye, and lactating mammary tissue. Iodide can be secreted in milk and can be actively accumulated by fetal thyroid tissue. Iodide not trapped in those tissues is removed by renal excretion. Because all isotopes of iodine are metabolized identically, radioactive isotopes (^{131}I and ^{123}I) can be substituted for stable iodine (^{127}I) and used for diagnostic imaging.

Sodium $^{99\text{m}}\text{Tc}$ -pertechnetate

$^{99\text{m}}\text{Tc}$ is a transitional metal (group VIIB of the periodic table) that imitates the actions of the halogens.¹⁷ $^{99\text{m}}\text{Tc}$ in the form of pertechnetate ($^{99\text{m}}\text{TcO}_4^-$) is trapped and concentrated by the follicular cells of the thyroid gland.^{14,18} Pertechnetate, because of its size and valence, is referred to as a “pseudohalogen” because it mimics the biologic behavior of iodide and chloride.¹² $^{99\text{m}}\text{Tc}$ -pertechnetate does not undergo organification and will not bind with the tyrosyl groups to form thyroglobulin.¹⁸ It is concentrated within the follicular cells of the thyroid, but is not formed into active hormone and is not retained within the colloid of the gland.

$^{99\text{m}}\text{Tc}$ -pertechnetate uptake peaks within hours following injection, after which thyroid activity declines. Peak pertechnetate thyroid uptake in normal dogs occurs between 2 to 3 hours after injection.¹⁹ In cats, peak thyroid uptake has been shown to occur between 45 and 60 minutes after injection. A gradual decline in uptake was then up to 420 minutes after injection.²⁰ In a later study, thyroid uptake of pertechnetate continued to increase up to 4 hours after injection in normal cats.²¹ Because the initial trapping mechanism of the follicular cells is proportional to the metabolic activity of the thyroid, quantification of the pertechnetate accumulation is a good predictor of the metabolic activity of the thyroid.²²

As noted previously, the mechanism of thyroglobulin formation can be divided into two major steps, iodide trapping and organification of thyroglobulin. Thyroid scintigraphy is based on the use of radionuclides that are either trapped (pertechnetate) or trapped and organified (radioiodine). Eight-hour ^{123}I and 4-hour $^{99\text{m}}\text{TcO}_4^-$ uptake reflect the trapping mechanism of the thyroid gland and the 24-hour ^{123}I uptake reflects organification and the formation of thyroid hormone.²¹ There is good correlation between the percent dose uptake of $^{99\text{m}}\text{TcO}_4^-$ at 4 hours and the 8 hour percent dose uptake of ^{123}I (correlation coefficient $[r] = 0.809$).²¹ There is a relatively poor correlation ($r = 0.232$) between the 4 hour $^{99\text{m}}\text{TcO}_4^-$ uptake and the 24-hour ^{123}I uptake.²¹ These findings suggest that the accumulation of radioiodine at these two time points represents the two mechanisms of thyroglobulin function: iodide trapping at 8-hours and then organification, iodination, and coupling at 24 hours.

A number of drugs and other compounds can interfere with iodide or $^{99\text{m}}\text{TcO}_4^-$ uptake by the thyroid. Thyroid hormone supplementation reduces thyroid stimulating hormone (TSH) concentrations and reduces thyroid uptake for several weeks. Increased dietary iodine, sulfonamide and phenylbutazone may reduce thyroid uptake for 1 to 2 weeks. Iodinated radiographic contrast media contain high concentrations of iodine and inhibit thyroid uptake after radiographic contrast procedures or contrast-enhanced computed tomography scans. Propranolol and other vasoactive drugs used to control the effects of hypertrophic cardiomyopathy in hyperthyroid cats do not interfere with thyroid uptake of iodide or $^{99\text{m}}\text{TcO}_4^-$. Antithyroid medications block iodine organification and thyroid hormone production but do not directly

affect the iodide trapping mechanism of the thyroid gland and it has been reported that thyroid imaging with $^{99m}\text{TcO}_4^-$ should not be affected by these medications.^{1,23,24} This concept has been stated as one of the major advantages for the use of $^{99m}\text{TcO}_4^-$ thyroid imaging over radioiodine. Methimazole, however, has been shown to cause a significant increase in the thyroid uptake in normal cats.²¹ This data suggests that trapping by normal thyroid tissue is significantly enhanced by antithyroid medication and continues to be increased for 15 days after withdrawal of the medication. This enhanced trapping is clinically significant because normal cats placed on methimazole have an elevated thyroid-salivary ratio that could cause the false appearance of hyperthyroidism on $^{99m}\text{TcO}_4^-$ thyroid scintigraphy (Figure 10.1).

The cause for increased thyroid uptake induced by methimazole may be explained by increased serum TSH concentration that stimulates the trapping mechanism of the thyroid gland. Elevated TSH increases all activities of the thyroid glandular cells, including iodide trapping, the iodination and coupling process, and increased secretion of stored T_4 . Enhanced uptake after discontinuing methimazole is evidence of what has previously been hypothesized as a “short-term rebound effect.” This effect has been described as an actual increase in iodide uptake seen shortly after discontinuing methimazole.²⁵ This effect also has been reported in humans where concurrent administration of thiouracil, propylthiouracil (PTU), and methimazole depresses 24-hour ^{131}I uptake that is then followed by a period of higher radioiodine uptake after withdrawal of these drugs. The rebound begins 2 days after discontinuing antithyroid medication and persists for approximately 5 days in humans.^{26,27}

Interpretive Principles

Normal Feline Thyroid Scintigraphy

The normal feline thyroid gland is composed of two lobes without an isthmus. The lobes are located ventral and lateral to the trachea just caudal to the larynx. Embryologically, the thyroid gland arises from the ventral floor of the pharynx from the endoderm of the fourth pharyngeal pouch.²⁸ Ectopic tissue results from failure of all or part of the thyroid gland to descend to its normal cervical location or to descend

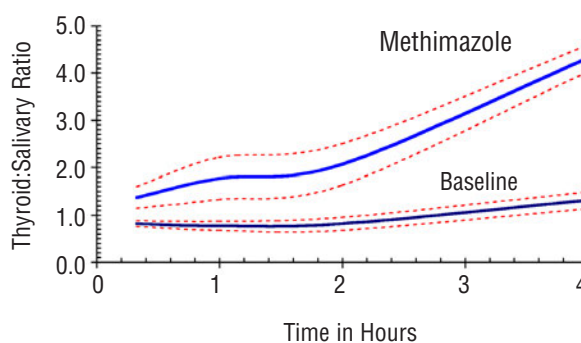


Figure 10.1: Graph showing the thyroid-salivary gland ratio for sodium ^{99m}Tc -pertechnetate before and 3 weeks after oral methimazole administration

The centerline represents the mean thyroid-salivary gland ratio of eight cats. The outer dashed lines represent one standard deviation.

beyond its normal location.²⁹ As a result, ectopic tissue may be found from the base of the tongue to the diaphragm. The appearance of the normal feline thyroid scan (using pertechnetate or radioiodine) is characterized by uniform distribution of radioactivity throughout both lobes of the thyroid gland (Figure 10.2). The feline thyroid lobes appear as elongated ovals, symmetrical in size and position. The thyroid lobe margins should be smooth and regular. Ectopic thyroid tissue is usually not seen in normal cats.

The intensity of thyroid gland uptake is evaluated by comparison to the zygomatic-molar salivary glands (Figure 10.3). Normal cats have a thyroid-salivary ratio of 0.87:1 (range 0.6:1 to 1.03:1).³⁰ Traditionally, thyroid imaging is performed 20 minutes after pertechnetate injection as Beck described. Others have recommended imaging an hour after injection. The thyroid-salivary ratio will change over time but there is not a significant difference in the thyroid-salivary ratio from 20 minutes to 2 hours after injection in normal cats (Figure 10.4). At 4 hours, the thyroid-salivary ratio in normal cats is significantly greater than the 20-minute ratio²¹ (Figure 10.1). As noted previously, there is discrepancy in the literature concerning the time to peak thyroid uptake. The time to peak salivary uptake has not been described in the cat. Because the thyroid-salivary ratio can be influenced by either thyroid or salivary disease, thyroid to background ratio may also be helpful to

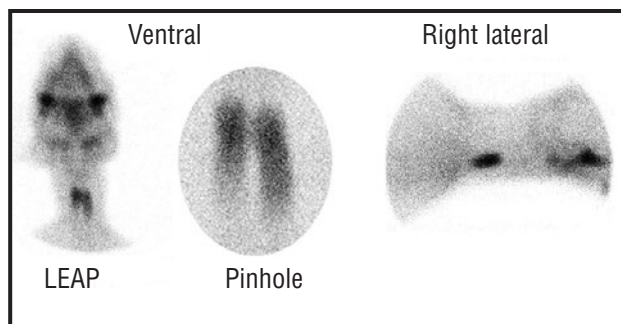


Figure 10.2: Normal feline thyroid scan

These images were acquired 20 minutes following injection of sodium ^{99m}Tc -pertechnetate. Note the uniform uptake by both thyroid lobes. The intensity of thyroid uptake is slightly less than the zygomatic-molar salivary tissue.

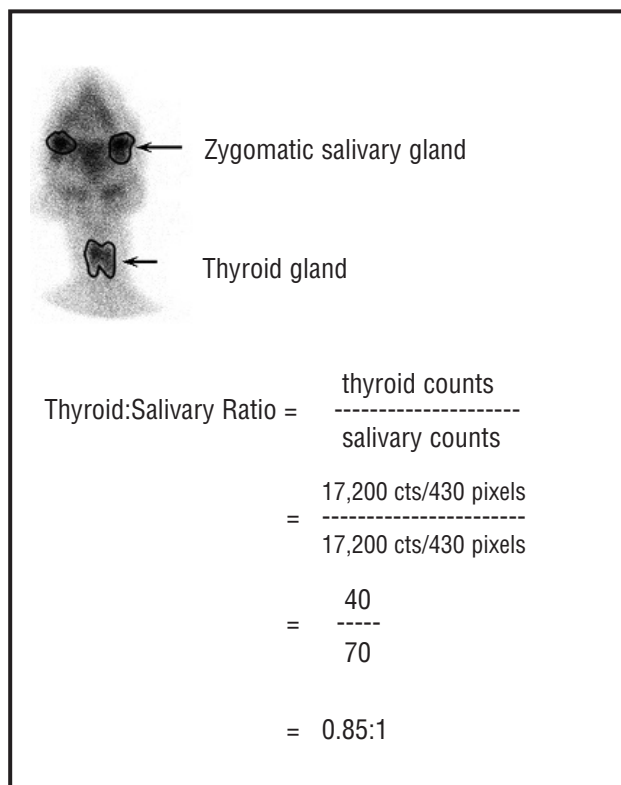


Figure 10.3: Quantitative analysis of thyroid uptake of sodium ^{99m}Tc -pertechnetate in the cat

Region of interests (ROIs) are placed around the thyroid and zygomatic/molar salivary tissue. A ratio of the count density of the thyroid and salivary tissue is used to quantify thyroid function.

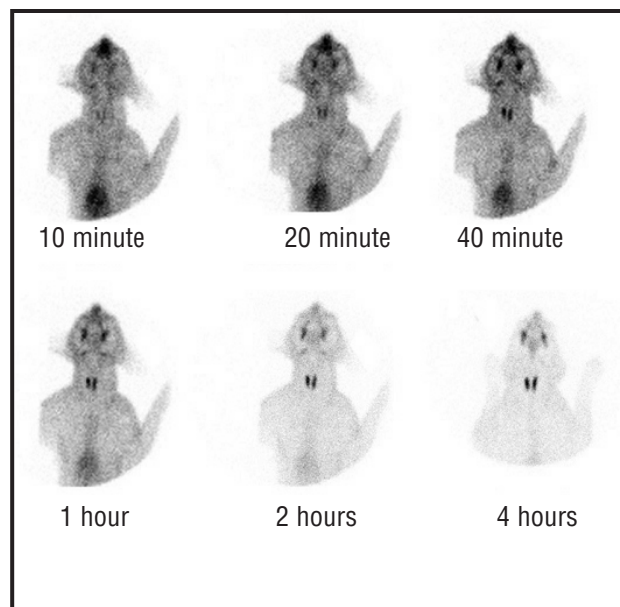


Figure 10.4: Ventral images of a normal cat taken at varying times following injection of sodium ^{99m}Tc -pertechnetate

Note that the thyroid gland uptake continues to increase over the 4-hour time period. Meanwhile, there is clearance of the radionuclide from the soft tissues.

evaluate thyroid function. The normal thyroid:background ratio is 2.76:1 (range 1.7-4.4).³⁰

Another method of quantifying thyroid function is by measuring the percent of the injected dose of the radionuclide that accumulates in the thyroid gland. These techniques are referred to as radioiodine uptake (RAIU) studies. Measurements can be made with either a thyroid detector probe or a gamma camera. The thyroid detector probe consists of a collimated sodium iodide crystal coupled to a single photomultiplier tube. The technique requires either measurement of the radionuclide dose prior to administration or a standard of the radionuclide that is to be used. Thyroid radioactivity is recorded in counts per minute (cpm). Background radioactivity is also recorded in cpm. The amount of radioactivity absorbed by the soft tissues between the thyroid and the nuclear detector must be determined and attenuation correction calculated. The soft tissue attenuation is based on the depth of the thyroid gland in cervical tissues. Figure 10.5 is a graph showing the percent of the injected dose that accumulates in the

feline thyroid gland from 0 to 120 minutes. Normal thyroid percent dose uptake in cats 20 minutes after injection was reported by Mooney to be 0.64% (mean) of the injected dose with a range of 0.25% to 1.55%.²³ Later, Nap et al, found that maximum uptake occurred between 45 to 60 minutes after intravenous injection, followed by a gradual decline and that the range of the percent thyroid uptake of the injected dose was from 0.8% to 3.9% of the injected dose (median 2.2%).²⁰

In one study using eight normal cats, the percent injected dose was calculated using correction techniques for background radioactivity and soft tissue attenuation based on thyroid depth (as measured using a 7.5 MHz ultrasound probe and instrumentation).²¹ In this study, the mean $\pm$ standard deviation percent injected dose was 0.21 ± 0.6 at 20 minutes, 0.37 ± 0.13 at 1 hour, 0.65 ± 0.3 at 2 hours, and 1.6

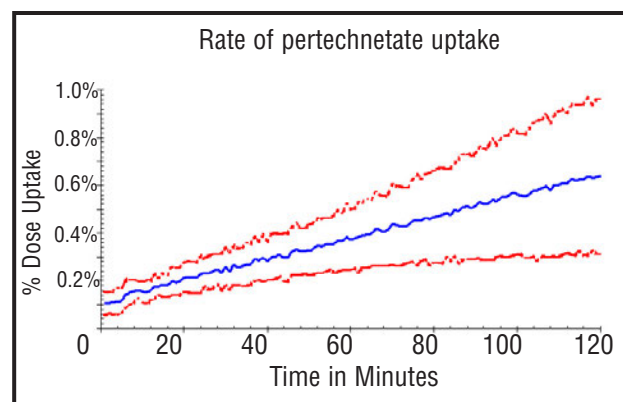


Figure 10.5: Graph showing the percent dose uptake of sodium ^{99m}Tc -pertechnetate by the normal feline thyroid

The center blue line represents the mean of eight cats. The outer dashed red lines represent one standard deviation.

Table 10.2: Imaging Parameters for Thyroid Scintigraphy with ^{99m}Tc Technetium

Radionuclide

Sodium ^{99m}Tc -pertechnetate ($\text{Na}^{99m}\text{TcO}_4$)

Dose

Species	mCi	MBq
Dog	2-5	74-185
Cat	1-4	37-148
Horse	20-30	740-1,110

Acquisition Parameters

Animal preparation	General anesthesia required for pinhole acquisition (cat). Sedation generally required (cat, dog, and horse).
Static frame acquisition	Minimum 250,000 counts thorax; minimum 100,000 counts cervical region.
Matrix	$256 \times 256 \times 16$.
Collimator	Low-energy, all-purpose, high-sensitivity or high-resolution; pinhole collimator (ventral cervical view – requires anesthesia).
Time of imaging	20 minutes after injection.
Positioning	Dogs and cats are recumbent over the camera; horses are imaged while standing.
Views	Ventral, right, and left lateral images of the cervical region (all species); ventral (or dorsal), right and left lateral images of the thorax (cat and dog); only lateral images of the thorax in horses.

± 1.0 at 4 hours. The differences are presumed to be based on the correction techniques and the imaging times (see Figure 10.5).

Normal Canine Thyroid Scintigraphy

In dogs the thyroid is a paired structure embedded in the deep cervical fascia adjacent to the trachea. It is an elongated structure that varies in size among breeds.³¹ Because of its intimate association with the aortic sac during embryogenesis, there is frequently ectopic thyroid tissue embedded in the fat around the base of the heart and origin of the aorta.³² The appearance of normal thyroid scans in dogs is characterized by symmetrical uptake in the paired thyroid lobes that are spherical to ovoid in shape. The uptake is homogeneous and the margins are smooth and regular (Figure 10.6). The intensity of thyroid gland uptake is compared with that of the parotid

salivary gland¹⁹ (Figure 10.7). The thyroid-salivary ratio changes with time after injection (Figure 10.8). The time of imaging varies among individual laboratories, most choosing either 20 minutes or 60 minutes postinjection. Fortunately, the thyroid-salivary ratio does not change significantly from 20 to 60 minutes but does decrease after 1 hour.¹⁹ The percent injected dose thyroid uptake in a group of 15 normal dogs was 0.42 ± 0.9 at 20 minutes, 0.53 ± 0.1 at 1 hour, 0.65 ± 0.2 at 2 hours, and 0.52 ± 0.2 at 4 hours. This data decay and attenuation depth (based on ultrasound measurements) corrected. Ectopic tissue is typically not seen in normal dogs, but sublingual ectopic tissue is seen often following thyroidectomy (Figure 10.9).

Abnormal Thyroid Scintigraphy

Uptake by the thyroid gland can be used to determine whether the thyroid disease is functional or

Table 10.3: Imaging Parameters for Thyroid Scintigraphy using Radioiodine (^{123}I)

Radionuclide

Radioiodine (^{123}I); Electron capture decay; 159 keV gamma photon (83% abundance); 13.1 hours physical half-life.

Dose

Species	μCi	MBq
Dog	300-600	11.1-22.2
Cat	200-400	7.4-14.8

Acquisition Parameters

Animal preparation	Sedation or anesthesia for dog and cat.
Acquisition	Static frame mode acquisition with a minimum of 100,000 counts for the thoracic images and a minimum of 50,000 counts for the cervical region.
Matrix	$256 \times 256 \times 16$.
Collimator	Low-energy, all-purpose, high-sensitivity or high-resolution; pinhole collimator (optional ventral cervical view that will require anesthesia).
Time of imaging	Eight hours after injection to evaluate trapping and 24 hours after injection to evaluate organification.
Positioning	Animal in lateral or sternal recumbency over the gamma camera.
Views	Right and left lateral cervical views; ventral cervical view; right and left lateral views of the thorax.

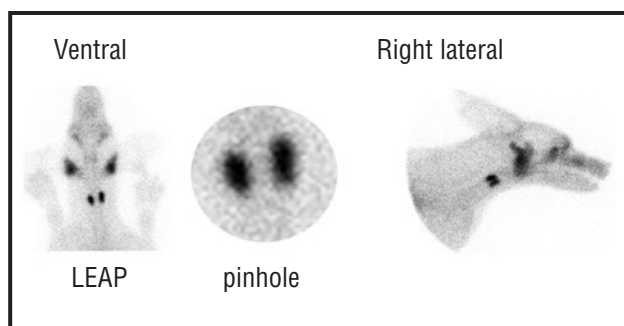


Figure 10.6: Normal canine thyroid scan

These images were acquired 20 minutes following injection of sodium ^{99m}Tc -pertechnetate. Note the uniform uptake by both thyroid lobes. The intensity of thyroid uptake is slightly more than parotid salivary tissue.

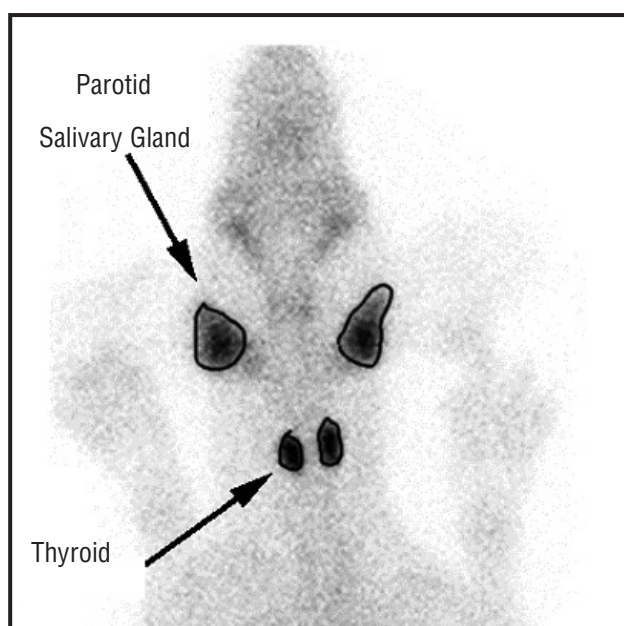


Figure 10.7: Quantitative analysis of canine thyroid uptake of sodium ^{99m}Tc -pertechnetate

Regions of interest are hand drawn around the thyroid and salivary tissue. A ratio of the count density of the thyroid and salivary tissue is used to quantify thyroid function.

nonfunctional. From a physiologic standpoint, a functional lesion is one that produces an excess of thyroid hormone. From a nuclear imaging and a radiation therapy standpoint, a functional lesion is one that demonstrates increased uptake of pertechn-

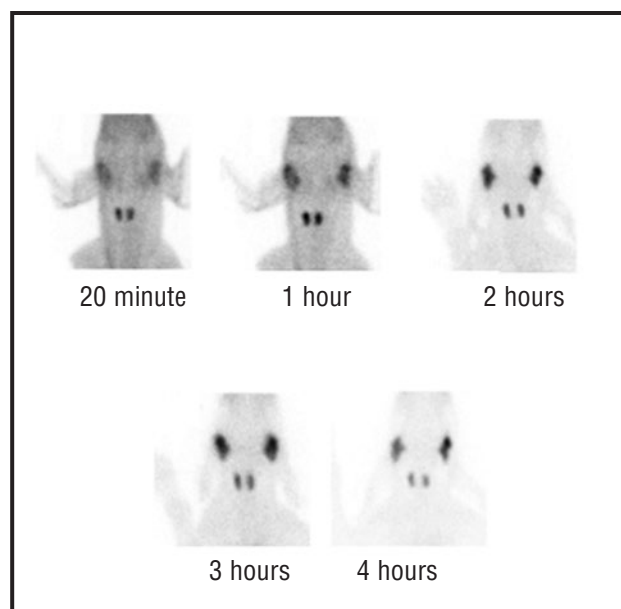


Figure 10.8: Ventral images of a normal dog taken at varying times following injection of sodium ^{99m}Tc -pertechnetate

Note the thyroid gland uptake reaches a maximum at 2 hours then clears. Meanwhile there is clearance of the radionuclide from the soft tissues.

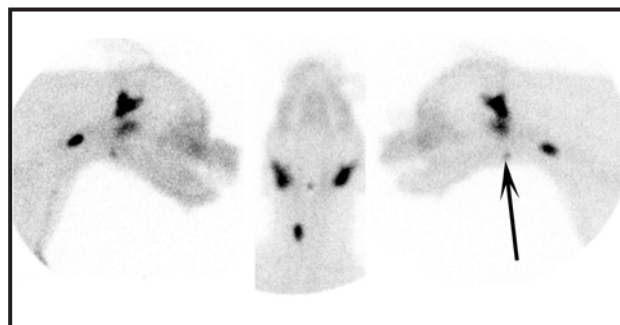


Figure 10.9: Thyroid scan in a dog 8 weeks following surgical removal of the left thyroid lobe

The arrow points to ectopic sublingual thyroid tissue.

tate or radioiodine by the thyroid. Increased uptake of radionuclide by the thyroid gland does not always correlate with an increased production of thyroid hormone. Dogs with thyroid carcinoma may have increased uptake of the radiopharmaceutical by the

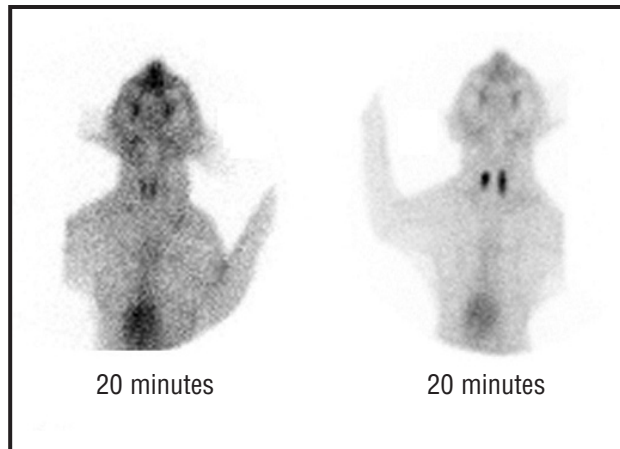


Figure 10.10: Ventral images of a normal cat taken 20 minutes following injection of sodium ^{99m}Tc -pertechnetate

These images are from the same cat but the image on the right was taken after 3 weeks of methimazole treatment. Note the increase in uptake by the thyroid gland giving the appearance of hyperthyroidism.

tumor but have normal or reduced thyroid hormone production. Cats with mild or early thyroid disease have an increased uptake by a hyperactive thyroid nodule, but serum thyroxine concentrations may be normal or fluctuate between normal and slightly increased.^{8,10,13} Normal cats on methimazole therapy can be hypothyroid but have markedly increased thyroid uptake (Figure 10.10), as a result of elevated TSH concentrations produced by the pituitary gland as a consequence of subnormal T_4 concentrations.

If a thyroid lesion is physiologically functional, then serum thyroxine concentration will be increased and there will be negative feedback on the pituitary gland resulting in decreased production of TSH and suppression of normal thyroid tissue. The functional thyroid lesion will exhibit increased uptake of the radionuclide, and there will be decreased uptake by normal thyroid tissue. This is the typical situation seen in a cat with thyroid disease. If a thyroid lesion is physiologically nonfunctional but remaining normal tissue is capable of maintaining normal thyroxine concentration, then the thyroid lesion may exhibit either increased or decreased uptake of the radionuclide; but the remaining normal tissue (contralateral lobe) should appear of normal intensity. If the thyroid lesion destroys enough of the thyroid gland to cause subnormal thyroxine concentration,

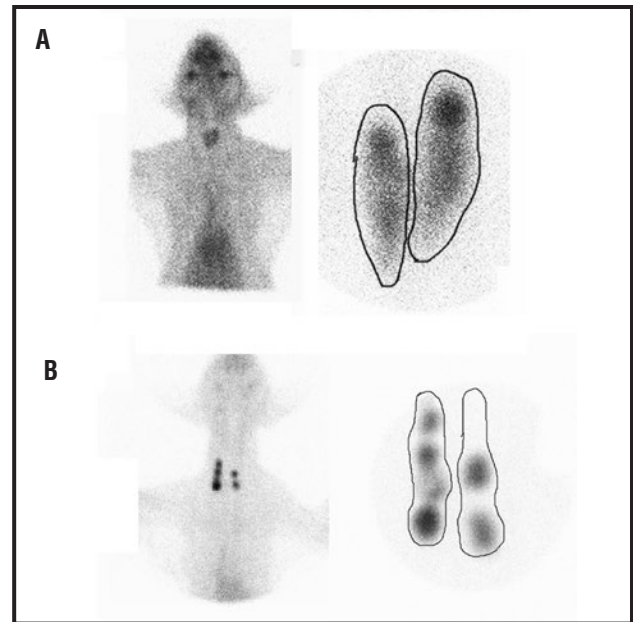


Figure 10.11: Thyroid scans from two hyperthyroid cats obtained 20 minutes after sodium ^{99m}Tc -pertechnetate administration

A, The degree of hyperthyroidism and hyperfunctional tissue is mild. There is a single hyperactive nodule with mild suppression of the surrounding thyroid tissue. **B**, The hyperthyroidism is more severe as there are multiple hyperactive nodules with marked suppression of surrounding thyroid tissue.

then the pituitary gland will increase TSH release and the remaining normal tissue will be stimulated resulting in increased uptake of the radionuclide. In this situation, the nonfunctioning thyroid lesion usually will have decreased uptake of the radionuclide but the remaining normal tissue will have increased uptake. The increased TSH may also cause uptake in ectopic tissue that was not apparent when the thyroid gland was normal.

Serum thyroid hormone levels may fluctuate considerably in cats with mild hyperthyroidism.^{8,10,13} If the thyroxine concentration is not consistently elevated, then TSH may remain normal or slightly subnormal. Figure 10.11 shows scintigrams from two cats with different degrees of hyperthyroidism. The cat in 10.11A has hyperactive nodules that are more intense than the surrounding tissue, but the uptake of the surrounding thyroid tissue is only slightly suppressed. The cat in 10.11B has hyperactive nodules with marked suppression of surrounding thyroid

tissue. An outline of the normal thyroid shape has been placed around the pinhole collimator images. Because trapping of the radionuclide by normal thyroid tissue is TSH dependent, it can be inferred that the cat in 10.11A was not overtly hyperthyroid because the remaining thyroid tissue is only slightly suppressed, but the cat in 10.11B was clearly hyperthyroid because the normal thyroid tissue was completely suppressed leaving only visualization of the hyperactive nodules. Both of these cases represent functional disease of varying severity.

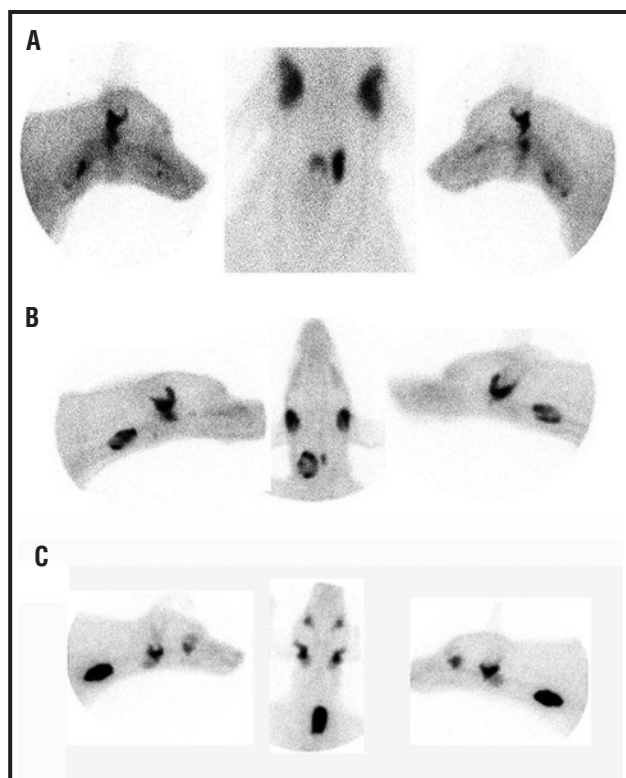


Figure 10.12: Sodium ^{99m}Tc -pertechnetate thyroid scans from three dogs with thyroid carcinoma

A, A tumor is present in the right thyroid lobe with decreased $^{99m}\text{TcO}_4^-$ uptake. The contralateral lobe is not suppressed so the tumor is considered to be nonfunctional. **B**, In this dog, the right thyroid lobe with increased uptake of the radionuclide and is considered functional based on scintigraphy, but is not producing excess thyroid hormone since there is minimal suppression of the contralateral thyroid lobe. **C**, A dog with a left thyroid lobe carcinoma where there is marked radionuclide uptake, so the right lobe is suppressed consistent with excessive thyroid secretion.

Most dogs with thyroid carcinoma have physiologically nonfunctional tumors. The affected thyroid lobe may exhibit either increased uptake, decreased uptake, or a mixed pattern of uptake; but the tumor usually does not produce excessive thyroxine and uptake in the contralateral thyroid lobe will not be suppressed. If a thyroid tumor is functional from a physiologic standpoint and produces excessive levels of thyroxine, then the tumor will have increased uptake and the contralateral thyroid lobe will have suppressed uptake. Figure 10.12 shows thyroid scans from three dogs with thyroid carcinoma. Dog A had a nonfunctional tumor. Note the decreased uptake of radionuclide by the tumor and increased uptake by the contralateral lobe. This dog would have normal to low serum thyroxine concentrations but elevated TSH levels. Dog B has a physiologically nonfunctional right thyroid tumor that exhibits a mixed pattern with areas of both increased and decreased uptake. Note the right thyroid lobe had regions of markedly increased uptake but the contralateral left lobe is only slightly suppressed because excessive thyroid hormone is not being secreted by the tumor. Dog C had a functional tumor in the left thyroid lobe. The tumor exhibited increased uptake with complete suppression of the contralateral lobe, because the tumor was secreting excessive thyroid hormone. This created a negative feedback on the pituitary, suppressing the release of TSH so that the normal left thyroid lobe is nonfunctional.

Feline Thyroid Disease

Hyperthyroidism results from excess thyroid secretion from hyperfunctional thyroid tissue.^{3-5,33,34} The thyrotoxicosis caused by increased serum hormone concentration results in a multisystemic disorder causing a variety of clinical signs. The most common clinical signs of feline hyperthyroidism are weight loss, hyperactivity, polyphagia, tachycardia, polyuria, and polydipsia.⁵ There are many other diseases of older cats that can result in similar clinical findings. Benign thyroid lesions, such as adenomatous hyperplasia or a single or multiple thyroid adenoma(s), usually cause feline hyperthyroidism. This thyroid disease usually involves both thyroid lobes in 70% of affected cats.^{3-5,11,32,33} In cases of bilateral involvement, the uptake of the thyroid lobes is often asymmetrical. The incidence of thyroid carcinoma in hyperthyroid cats is reported to be

approximately 2% to 5%.³⁵

Feline Thyroid Hyperplasia

Multifocal nodular hyperplasia, also called adenomatous hyperplasia, can be unilateral or bilateral and is characterized by a moderate enlargement of the thyroid lobe(s). Often the thyroid lobe(s) will have an irregular contour.^{29,32} Multifocal nodular hyperplasia is characterized histologically by follicular cell hyperplasia in multiple areas that are not encapsulated and do not compress adjacent tissue.³² It is often difficult to differentiate multifocal nodular hyperplasia and multiple follicular cell adenomas.²⁹ With thyroid scintigraphy, hyperactive thyroid lobe(s) exhibit increased radionuclide uptake. Typically the margins of the thyroid are smooth with regular borders, and the affected lobe(s) have a homogeneous pattern of increased uptake. Adenomatous thyroid hyperplasia usually is bilateral, but unilateral disease is seen in approximately 30% of hyperthyroid cats³⁶ (Figure 10.13). True unilateral hyperplasia causes complete suppression of the contralateral thyroid lobe by negative feedback mechanisms through the pituitary gland. If one lobe exhibits markedly increased uptake and the opposite lobe is seen and exhibits normal or decreased uptake, both lobes should be considered abnormal. Lack of complete suppression of a lobe despite marked hyperactivity of the paired lobe is indicative of autonomous function. Asymmetric bilateral thyroid dysfunction is often seen in hyperthyroid cats.



Figure 10.13: Ventral pinhole images from two hyperthyroid cats with adenomas

The image on the left is from a cat with bilateral thyroid disease. The image on the right is a cat with unilateral thyroid disease. Note the suppression of the contralateral lobe in the cat on the right.

Feline Thyroid Adenomas

Hyperthyroidism may be the result of one or more thyroid adenomas. Adenomas may arise from within one or both lobes. They may also arise from ectopic tissue. The hyperactive nodules are seen as focal areas of increased uptake. The surrounding normal tissue will be suppressed to varying degrees depending on the serum thyroxine concentration. If a pin-hole collimator is used, the multifocal appearance

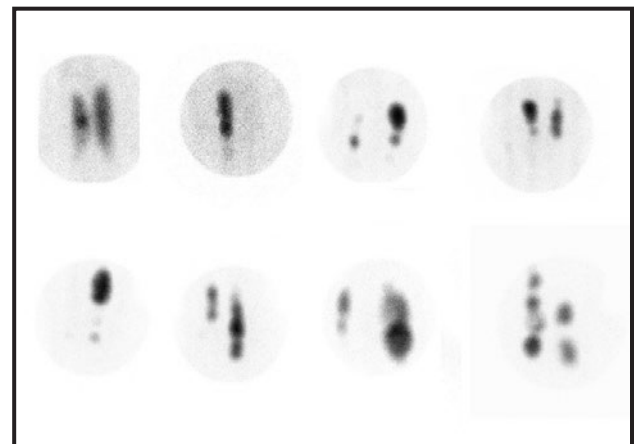


Figure 10.14: Ventral pinhole images acquired from eight different hyperthyroid cats 20 minutes after the intravenous administration of sodium ^{99m}Tc -pertechnetate

Abnormal uptake is present showing the variability of uptake from cats with multinodular adenomas.

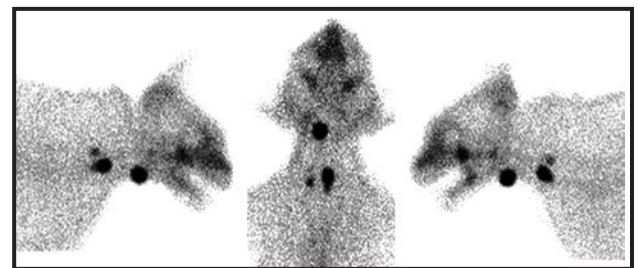


Figure 10.15: Ventral and lateral views acquired from a hyperthyroid cat 20 minutes after the intravenous administration of sodium ^{99m}Tc -pertechnetate

There is increased uptake by both thyroid lobes. In addition, there is a focal area of uptake seen in sublingual region, ventral to the larynx that represents ectopic, functional, thyroid tissue.

of multinodular adenomas will be more apparent, (Figure 10.14). This is the most common pattern of feline thyroid disease. The appearance of hyperactive thyroid nodule(s) varies from enlargement of a portion of a lobe, to hyperactive nodules at both ends of a thyroid lobe to a linear alignment of hyperactive nodules appearing as a “string of pearls.” Most often hyperactive nodules are confined to the area of the original thyroid lobes, but they can extend both cranially and caudally when nodules occur in ectopic tissue. Figure 10.15 is a scintigraphic image from a cat with a hyperactive nodule arising from ectopic sublingual tissue. Some thyroid adenomas are composed of thin-walled cysts filled with a yellow to red fluid.³² This cystic area will appear photopenic on a thyroid scan. Often there are hyperactive nodules surrounding the cystic area. Ultrasound is useful to help confirm the reason for the photopenic void in cases of cystic adenoma (Figure 10.16). In early or mild disease, the thyroid scan may appear normal on images obtained using a LEAP collimator; but a hyperactive nodule is seen if a pinhole collimator is used (Figure 10.17).

Feline Thyroid Carcinoma

Malignant thyroid neoplasia is uncommon in hyperthyroid cats. Thyroid carcinoma can have similar scintigraphic appearances to benign hyperactive thyroid disease. Scintigraphy cannot reliably differentiate malignant and benign thyroid lesions in humans or animals, but there are patterns that are associated

Figure 10.16: Ventral image of a cat with a cystic adenoma in the right lobe

An area of photopenia is present centrally on the ventral thyroid scintigraphic image. Several hyperactive nodules surrounding the cyst are present. The photopenic area was shown to be cystic with ultrasound (image on right). The histologic diagnosis was a cyst adenoma.

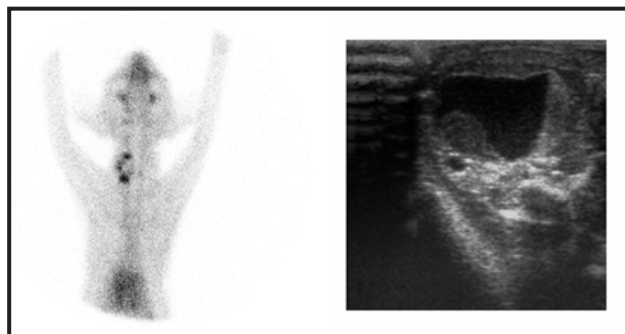


Figure 10.17: Ventral images of a cat with a single hyperactive nodule in the right lobe

The image on the left was acquired with a LEAP collimator. The image on the right was acquired with a 2 mm aperture pinhole collimator for a total of 100,000 counts. Note the thyroid and salivary tissue appear to be equal and the cat has minimal T_4 elevations. A single nodule is seen in the central portion of the right thyroid lobe.

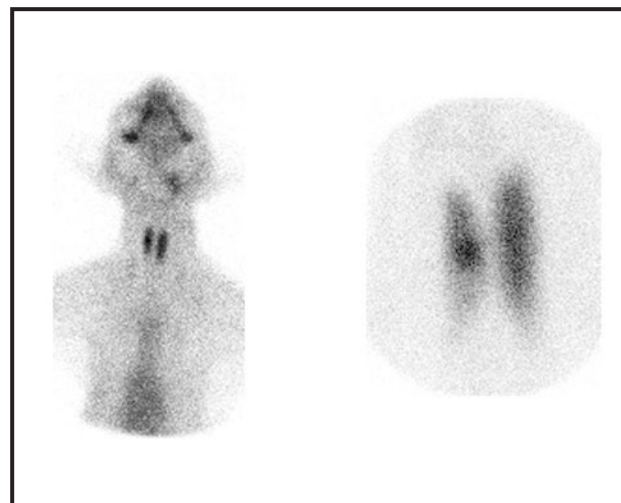
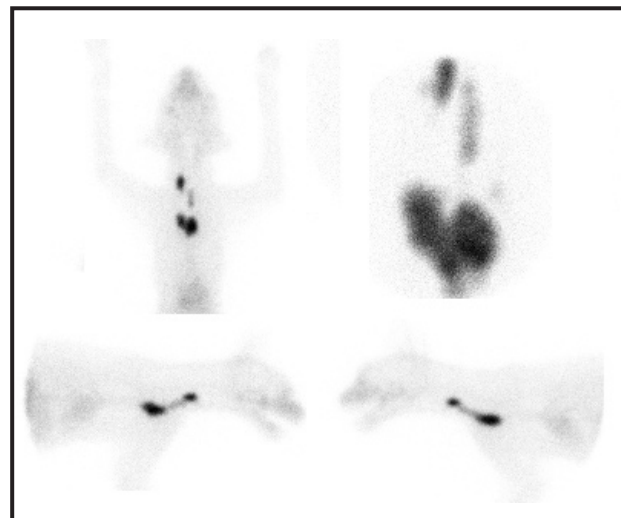


Figure 10.18: Ventral and lateral images of a cat with thyroid carcinoma

Note the irregular and disorganized pattern of radiopharmaceutical uptake. There are numerous areas of radiopharmaceutical uptake outside the confines of the left and right thyroid lobes.

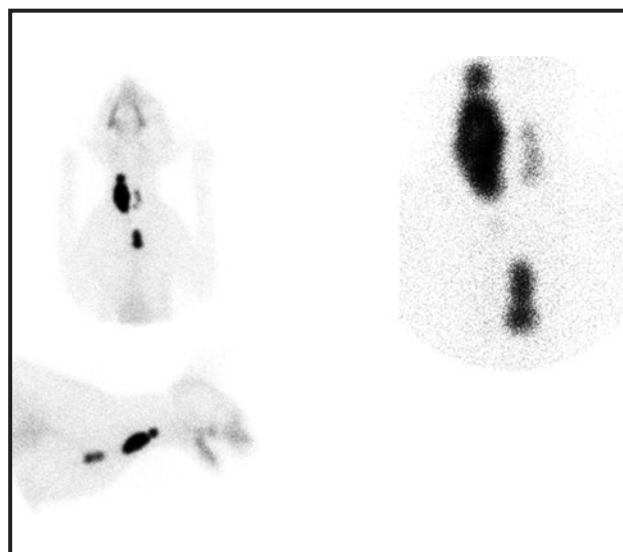


with higher probability of carcinoma. Carcinomas tend to have a heterogeneous pattern of uptake with irregular, spiculated margins. A multifocal pattern of uptake with foci of uptake outside the confines of the thyroid lobes indicates a higher probability of carcinoma (Figure 10.18). A linear multifocal pattern of increased uptake may be seen with tumor extension along fascial planes; but can be seen with multinodular adenomas that have ectopic sites. Accumulation of radionuclide within the mediastinum and lung may be seen with metastases. Hyperplastic ectopic thyroid tissue, esophagus containing salivary secretions, and vascular blood pool activity are differentials for abnormal cranial mediastinal uptake. Accumulation of radionuclide within the lung is usually associated with malignancy but not necessarily thyroid tumor because primary lung tumors also may accumulate radionuclide. In cases with questionable accumulation of pertechnetate in the thorax, a radioiodine scan is recommended because radioiodine scans have lower background activity.

Nonmalignant disease may mimic the scintigraphic appearance of thyroid carcinoma. Cats that have had a prior intracapsular thyroidectomy can have a multifocal pattern of uptake throughout the cervical

Figure 10.19: Ventral and lateral images from a cat with thyroid carcinoma

Note the multiple areas of increased uptake in the cervical and cranial mediastinal regions. This pattern could represent thyroid carcinoma or multiple hyperactive ectopic sites. A biopsy was required to confirm the diagnosis of thyroid carcinoma.



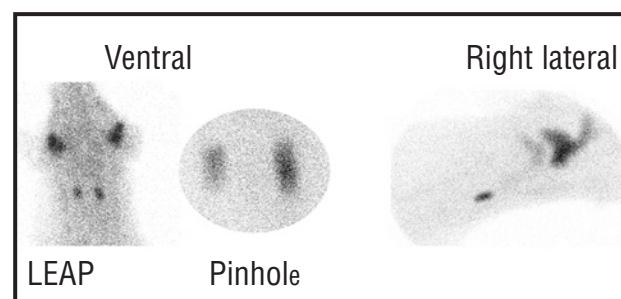
region. As described earlier, many of the benign thyroid lesions may have a multifocal pattern of thyroid uptake with irregular margins. If the scintigraphic pattern is suggestive of malignancy, then a biopsy should be performed to confirm the diagnosis. If the lesion is benign and all of the hyperactive tissue is removed, surgery will be curative. If the excisional biopsy indicates malignancy, a repeat scan is recommended 4 to 6 weeks after surgery to evaluate for residual disease or to identify metastatic sites. Radioiodine is especially useful for these follow-up scans because of its high target-to-background ratio.

Evaluation of Canine Thyroid Function

Dogs with hypothyroidism are usually evaluated by in vitro assays, and thyroid scintigraphy is infrequently used. Scintigraphy is valuable in determining whether congenital hypothyroidism is caused by thyroid dysgenesis (thyroid glands are not visualized on the thyroid scan) or by inherited iodination defects (thyroid scan shows large thyroid lobes with normal to increased radionuclide accumulation). In adult hypothyroidism, stimulation tests can be used to differentiate primary hypothyroidism from secondary hypothyroidism. Thyroid uptake will be reduced or absent in all cases of hypothyroidism on the initial or baseline scan (Figure 10.20). A thyroid scan made after administering TSH for several days will show continued subnormal accumulation of the radionuclide in primary hypothyroidism but normal

Figure 10.20: Hypothyroidism in a dog

Ventral low-energy, all-purpose collimator image, ventral pinhole image, and right lateral image from a dog with hypothyroidism. The thyroid is of normal size and shape. The left lobe is slightly more uptake than the right but both lobes are less intense than the parotid salivary glands.



accumulation in dogs with secondary hypothyroidism. Dogs with low serum thyroid hormone concentration caused by factors not directly related to the thyroid gland (euthyroid sick syndrome) will have normal to slightly increased thyroid scintigrams even on initial studies.

Evaluation of Cervical Masses

Thyroid scintigraphy is useful to determine whether cervical masses arise from the thyroid or from other tissue when cytology or histopathologic diagnosis is equivocal (Figure 10.21). When the mass arises from the thyroid, the appearance of the thyroid gland is abnormal. When the mass arises from tissues other than the thyroid, both thyroid lobes should exhibit a normal size. Thyroid uptake may appear suppressed from attenuation by the mass or the thyroid lobes may be displaced.

The scintigraphic appearance of canine thyroid carcinoma can be unilateral or bilateral. The patterns of uptake can vary with regard to the intensity of uptake and the size of the mass. Three common uptake patterns can be seen: (1) diffuse increased uptake throughout the thyroid mass or follicular cell tumor (Figure 10.22), (2) thyroid mass with decreased uptake of the radionuclide, effacing the normal thyroid tissue in a tumor of stromal origin (Figure 10.23), and (3) irregular, multifocal areas of radionuclide accumulation with areas of both increased and decreased uptake in tumors with mixed cell populations (Figure 10.24). The appearance of the thyroid gland can also

be characterized by its margins. Some tumors will have well-defined borders, and other masses will have ill-defined or spiculated borders. An interpretation scheme has been proposed in which the scintigraphic appearance is divided into two patterns. The first pattern consists of a thyroid mass with well circumscribed, homogeneous, radionuclide uptake (Figure 10.24). The second pattern has a heterogeneous uptake of the radionuclide within a poorly circumscribed thyroid mass (Figure 10.25).³⁷ The patterns did not predict the tumor type but were helpful in predicting the surgical respectability of the mass. Surgical dissection was more easily accomplished in dogs with thyroid masses that had the first type of imaging pattern with a homogeneous, well-circum-

Figure 10.22: Ventral and lateral images from a dog with thyroid carcinoma in both thyroid lobes

There is diffuse increased uptake indicating increased follicular cell function.

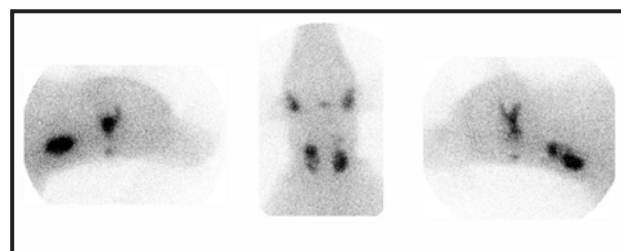


Figure 10.21: Ventral and lateral views of a dog with a carotid body tumor.

This is an example of a non-thyroidal cervical mass. Both thyroid lobes are of normal size, shape and intensity. The thyroid is displaced to the left by the mass. There is diffuse low intensity uptake within the mass that is due to passive blood pool activity.

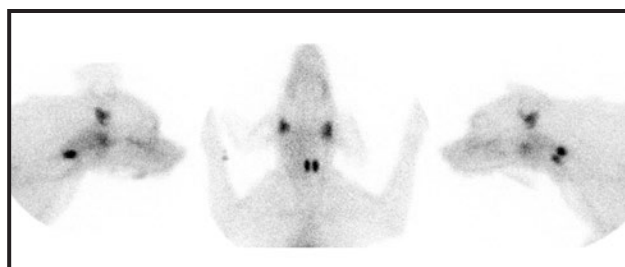
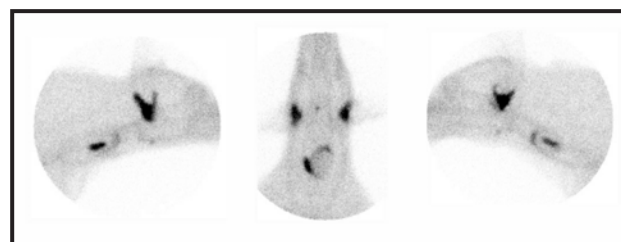


Figure 10.23: Ventral and lateral images from a dog with a left thyroid carcinoma

There is lack of radionuclide uptake by the tumor. The tumor has effaced the majority of the left lobe. Only remnants of the follicular cell activity are seen at the margins of the lobe. Note the sublingual thyroidal tissues on midline in the ventral laryngeal regions. This ectopic tissue often becomes functional when a thyroid lobe is removed by surgery or, in this dog, by the neoplastic process.



scribed margin.

Scintigraphy can be useful to help stage thyroid carcinoma. Thyroid tumors can be locally invasive and can metastasize to the lung. Tumor spread in a cranial or caudal cervical direction indicates likely extension of the carcinoma along lymphatic structures or fascial planes. Lymphatic drainage from the cranial pole of the thyroid is to the medial retropharyngeal lymph node. Tumor extension to the medial retropharyngeal lymph node is seen as a mass dorsal to the trachea and lateral to midline and is easily differentiated from sublingual ectopic thyroid tissue, which is seen ventral to the larynx and located on midline. The lymphatic drainage for the caudal portions of the thyroid glands is into the right lymphatic

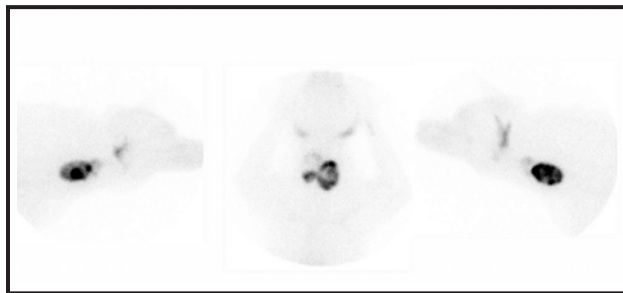


Figure 10.24: Ventral and lateral images from a dog with thyroid carcinoma of both thyroid lobes

There are areas of heterogeneous uptake within each lobe tumor indicating a mixed cell origin. The thyroid tumor appears to be well-circumscribed without scintigraphic evidence of invasion into the surrounding tissues.

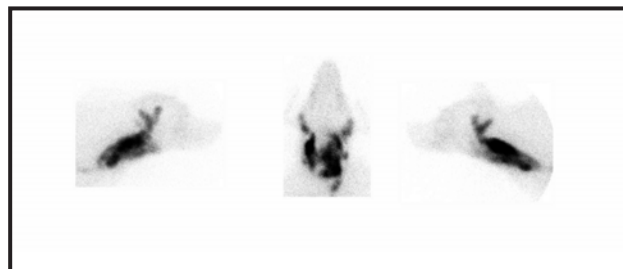


Figure 10.25: Ventral and lateral views of a dog with an invasive thyroid carcinoma involving both lobes

Note the ill-defined borders and the extension in the proximal cervical soft tissues. This tumor would be difficult to remove surgically.

duct.^{31,32,38-40} The venous return from the thyroid is through the internal jugular vein.

Mediastinal uptake of the radiopharmaceutical can be caused by tumor extension to mediastinal lymph nodes or by ectopic tissue stimulated by TSH or by neoplastic transformation of ectopic tissue (Figure 10.26). Ectopic thyroidal tissue is common in the dog. About 50% of adult dogs have ectopic thyroidal tissue embedded in the fat on the intrapericardial aorta.³² Uptake in the area of the heart base is often seen in dogs and probably represents stimulation

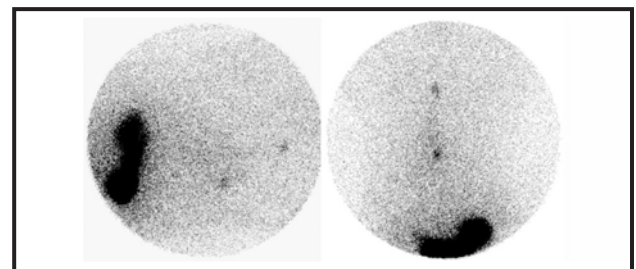


Figure 10.26: Ventral and lateral views of the thorax in a dog 9 months following surgical excision of a thyroid carcinoma

This scan was acquired 20 hours following oral administration of 425 μCi of ^{123}I . There are two foci of uptake within the mediastinum and heart region representing tumor extension. Thoracic metastases of thyroid tumors are easier to detect with ^{123}I because of its high target-to-background ratio.

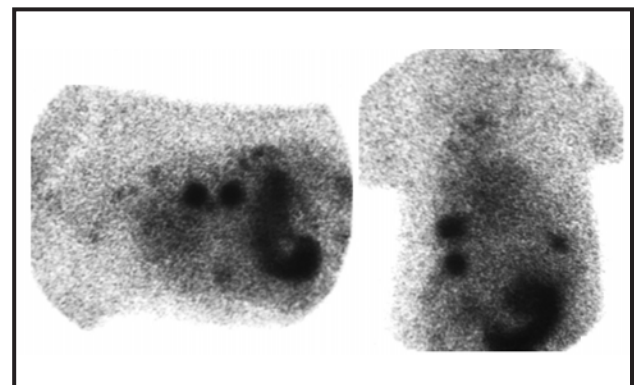


Figure 10.27: Ventral and lateral views of the thorax in a dog with metastatic thyroid carcinoma in both lungs

These images were acquired 20 minutes following injection of $^{99\text{m}}\text{TcO}_4^-$.

of the remnant of thyroidal tissue or its neoplastic transformation.

Pulmonary metastatic lesions may be seen as multifocal areas of abnormal pulmonary radioactivity on thyroid scans in dogs (Figure 10.27), but it is likely that many metastatic lesions are missed because of low uptake if the primary tumor has not been ablated. Critical evaluation for metastasis is best achieved by repeat scans made after primary tumor ablation. It is generally considered that ^{123}I is superior to $^{99\text{m}}\text{TcO}_4^-$ for detecting metastatic thyroid lesions because of the organification of the ^{123}I . Delayed imaging at 24 to 72 hours is possible with ^{123}I and allows superior target-to-background radioactivity.^{2,6,9,12} Abnormal foci of activity in the thorax may be seen on initial $^{99\text{m}}\text{TcO}_4^-$ scans, but the uptake may represent either metastases that can trap $^{99\text{m}}\text{TcO}_4^-$ or passive blood pool activity. It is important to note that nonthyroidal masses can also cause abnormal focal radionuclide accumulation(s) in the thorax. Scintigraphic correlation with thoracic radiographs is necessary whenever there is abnormal radionuclide accumulation in the thorax.

Summary

Thyroid scintigraphy has the unique ability to provide both functional and anatomic information about the thyroid gland. Thyroid scintigraphy is most often used to evaluate for hyperthyroidism in cats. The thyroid scan provides important information that therapeutic consideration must rely on for proper treatment of feline hyperthyroidism. Canine thyroid scintigraphy is most often used for evaluation of dogs with a cervical mass. These dogs are usually not hyperthyroid, therefore the origin of the mass is frequently unknown at the time of the initial workup. The thyroid scan can determine if the mass is thyroid or nonthyroid in origin. Similar to the cat, the thyroid scan provides important information needed for therapeutic considerations. The success of radioiodine therapy depends on the uptake characteristics of the thyroid tumor. The thyroid scan will also give the surgeon an idea of the extent of the lesion and how invasive the lesion is in the surrounding tissue. The thyroid scan is quick and easy to perform and due to the biologic characteristics of the radionuclides (sodium $^{99\text{m}}\text{Tc}$ -pertechnetate and radioiodine [^{123}I]), the image quality is excellent.

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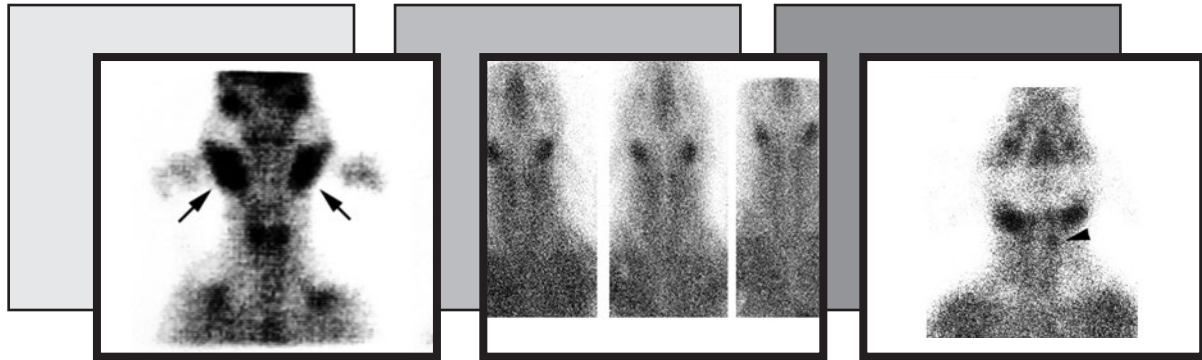
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Parathyroid Scintigraphy

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Introduction

In humans, parathyroid scintigraphy has an active role in the management of patients with hypercalcemia. There are two pairs of parathyroid glands. The internal glands are embedded in the caudal aspect of the thyroid glands, and the external parathyroid glands are located external to the thyroid tissue capsule cranially. The parathyroid gland produces parathyroid hormone or parathormone which regulates calcium and phosphorus metabolism. Parathyroid hormone stimulates osteoclastic activity in bone increasing bone resorption and thereby releasing calcium. Calcium levels within the plasma will become elevated. Excess parathyroid hormone results in elevation of serum calcium beyond normal limits. Hypercalcemia can cause primary or secondary diseases of the parathyroid gland or non-parathyroid tumors (hypercalcemia of malignancy). Parathyroid adenoma, parathyroid adenocarcinoma, and parathyroid hyperplasia are primary diseases of the parathyroid glands. It is important to identify the site(s) of excess parathyroid hormone production in cases of parathyroid adenoma. Parathyroid adenomas are found in a variety of locations adjacent to the thyroid gland but can also be found away from the thyroid gland. Identification of hyperfunctioning parathyroid tissue aids in surgical planning.

The diagnostic workup of hypercalcemia in the dog is similar to that in humans. An imaging technique that would identify and locate hyperfunctioning parathyroid tissue would be desirable. Ultrasound has been used to identify parathyroid lesion but small lesions (< 4mm) can not be differentiated from normal tissue. Parathyroid tissue in the normal locations can be identified by an experienced sonographer but it is far more difficult to identify hyperfunctioning ectopic parathyroid tissue.

Table 11.1: Indications for Parathyroid Scintigraphy.

Help identify the etiology of hypercalcemia.
Identify presence and location of hyperfunctioning parathyroid tissue.
Differentiate between parathyroid adenoma, parathyroid hyperplasia.

There have been a variety of radionuclides used to detect hyperfunctioning parathyroid tissue. Today the most commonly used radiopharmaceutical is ^{99m}Tc -sestamibi used alone or in combination with ^{123}I . Initial studies in dogs appeared encouraging but the sensitivity and specificity is far less than what is reported in humans. The indications for parathyroid scintigraphy are summarized in Table 11.1. The acquisition parameters for parathyroid scintigraphy are summarized in Table 11.2.

Mechanism of Localization and Elimination

^{99m}Tc -sestamibi

^{99m}Tc -sestamibi is a lipophilic cationic molecule that accumulates in metabolically active cells, including myocardium, liver, kidney, muscle, and various malignant tumors.¹⁻⁴ ^{99m}Tc -sestamibi also accumulates in the thyroid gland and in hyperfunctioning parathyroid tissue.⁵ Factors proposed to play a role in cellular uptake of ^{99m}Tc -sestamibi include: blood flow, cationic charge, lipophilicity, plasma and mitochondrial membrane potentials, and cellular mitochondrial content.¹⁻⁶

Uptake of ^{99m}Tc -sestamibi is believed to be primarily determined by plasma membrane and mitochondrial membrane potentials, similar to the mechanisms of localization known for other cationic lipophilic molecules.^{1-4,6} The lipophilic nature of these molecules enables them to pass through the lipid bilayer cell membrane.^{1,2} The negative plasma membrane potential results in accumulation of lipophilic cations in the cytoplasm relative to the extracellular space.^{1,2} Strongly negative mitochondrial membrane potentials further concentrate the molecules within the inner mitochondrial matrix relative to the cytoplasm.^{1,2} Therefore, the net mitochondrial concentration is a function of both plasma and mitochondrial membrane potentials. Cells with highly negative membrane potential and a relatively high number of mitochondria (including cardiac and skeletal muscle as well as liver and kidney cells) have enhanced avidity for ^{99m}Tc -sestamibi.^{4,6} Increased accumulation of ^{99m}Tc -sestamibi in malignant tumors may be secondary to increased metabolic requirements that promote a more negative membrane potential.⁴

^{99m}Tc -sestamibi has been identified as a substrate for p-glycoprotein, a transmembrane protein encoded by the multidrug resistance gene.⁷ p-Glycoprotein is an energy-dependent drug efflux pump and many drugs interacting with p-glycoprotein are lipophilic and cationic.^{4,7} Studies have indicated that clearance of ^{99m}Tc -sestamibi is accelerated in a variety of tumor types with p-glycoprotein expression.^{3,4,8,9}

The mechanism by which ^{99m}Tc -sestamibi accumulates in hyperfunctional parathyroid tissue is not known. Lesion detectability appears to correlate with parathyroid gland size, with larger parathyroid glands being more readily detected.¹⁰⁻¹⁴ Very small lesions have been detected, and reports of false-negative results have been observed with relatively large adenomas.¹⁰⁻¹⁴ These findings suggest that factors other than lesion size play a role in uptake and identification. Parathyroid oxyphil cells contain abundant mitochondria, prompting speculation that these cells are responsible for uptake and retention of ^{99m}Tc -sestamibi in parathyroid lesions. In one study, positive uptake during the delayed phase of imaging occurred more frequently in parathyroid lesions with a histologic makeup of greater than 25% oxyphil cells.¹⁵ However, no clear correlation between scintigraphic results and oxyphil cell content was observed in other studies.^{13,14} The role of p-glycoprotein has been investigated in people and often parathyroid tumors that do not have ^{99m}Tc -sestamibi uptake during the delayed images have the p-glycoprotein transmembrane protein.³³ Studies are needed in the dog to determine if p-glycoprotein could be associated the the false-negative studies.

^{123}I odine

^{123}I is trapped and organified in the thyroid follicular cells in the same fashion as stable iodine (see Mechanisms of Localization; Chapter 10). ^{123}I does not accumulate in the parathyroid glands.

Principles of Interpretation

^{99m}Tc -sestamibi

In humans, ^{99m}Tc -sestamibi rapidly accumulates in thyroid and hyperfunctional parathyroid tissue.⁵ Over time, ^{99m}Tc -sestamibi washes out of normally functioning thyroid tissue but persists in

hyperfunctioning parathyroid tissue. This process is called differential washout.⁵ In humans, images are acquired 10 to 15 minutes after administration of ^{99m}Tc -sestamibi (initial or “thyroid” phase) and 2 to 3 hours after administration (delayed or “parathyroid” phase).⁵ The initial phase images are compared to the delayed phase images by visual inspection. During the initial phase, activity is present in both the thyroid and diseased parathyroid glands, but no activity remains in the thyroid glands during the delayed phase.⁵ In hyperfunctioning parathyroid tissue, however, activity persists and appears as a focal area of increased radiotracer uptake.⁵ Sensitivity of this dual-phase technique for detection of parathyroid adenomas in humans ranges from 83% to 95%.^{5,10-12,16,17} Sensitivity is lower for detection of hyperplastic glands, ranging from 37% to 62%.^{10-12,16-18} For detecting hyperfunctioning parathyroid tissue (parathyroid adenomas and parathyroid hyperplasia), reported sensitivities range from 77% to 83%.^{11,17} False-positive results can occur with benign or malignant thyroid nodules.¹⁹

In dogs, uptake of ^{99m}Tc -sestamibi is evident in the thyroid region by 20 minutes after intravenous administration.²⁰ Most radioactivity is gone by 4



Figure 11.1: Scintigraphic images (ventral view) obtained at 20 minutes (left) and 4 hours (right) after injection of ^{99m}Tc -sestamibi in a clinically normal dog

Left, Uptake in the thyroid/parathyroid region is evident. Right, On the delayed-phase image, a focal area of radioactivity is not detected in the thyroid/parathyroid region. Typical uptake of ^{99m}Tc -sestamibi is evident in the salivary glands (arrows). Reprinted from reference 20 with permission.

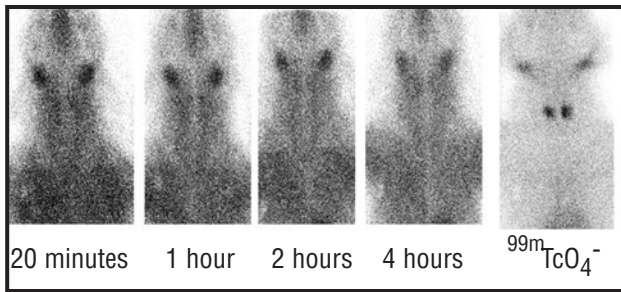


Figure 11.2: Ventral images obtained at 20 minutes, 1 hour, 2 hours, and 4 hours after the injection of ^{99m}Tc -sestamibi (first 4 images) and 20 minutes after injection with ^{99m}Tc -pertechnetate (far right) in a dog with a parathyroid adenoma

There is no specific uptake of ^{99m}Tc -sestamibi by the thyroid or parathyroid glands at any time during the study. The thyroid lobes are clearly visualized following injection of pertechnetate. Reprinted from reference 21 with permission.

hours after injection (Figure 11.1).²⁰ In some dogs, however, the thyroid glands are not visualized at any time after injection (Figure 11.2).^{21,22}

^{99m}Tc -sestamibi parathyroid scintigraphy has successfully identified and localized a parathyroid adenoma in a dog²⁰ (Figure 11.3), but overall this technique appears to have poor sensitivity and specificity in dogs. In a study of 15 hypercalcemic dogs, sensitivity of dual-phase ^{99m}Tc -sestamibi scintigraphy for detecting hyperfunctioning parathyroid tissue was 11%, specificity was 50%, and overall accuracy was 27%.²¹ The sensitivity for detecting parathyroid adenomas was 25%, and for hyperplastic glands was 0%.²¹ Dual-phase parathyroid scintigraphy using ^{99m}Tc -sestamibi by itself does not appear to have clinically acceptable accuracy for detecting hyperfunctioning parathyroid tissue in dogs.

^{99m}Tc -sestamibi parathyroid scintigraphy using single photon emission computed tomography (SPECT)²³ or a pinhole collimator²⁴ are used to improve sensitivity of parathyroid scintigraphy in humans. ^{99m}Tc -tetrofosmin is an agent similar to ^{99m}Tc -sestamibi and has been used as a parathyroid imaging agent in humans both as a single agent and in subtraction studies.²⁵ Use of SPECT, pinhole collimators, or ^{99m}Tc -tetrofosmin has not been reported in dogs.

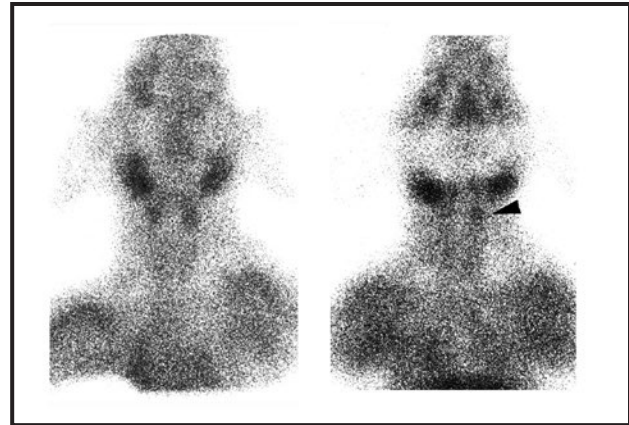


Figure 11.3: Scintigraphic images (ventral view) obtained at 20 minutes (A) and 4 hours (B) after injection of ^{99m}Tc -sestamibi in a dog with primary hyperparathyroidism.

(A) Initial-phase image indicates thyroid and parathyroid uptake of ^{99m}Tc -sestamibi. Uptake in the left thyroid region appears slightly greater than in the right. (B) On the delayed-phase image there is persistent focal uptake in the left cranial portion of the neck corresponding to a parathyroid adenoma (arrowhead). [Reprinted with permission, J Am Vet Med Assoc, 1996; 209:1733-1736.]

^{99m}Tc -sestamibi and ^{123}I Subtraction Imaging

To date, no radiopharmaceutical that concentrates solely in the parathyroid glands has been identified. ^{99m}Tc -sestamibi accumulates in normal thyroid tissue and hyperfunctional parathyroid tissue. ^{123}I accumulates only in thyroid tissue so subtracting the ^{123}I image (thyroid) from the ^{99m}Tc -sestamibi image (thyroid and parathyroid) yields an image of parathyroid uptake that represents hyperfunctional parathyroid tissue.²⁶⁻²⁹ Images must be assessed and corrected for patient motion, if necessary, prior to subtraction. Misregistration of the images may result in false-positive results. To the author's knowledge, there are no reports of ^{99m}Tc -sestamibi and ^{123}I subtraction parathyroid combination imaging in small animals.

Summary

^{99m}Tc -sestamibi has been shown to have avidity for other tumors in humans. One study looked at the uptake characteristics of ^{99m}Tc -sestamibi in benign

Table 11.2: Imaging Parameters for Parathyroid Scintigraphy**Radiopharmaceutical**

^{99m}Tc -sestamibi (^{99m}Tc -hexakis-2-methoxy-isobutyl-isonitrile) used as a single agent with a dual-phase technique.

^{123}I used in combination with ^{99m}Tc -sestamibi for parathyroid and thyroid subtraction imaging.

Dose

Radiopharmaceutical	mCi	MBq
^{99m}Tc -sestamibi	5-10	185-370
^{123}I	0.2-0.4	7.4-14.8

Acquisition Parameters: ^{99m}Tc -sestamibi Dual-Phase Technique

Animal preparation	Sedation or anesthesia.
Acquisition	Static frame mode acquisition Images are acquired for between 250,000 and 1,000,000 counts.
Matrix	$256 \times 256 \times 16$.
Collimator	Low-energy, all-purpose, high-sensitivity or high-resolution. The use of a pinhole collimator requires the use of general anesthesia.
Time of imaging	^{99m}Tc -sestamibi dual-phase technique.
	Initial-phase image: obtained 20 minutes to 1 hour after injection.
	Delayed-phase image: 4 hours after injection.
Positioning	Animal in sternal recumbency over the gamma camera.
Views	Ventral, right lateral, and left lateral cervical images.

Acquisition Parameters: ^{99m}Tc -sestamibi and ^{123}I Subtraction Imaging

Animal preparation	General anesthesia is required to ensure no movement occurs so ^{123}I and ^{99m}Tc -sestamibi images can be superimposed.
Acquisition	^{123}I : A static frame mode image of the ventral neck is obtained using a pinhole collimator. Images are acquired for 150,000 counts. ^{99m}Tc -sestamibi: A static frame mode image of the ventral neck is obtained using a pinhole collimator. Images are acquired for 400,000 counts.
Matrix	$256 \times 256 \times 16$.
Collimator	Pinhole.
Time of imaging	^{99m}Tc -sestamibi and ^{123}I subtraction scintigraphy: Image 4 hours after ^{123}I injection, then administer ^{99m}Tc -sestamibi and image 5 minutes later.
Positioning	Animal in sternal recumbency over the gamma camera.
Views	Ventral cervical image.

Alternative Technique: Inject ^{123}I ; after 2 hours inject ^{99m}Tc -sestamibi, and acquire images of both radiopharmaceuticals simultaneously using dual isotope imaging 5 minutes later.

Positioning	Animal in sternal recumbency over the gamma camera.
Views	Ventral cervical image.
Subtraction Technique	The ^{99m}Tc -sestamibi image is normalized to the ^{123}I image for maximum counts in the frame. The ^{123}I image is then subtracted from the ^{99m}Tc -sestamibi image. Alternatively, the ^{123}I and ^{99m}Tc -sestamibi images may be acquired simultaneously by double isotope acquisition using two separate energy windows without overlap. The energy windows are set at 140 keV $\pm$ 7% for ^{99m}Tc and at 159 keV with a 4% lower limit and a 10% upper limit for ^{123}I . The asymmetric window settings will avoid crossover. A static frame mode image of the ventral neck and cranial mediastinum is acquired using a low-energy, all-purpose collimator. This image is acquired for 5 minutes. A static frame mode image of the thyroid/parathyroid region is then acquired using a pinhole collimator. This image is acquired for 10 minutes. Images are stored in a $256 \times 256 \times 16$ matrix. The ^{123}I image is subtracted from the ^{99m}Tc -sestamibi image.

and malignant bone lesions and found that there was significantly higher uptake within the malignant lesions as compared with the benign lesions. Use of ^{99m}Tc -sestamibi in a similar fashion as ^{201}Tl subtraction parathyroid imaging for determining tumor viability and tumor response to therapy has yet to be explored. There are two reports in the literature regarding the ^{99m}Tc -sestamibi of other scenarios. The first study documented the uptake patterns of ^{99m}Tc -sestamibi seen in a group of normal dogs. Complete kinetics were not done, but myocardial and hepatic uptake were the two organs that, from an appearance basis, had the highest uptake of the ^{99m}Tc -sestamibi. This is similar to humans, with a hepatobiliary route of excretion. The second study looked at ^{99m}Tc -sestamibi uptake patterns in dogs with lymphoma and found that ^{99m}Tc -sestamibi did have an affinity for active lymphoma lesions. Follow-up studies, however, have not been done.

In summary, while techniques for parathyroid scintigraphy in dogs have been described, a simple method with acceptable clinical accuracy for the diagnosis of parathyroid adenomas has to be realized. Use of a pinhole collimator, ^{99m}Tc -tetrofosmin, or the potential for subtraction techniques should be considered for future evaluation of parathyroid adenomas.

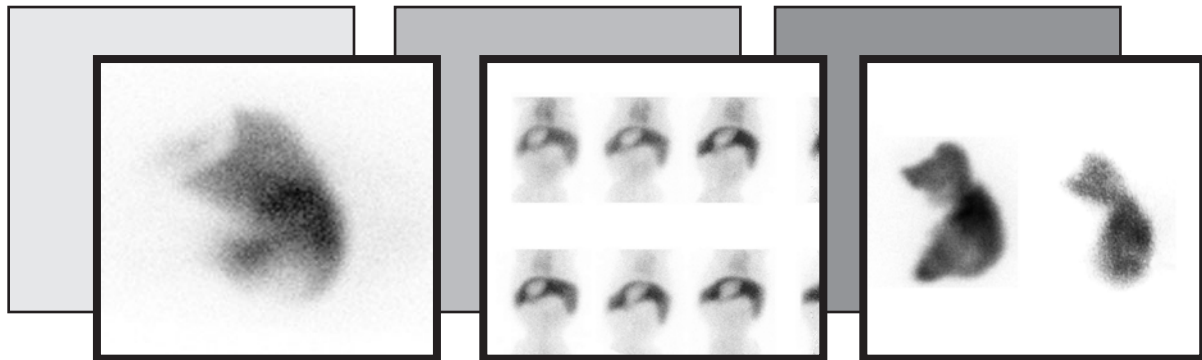
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Hepatic Scintigraphy

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Introduction

Hepatobiliary scintigraphy and ^{99m}Tc -sulfur colloid scintigraphy are used to assess the two primary functional cellular components of the liver. Hepatobiliary scintigraphy evaluates the hepatic parenchymal cells (hepatocytes) while sulfur colloid scintigraphy evaluates the mononuclear phagocytes (Kupffer cells).¹⁻¹¹ Hepatobiliary scintigraphy can be used to quantify liver function, evaluate liver morphology, assess patency of the biliary tract, and document cholecystitis or other diseases of the intra and extrahepatic biliary system.^{3,12-18} Hepatobiliary scintigraphy is used to evaluate cholestasis and can help differentiate between intrahepatic and extrahepatic causes of biliary obstruction.^{16,19-22} Many scintigraphic methods have been developed to quantify hepatic function. Most of these techniques quantify the uptake of a radiopharmaceutical by the liver as a measure of hepatic parenchymal cell function.^{3,10,11} Hepatic extraction fraction (HEF) is one of the quantification techniques that have been used to assess hepatic parenchymal cell function in man, dogs, and cats.^{1,7,9,23-28} Hepatic extraction fraction is that portion of the radiopharmaceutical removed from the plasma on each circulatory pass through the liver.⁷ The HEF can be measured by direct injection of the radiopharmaceutical into the afferent blood supply of the liver or estimated by deconvolution analysis following peripheral intravenous injection.²³⁻²⁵ In either method, the quantification is based on the entire bolus being delivered to the liver at one time, in actuality or mathematically. Newer methods of quantifying liver function are based on the speed at which the radiopharmaceutical is cleared from the blood plasma.

^{99m}Tc -sulfur colloid is used to evaluate hepatic and splenic morphology based on the colloidal uptake by the mononuclear phagocytes that are resident in the

liver and spleen.^{13,29} An assessment of functional hepatic mass can be made by the distribution of radiopharmaceutical. In normal dogs, the majority of the radiopharmaceutical localizes within the liver (80%), with only a small portion retained by the spleen (15%) and bone marrow (5%).² As the functional mass of the liver decreases, a greater proportion of the radiopharmaceutical localizes in the spleen, bone marrow, and lung.^{5,6,30}

Hepatobiliary Scintigraphy

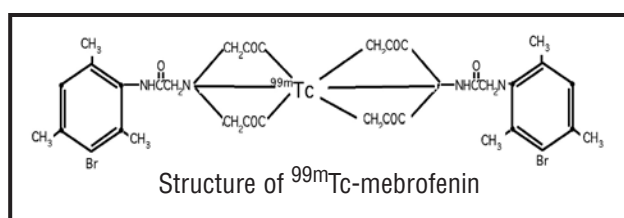
Mechanism of Localization

Before a radiopharmaceutical can localize in an organ, it has to be delivered to the organ. Radiopharmaceuticals can reach the liver from two different blood pathways. The liver receives approximately 70% of its total blood supply from the portal venous system and 30% from the hepatic arteries. The portal blood and hepatic arterial blood merge together in the hepatic sinusoids. Compounds will diffuse from the sinusoidal space to the space of Disse where they come in contact with receptors on the hepatic parenchymal cells.³¹

Hepatobiliary agents are lidocaine analogues, (Figure 12.1).³² The liver is the primary site of uptake and metabolism of lidocaine, which has a molecular weight of 270 daltons and is cleared from the blood in a bi-exponential fashion. Lidocaine has a high first-pass extraction by the liver. It was hypothesized that technetium-99m-labeled lidocaine would be a good liver imaging agent. As technetium-99m could not be attached directly to lidocaine, iminodiacetic acid (IDA) was used as a bifunctional chelate to carry the ligand (lidocaine) on one end and the radionuclide on the other. Technetium-labeled iminodiacetic acid analogues (^{99m}Tc -IDA) are the radiopharmaceuticals that are currently used for functional imaging of the hepatocytes. ^{99m}Tc -mebrofenin and ^{99m}Tc -disofenin are the two most commonly used hepatobiliary radiotracers.

^{99m}Tc -IDA agents are transported to the liver loosely bound to serum albumin. Protein binding enhances hepatic delivery, and hepatic uptake and decreases renal excretion. Hypoalbuminemia will decrease the hepatic delivery of the ^{99m}Tc -IDA resulting in increased renal excretion. The protein-bound ^{99m}Tc -IDA leaves the sinusoidal space through the fenestrae

Figure 12.1: Chemical structure of mebrofenin



trae of the endothelial cells and enters the space of Disse. The albumin ^{99m}Tc -IDA complex dissociates in the space of Disse where the ^{99m}Tc -IDA comes in contact and binds with cell membrane receptors of the hepatocyte. The organic anion receptor is responsible for ^{99m}Tc -IDA uptake by the liver. The liver concentrates three types of organic anions: bile acids, free fatty acids, and nonbile acid cholephils (bromosulphalein, bilirubin, rose bengal, indocyanine green, and ^{99m}Tc -IDA). The ^{99m}Tc -IDA binds to the organic anion receptors and is taken up into the hepatocytes by a carrier-mediated, nonsodium-dependent, transport mechanism similar to that used by bilirubin. After dissociating from the albumin in the space of Disse, the ^{99m}Tc -IDA attaches to a specific receptor protein. Receptor proteins are found within invaginations along the basolateral cell membrane of the hepatocyte. After the ^{99m}Tc -IDA combines with the specific receptor protein called ligandin, the receptor-IDA complex internally separates from the surface of the cell and becomes an internalized vesicle within the hepatocyte cytoplasm. The vesicle loses its protein covering and becomes an endosome. The receptor and the ^{99m}Tc -IDA then separate. The receptor protein then moves back to the basolateral cell membrane surface of the hepatocyte for recycling.³³

The ^{99m}Tc -IDA moves to the bile canaliculi where it is secreted in its native state without being metabolized. Active transport of solutes across the canalicular membrane is the rate-limiting step in the amount of bile produced per day. The canalicular lumen is situated between two adjacent hepatocytes. The walls of the canaliculi contain microvilli. The canalicular wall contraction, along with microvilli movement, propels bile and the ^{99m}Tc -IDA toward the larger intrahepatic biliary ducts. The bile and ^{99m}Tc -IDA then travel to the common collection point of the specific lobar intrahepatic bile ducts into the common hepatic duct. This hepatic duct joins the cystic duct from the gallbladder to form the bile duct. The bile and ^{99m}Tc -IDA will travel from the hepatic ducts through the cystic duct and then into the gallbladder for storage. Biliary flow into and out of the gallbladder is not regulated by a specific smooth muscle sphincter, but at the neck of the gallbladder there is a spiral mucosal fold called the valve of Heister formed by the epithelial layer at the entrance of the cystic duct into the gallbladder lumen. The

muscularis layer of the wall of the gallbladder is lined by smooth muscle cells. These smooth muscle cells contract in the presence of cholecystokinin (CCK), a gastrointestinal hormone that is released by duodenal cells secondary to high concentrations of dietary fats. The CCK will also stimulate the release of pancreatic enzymes from the exocrine pancreas and the simultaneous relaxation of the sphincter of Oddi, found at the junction of the bile duct and major pancreatic duct into the duodenum (minor duodenal papilla in the dog).

Principles of Interpretation

Normal Hepatobiliary Scintigraphy

Interpretation of the hepatobiliary scan is divided into three separate categories of review: hepatic morphology, hepatocyte function, and biliary kinetics and patency. Indications for hepatobiliary scintigraphy are summarized in Table 12.1. Routine acquisition parameters for imaging ^{99m}Tc -IDA in the dog and cat are summarized in Table 12.2.

1. Hepatic Morphology

Morphology of the liver is determined from the early static images (5 and 10 minutes postinjection). The size, shape, and margin of the liver are assessed along with the homogeneity of uptake within the hepatic parenchyma. The shape and size of the liver vary with the breed of dog but should appear similar to those seen with sulfur colloid imaging (Figure 12.2). Hepatic margins may appear rounded and the liver size enlarged with infiltrative liver disease or a diffuse hepatopathy. Photopenic defect(s) can be seen in the liver if space-occupying masses are present. Early images will show a photopenic area in the region of the gallbladder prior to biliary accumulation of the ^{99m}Tc -IDA (Figure 12.3). In general, morphologic evaluation of the liver is inferior to sulfur colloid images because of the dynamic changes in liver radioactivity and the excretion of the radiopharmaceutical into the biliary system.

2. Hepatocyte Function

There are two aspects of hepatocyte function: one is related to the ability of the hepatocyte to extract the radiopharmaceutical from the blood, and the second is the ability of the hepatocyte to excrete the radio-

Table 12.1: Indications for Hepatobiliary Scintigraphy

Evaluate hepatocyte function and quantify Hepatic Extraction Fraction.
Hepatic morphology (inferior to using ^{99m}Tc -sulfur colloid).
Biliary tract patency.
Extrahepatic biliary obstructive lesions.
Evaluate biliary kinetics and gall bladder ejection fraction.
Evaluate for the presence of acute or chronic cholecystitis.
Evaluate for intra or extrahepatic causes of cholestasis.

Table 12.2 Imaging Parameters for Hepatobiliary Scintigraphy**Radiopharmaceutical**

Derivatives of iminodiacetic acid (IDA) . These include:

1. ^{99m}Tc -disofenin (Hepatolite, DuPont Merck)
2. ^{99m}Tc -mebrofenin (Choletec, Bracco Diagnostics, Inc.).

Dose

Species	mCi	MBq
Dog	2-5	74-185
Cat	1-4	37-148

Acquisition Parameters

Animal preparation	Best to image 4-6 hours postprandial.
Static frame acquisition	Time-limited acquisition for 60 or 90 seconds.
Matrix	256 × 256 × 16.
Collimator	Low-energy, all-purpose or high-resolution.
Time to image	Dynamic Acquisition starts simultaneously with injection of the radiopharmaceutical, and is imaged for 60 frames at 5 seconds per frame (total of 5 minutes). Static images taken at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, and 240 minutes after injection and the following morning, if necessary. The endpoint of the study after 90 minutes (minimum for all studies) is dependent on hepatic uptake, identification of the gallbladder, and presence of radioactivity within the duodenum and small intestinal tract. Abnormal studies should be continued until the next morning or until radioactivity is documented within the small intestine.
Positioning	Animal is in lateral recumbency over the imaging table or gamma camera. Place animal in right lateral recumbency for acquisition of the dynamic data set.
Views	Right lateral - abdomen (include heart within field of view, particularly for the dynamic data set). Ventral view of the abdomen; include heart within field of view.

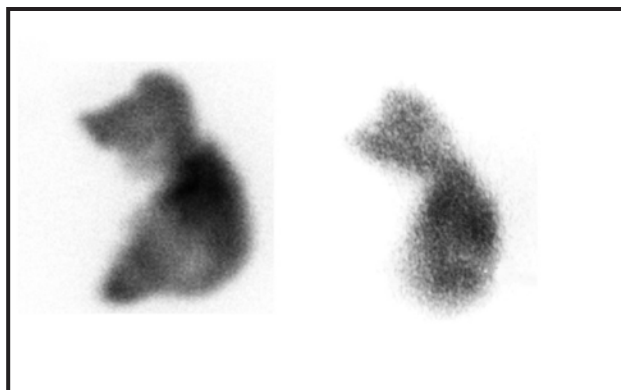


Figure 12.2: Right lateral views of the liver in two dogs

The image on the left was acquired 5 minutes following injection of ^{99m}Tc -mebrofenin. The image on the right was taken 20 minutes following injection of ^{99m}Tc -sulfur colloid. Note that the morphologic features of the liver appear similar. ^{99m}Tc -sulfur colloid is used primarily to evaluate liver morphology. The early images of a ^{99m}Tc -mebrofenin scan can be used for the same purpose.

pharmaceutical into the biliary tree. The ability of the hepatocyte to extract the radiopharmaceutical from the blood is assessed by hepatic uptake and/or blood clearance of ^{99m}Tc -IDA. The uptake by the normal canine liver is rapid, reaching peak radioactivity between 6 and 8 minutes postadministration.^{1,3,23,34} The hepatic uptake is seen in conjunction with a rapid clearance of the blood pool radioactivity (Figure 12.4). Evaluation of the intensity of hepatic uptake and duration of blood pool radioactivity can be used as a visual tool to subjectively estimate hepatic function from static images.¹⁰ Visual assessment of time to maximum hepatic uptake and time to cardiac washout has been described in the cat.¹⁰ This visual assessment is susceptible to error if there is variation in acquisition parameters or a lack of standardization of image gray scale during image formatting. With hepatocellular disease, the liver uptake is slower, there is prolongation of the blood pool radioactivity, and the renal excretion of the ^{99m}Tc -IDA may become evident.

To quantify hepatic uptake, there are three requirements that an ideal radiotracer must fulfill. First, the radiotracer must be extracted from the blood pool only by the functional hepatocyte. Second, the radiotracer must be excreted into the biliary cana-

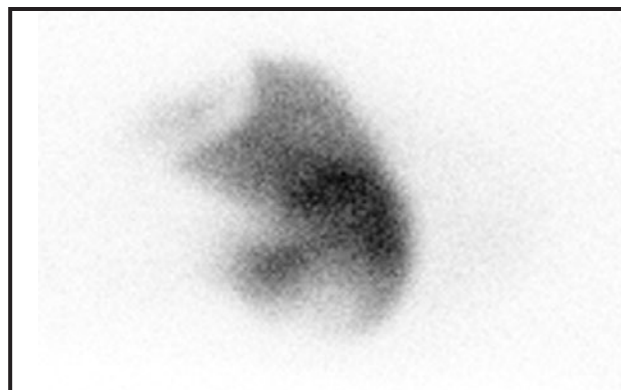


Figure 12.3: Right lateral image of a canine liver acquired 5 minutes following injection of ^{99m}Tc -mebrofenin

The liver is enlarged with rounded margins. The photopenic defect in the ventral liver region is caused by a distended gallbladder.

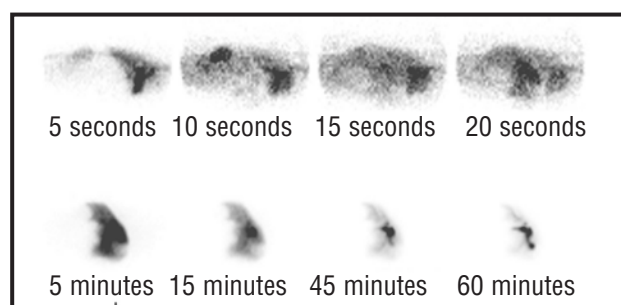


Figure 12.4: Right lateral images of a normal canine liver acquired at various times injection of ^{99m}Tc -mebrofenin

Note the rapid uptake of the radiopharmaceutical by the liver. The clearance of the radiopharmaceutical can be assessed by the disappearance of the radioactivity from the heart.

liculi without leakage back into the vascular space. Third, the radiotracer must be presented to the entire liver in the form of a single discrete intravascular bolus.^{1,7,23,27} In reality, none of the radiopharmaceuticals can fulfill all of these requirements. In the dog, ^{99m}Tc -IDA is extracted primarily by the liver. In cases of liver failure, the kidney acts as an alternate route of excretion. In the normal cat, urinary tract radioactivity is seen, indicating the kidney normally removes a portion of the circulating ^{99m}Tc -IDA.^{9,10} The second criterion of excretion of the radiophar-

maceutical into the bile with minimal back-diffusion cannot be completely met. A study in people has shown that back-diffusion of the ^{99m}Tc -IDA analogues does occur and this does introduce some error in the quantification of hepatic function.³³ The last criterion of a discrete intravascular bolus delivered to the liver cannot be met by a peripheral intravenous injection. Only 20% the cardiac output goes to the liver, so 80% of the radiotracer within the blood pool is recirculated (not presented to the liver). This results in the liver being continually presented with changing concentrations of the radiotracer. Transforming the data using deconvolutional analysis has been shown to help solve this problem.

Deconvolutional analysis transforms data from an intravenous injection to mathematically imitate a direct injection of the radiopharmaceutical into the afferent blood supply of the liver.^{7,28,35} Regions of interest are drawn over the heart and the peripheral regions of the liver to create time-activity curves. The cardiac time-activity curve will serve as the input function and represents the changing plasma concentration of the radiopharmaceutical. The hepatic time-activity curve is the response function. The deconvolution process removes the effects of spreading of the bolus and the recirculation of the radiopharmaceutical. The “true” hepatic response is deconvoluted from the input (cardiac) and output (hepatic) curves utilizing a Fast Fourier Transformation technique. The first 30 minutes of

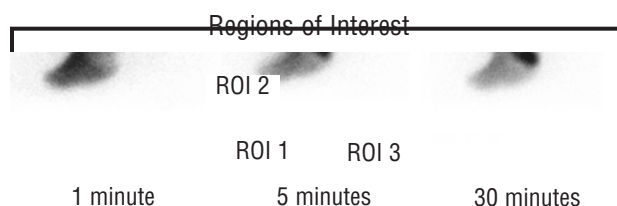


Figure 12.5: Right lateral images of a normal canine liver acquired at 1, 5, and 30 minutes following injection of ^{99m}Tc -mebrofenin

Regions of interest are drawn around the peripheral areas of the liver and the heart. Time-activity curves are then created. The cardiac curve represent the input function and the hepatic curve represents the output function needed for Fourier Transformation as part of the calculation of the hepatic extraction fraction.

data are used for deconvolution analysis. Because the hepatic radioactivity is considerably above baseline at the end of the 30-minute interval, an abrupt cutoff of data will introduce errors during deconvolution analysis. Before performing deconvolution analysis, a gradually tapering tail must be added to the hepatic time-activity curve in order to prevent high frequency artifacts, (Figure 12.6).³⁶ A smoothly decreasing long tail in the shape of one-half of a cosine wave is appended to the tail of the liver curve. The tail begins at the 30-minute frame and falls to zero at the 128th

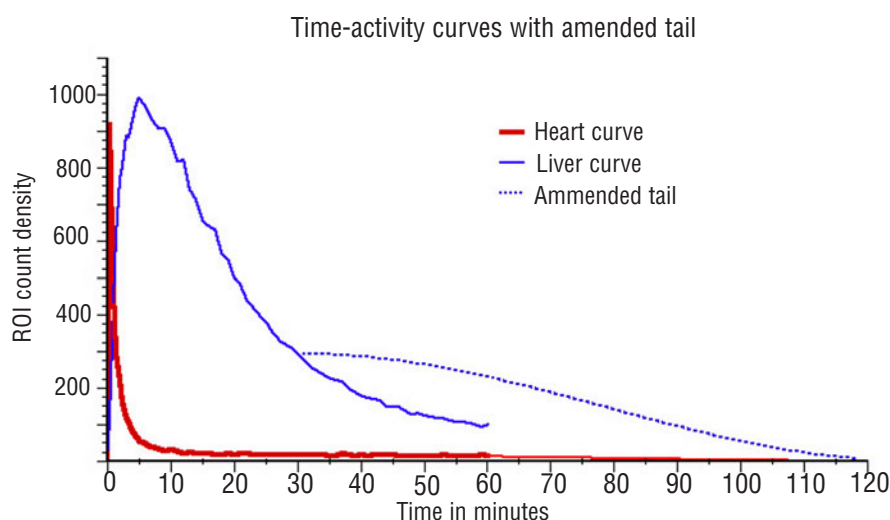


Figure 12.6: A gradually tapering tail is added to the end of the hepatic and cardiac curve to prevent high frequency artifacts that would occur during Fourier transformation

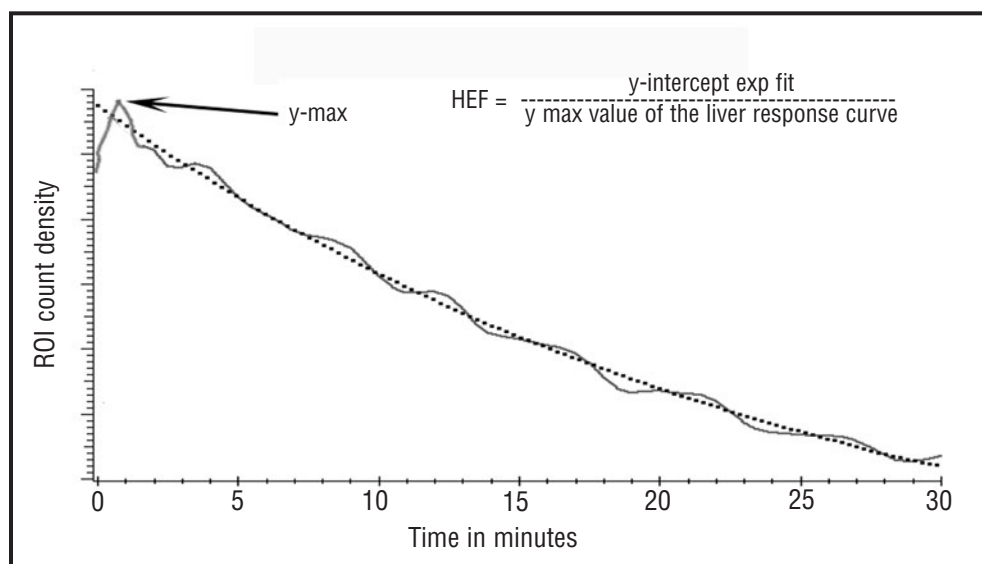


Figure 12.7: Liver response curve

This curve is a mathematical representation of liver radioactivity following a discrete afferent administration of the radiopharmaceutical. The dotted line represents the regression fit of the hepatic response curve as it is used to find the y-intercept, which is used in people to calculate hepatic extraction fraction.

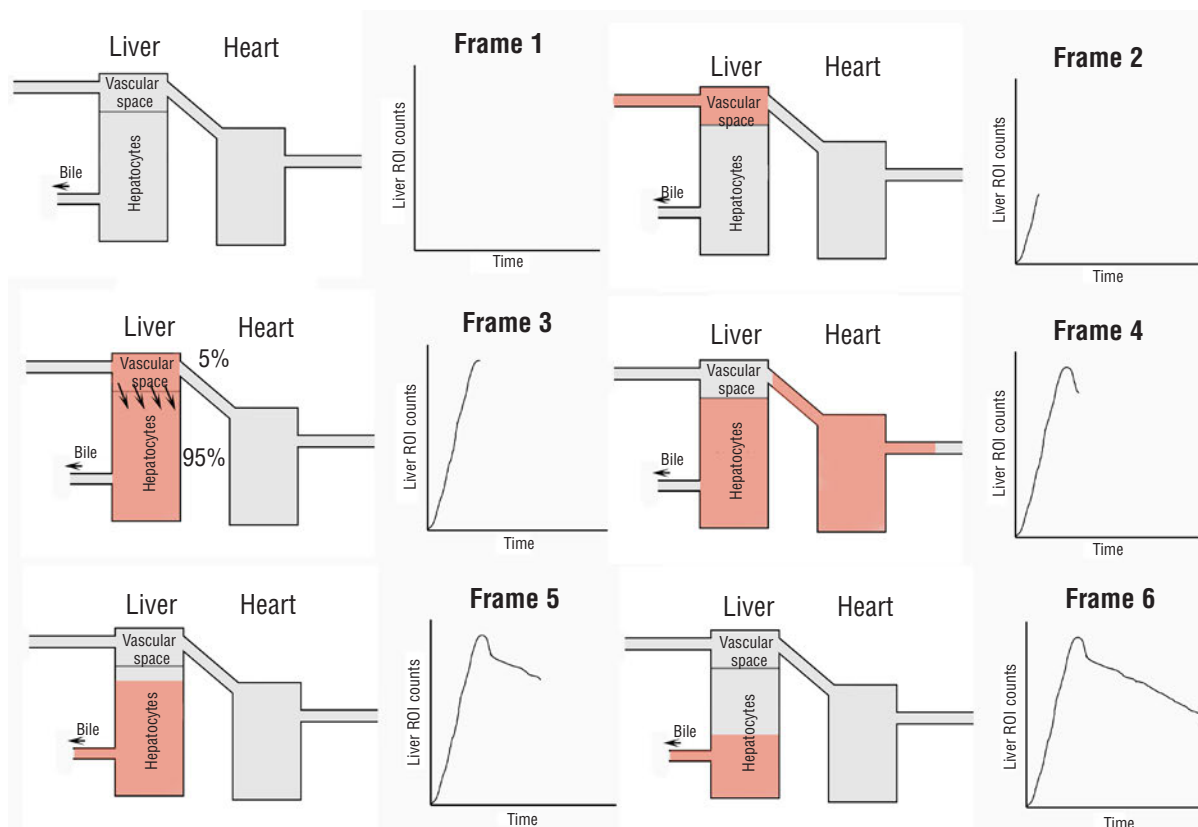


Figure 12.8: Model showing the various hepatic compartments

See text for details.

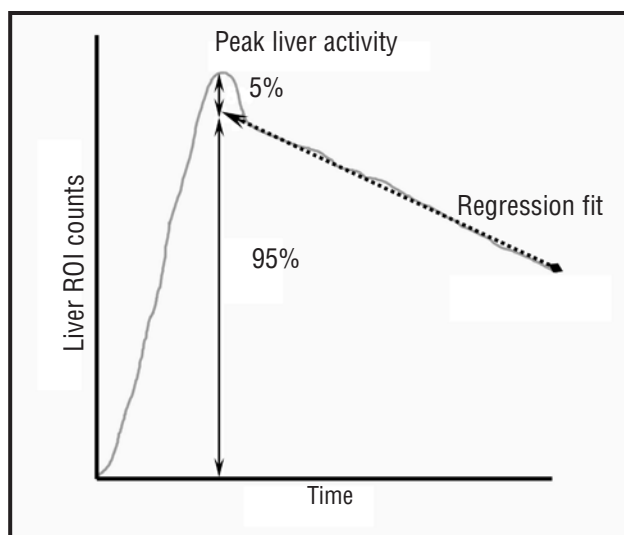


Figure 12.9: Liver response curve as used in a normal dog to calculate hepatic extraction fraction

See text for details.

added frame. The formula for the tail is:

$$\text{Tail} = 0.5 \times \text{AMP} \times (\cos [\pi \times (i - 30)/(128 - 30)] + 1)$$

Where $i = 30$ through 128 and AMP is the counts per pixel (measured radioactivity) of either the blood pool or hepatic time-activity curve at 30 minutes.

The HEF is determined by applying a first order exponential fit to the end of the liver response curve and extrapolated from 30 minutes to time zero (Figure 12.7).^{1,7,24} In dogs, the hepatic extraction fraction is calculated from the ratio of the value of the exponential fitted curve at the time of peak liver activity over the maximum value from the liver response curve.

$$\text{HEF} = \frac{(y - \text{value of the exp fitted input curve})}{(\text{Maximum } y \text{ value from liver response curve})} \times 100$$

Figure 12.8 is a model to help understand the principle of analysis of the liver response curve. The liver response curve is a mathematical simulation of the entire dose of the radiopharmaceutical presented

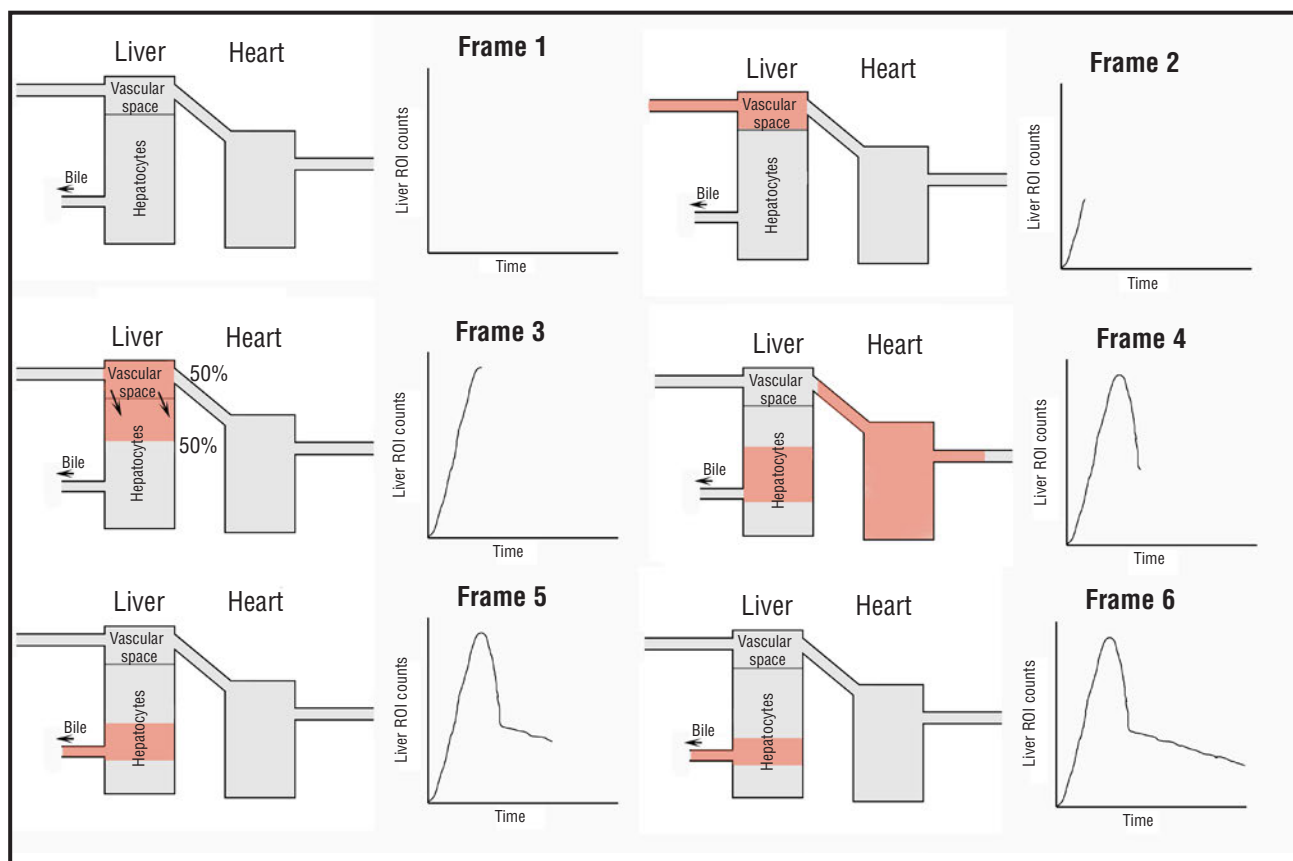


Figure 12.10: Model showing the various hepatic compartments

See text for details.

Table 12.3 Calculated HEF From a Group of Dogs Under Various Experimental Protocols: Sedation and Anesthesia Using Intravenous [IV] Injection and General Anesthesia Using Direct Portal Vein [PV] Injection¹

Method (Injection site, and Anesthesia vs. Sedation)	HEF, Mean $\pm$ Standard Deviation
IV, Anesthesia	98.6 $\pm$ 0.8%
IV, Sedation	100.7 $\pm$ 3.8%
PV, Anesthesia	97.3 $\pm$ 0.9%

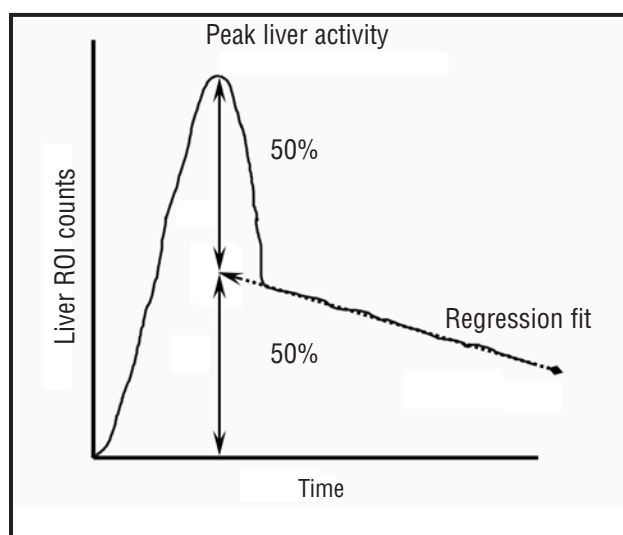


Figure 12.11: Liver response curve in a dog with hepatic parenchymal cell dysfunction

The hepatic extraction fraction is calculated from the ratio of the value of the exponential fitted curve at the time of peak liver activity over the maximum value from the liver response curve. In this case the value of the fitted regression curve is 50% of the maximum liver activity. HEF is 50%.

to the liver as a single discrete bolus. The model in Figure 12.8 is of a normal dog. In frame 2, the ^{99m}Tc -mebrofenin first enters the vascular space of the hepatic sinusoids. There is active uptake of the ^{99m}Tc -mebrofenin by the organic anion receptors of the hepatocytes. In a normal dog, 95% of the ^{99m}Tc -mebrofenin is taken up by the hepatocytes leaving only 5% in the vascular space (Frame 3 of Figure 12.8). The liver region of interest (ROI) records the

total amount of ^{99m}Tc -mebrofenin in the liver but it cannot differentiate between the activities within the hepatocytes versus the vascular space. In the 4th frame, the ^{99m}Tc -mebrofenin remaining in the vascular space leaves the liver through the efferent venous drainage. The radioactivity within the blood pool leaves the hepatic ROI resulting in a slight reduction in the time-activity curve. The ^{99m}Tc -mebrofenin trapped by the hepatocytes remains and is eventually excreted into the bile resulting in a gradual decrease in hepatic radioactivity. Note the gradual reduction in hepatic radioactivity in Frames 5 and 6 as the radiopharmaceutical is being excreted into the biliary tract.

Because hepatic excretion in the biliary tract is a first order process, the gradual decline in liver radioactivity can be fitted by the formula:

$$\text{Hepatic radioactivity} = e^{-\lambda t}$$

This formula is fitted to the excretion phase of the hepatic response curve by a least squares approximation. The regression is fitted in a backward direction, ie, from 30 minutes backward toward the peak. The regression is used to predict the amount of radioactivity within the hepatocytes on the initial first passage of the radiopharmaceutical through the liver. Figure 12.9 is a representation of the initial passage of the radiopharmaceutical through the liver. The regression line is used to predict how much radioactivity was contained within the hepatocytes (Frame 3 of Figure 12.8).

The simulation in Figure 12.10 is a dog with hepatocellular disease. In the second frame, the ^{99m}Tc -mebrofenin enters the liver sinusoids. There is active

uptake of the ^{99m}Tc -mebrofenin by the organic anion receptors of the hepatocytes. In this dog, only 50% of the ^{99m}Tc -mebrofenin is taken up by the hepatocytes leaving 50% in the vascular space (Frame 3, Figure 12.10). The hepatic ROI records the total amount of ^{99m}Tc -mebrofenin in the liver, but it cannot differentiate between the radioactivities within the hepatocytes versus the vascular space. In the 4th frame, the ^{99m}Tc -Mebrofenin remaining in the vascular space leaves the liver through the efferent venous drainage of the liver. Since only 50% of the ^{99m}Tc -mebrofenin was retained by the hepatocytes there is a marked reduction in liver radioactivity recorded by the time-activity curve. The ^{99m}Tc -mebrofenin trapped by the liver is excreted into the bile resulting in a gradual decrease in liver radioactivity.

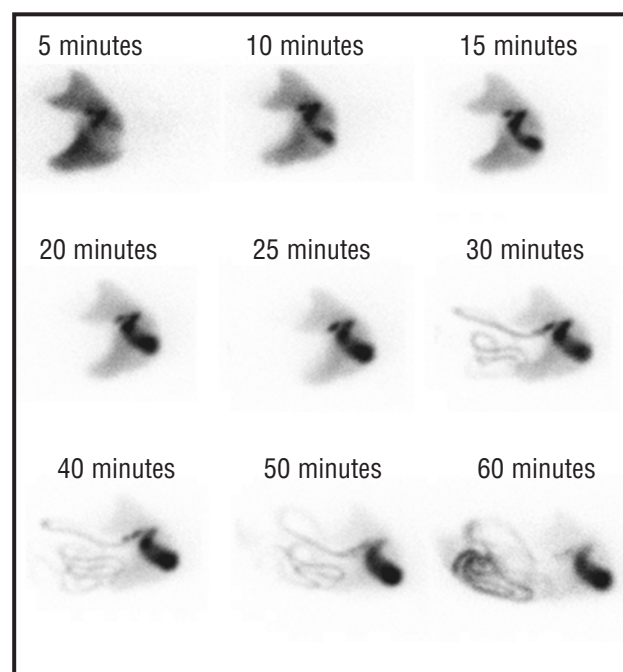
The HEF is determined by using a monoexponential curve fit to the hepatic response curve. This curve is fit to the excretion phase of the hepatic response curve (Figure 12.11). This technique of analysis has been used for years in humans.^{19,21,22,27,35,37-41} The normal hepatic extraction of ^{99m}Tc -mebrofenin in humans and dogs is generally considered to be 92% to 100%.^{1,2,7} In a series of normal dogs HEF from deconvolutional analysis was compared to the hepatic extraction from measured from direct afferent injection.¹ There were no significant differences in the values obtained from either method. The HEF also did not differ in sedated dogs compared with dogs under general anesthesia (Table 12.3).

With hepatocellular disease, the HEF is expected to decrease proportionally to the severity of liver insult. The HEF derived by deconvolutional analysis has been compared to the HEF measured from direct afferent injection in a series of dogs with experimentally induced liver disease.^{24,25} There was a marked reduction in HEF in dogs with experimentally induced liver disease (secondary to a hepatocellular toxin model). The control values of the HEF were greater than 90% in normal dogs and decreased to less than 50% in the most severely affected dog. There was good correlation noted between the direct measurement of HEF (via direct portal vein injection) to that measured using deconvolutional analysis with intravenous injection of the radiopharmaceutical, ($r = 0.92$). The reduction in HEF was also significantly correlated with the severity of liver damage as assessed by quantitative histopathology.

In humans, HEF decreases as the hepatocellular function and hepatocyte number decrease, as in the case of hepatic cirrhosis.^{14,40} The HEF is initially normal when the primary abnormality is confined to the extrahepatic biliary tree. For example, in humans, HEF is normal in patients with acute common bile duct obstruction. HEF will drop into the range of 50% to 80% 3 to 5 days following complete extrahepatic obstruction and may drop below 50% when total obstruction persists longer than 5 days.¹⁴ This pattern also has been seen in a dog. The confusing factor in dogs is that dogs usually do not present for evaluation by the veterinarian until the disease process is chronic and potentially end-stage. Chronic extrahepatic biliary obstruction leads to elevation in serum bilirubin and because they compete for the same hepatic receptor site, the competitive inhibition reduces ^{99m}Tc -mebrofenin uptake by the liver. If the

Figure 12.12: Right lateral images of a normal canine liver acquired from 5 to 60 minutes following injection of ^{99m}Tc -mebrofenin

Note the rapid excretion of the radiopharmaceutical into the biliary tract. The gallbladder is seen on the 10-minute images followed by visualization of the small intestine by 30 minutes. Note how completely the radiopharmaceutical clears from the liver over time.



obstruction is long-term, then the liver will develop secondary biliary cirrhosis. The biliary cirrhosis will result in decreased HEF. With partial biliary obstruction, the HEF remains high until secondary cirrhosis develops. Still the HEF may help differentiate primary hepatic disease from obstructive biliary disease. It is crucial to distinguish between these two causes of jaundice as the former is treated medically and the latter may need to be treated surgically.

Finally, as the HEF provides an objective measure of hepatocyte function it can be used to assess the severity of hepatocellular damage and response to treatment. Deconvolution analysis is technically demanding to perform. Clinical patients are scanned awake, with sedation only when necessary. General anesthesia is not used in clinic patients. The typical clinical imaging protocol calls for a 5-minute dynamic acquisition followed by a series of static images at 5-minute intervals for the first 30 minutes following injection, then at 10-minute intervals for the next 30 minutes. Analysis of these images requires placement of an ROI over the liver and heart. The liver region of interest is more difficult to place because ROI must be positioned in a peripheral region that does not contain a major biliary duct (Figure 12.12). Drawing these regions of interest is time-consuming. Variation in ROI position over the liver can result in marked changes in recorded radioactivity resulting

in jagged time-activity curves.²⁶

High frequency artifacts are created if jagged curves are used in the Fourier transformation needed for deconvolution analysis. In dogs with normal or near-normal hepatic function the liver rapidly excretes the radiopharmaceutical into the biliary-tract, and it is difficult to identify the original landmarks used to place the liver ROI after 30 minutes. Also, bloom or cross-talk from adjacent high biliary tract radioactivity will introduce errors in the quantification of true hepatic radioactivity and function.

Nondeconvolution techniques to quantify hepatic function include the use of hepatic time-activity curves to calculate time to maximum hepatic uptake ($T_{\max}$) and time from $T_{\max}$ to one-half maximum radioactivity ($T_{1/2}$) as measures of hepatic parenchymal cell accumulation and hepatic excretion, respectively.¹¹ Compartmental analysis of the hepatic time-activity curves has been used to determine the rate constants between the hepatocyte, plasma, urinary, and biliary tracts. This method has been described in normal dogs and dogs with cholestatic disease.^{11,34} Although this method provides a quantitative measurement of cholestasis (hepatic excretion), it is not a reliable method for quantitative assessment of hepatic uptake.

Plasma clearance of the ^{99m}Tc -mebrofenin is depen-

Figure 12.13: Hepatic time-activity curve (solid line) in a normal dog

The dotted line is a regression line fitted to the down slope of the hepatic time-activity curve. The clearance half-time can be determined from the excretion coefficient. Clearance half-time in this dog was 19 minutes.

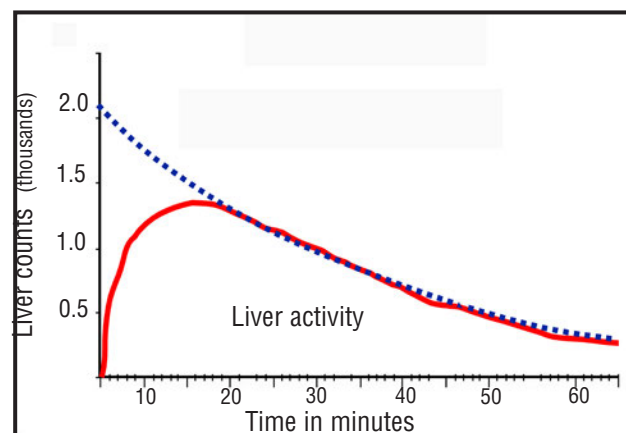
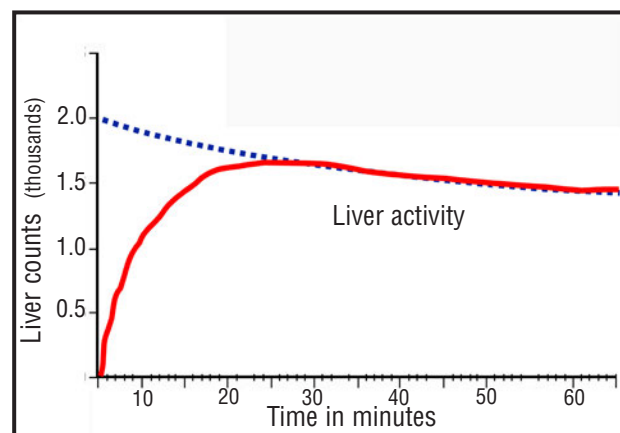


Figure 12.14: Hepatic time-activity curve (solid line) in a dog with intrahepatic cholestasis

The dotted line is a regression line fitted to the down slope of the hepatic time-activity curve. The clearance half-time can be determined from the excretion coefficient. Clearance half-time in this dog was 229 minutes.



dent on hepatobiliary function. Analysis of plasma disappearance curves has been shown to be a good predictor of hepatic extraction of ^{99m}Tc -mebrofenin and a good predictor of the degree of histologic damage to the liver.⁴² The disadvantage of this technique is that multiple blood samples must be obtained and counted in a well detector. Qualitatively, persistence of blood pool radioactivity can be used as a visual tool to analyze hepatobiliary images. An assessment of hepatic function can be determined by comparing the relative amount of radioactivity in the heart and liver over time.²⁶ This method has been described in the cat and requires the evaluator to identify the times of maximum hepatic uptake and the time of blood pool disappearance of the radiotracer. The method is susceptible to error if there is variation in acquisition parameters or a lack of standardization of image gray scale during image formatting and viewing.

The computer can be used to measure radioactivity in the heart on the hepatobiliary images as an indicator of plasma concentration. An ROI is placed around the heart, and the radioactivity within the heart from 0 to 30 minutes is plotted to create a cardiac time-activity curve. Because of variation in the administered dose and body size, the cardiac time-activity curves are normalized to a peak value of 1,000. The value of 1,000 is arbitrary, but standardization is necessary. The areas under the curve from 0 to 30 minutes and 0 to 60 minutes are determined. Alternately, the clearance half-time of the cardiac time-activity curve can be analyzed using a two-compartment model. In a previous study linear regression analysis was used to describe the relationship between the area under the normalized cardiac time-activity curve and hepatic extraction in normal dogs and dogs with induced hepatic disease.²⁶ In this study, there was good correlation between the area under the normalized cardiac time-activity curve and hepatic extraction. The best correlation was obtained from the 0 to 30-minute data ($r^2 = 0.92$). A formula for calculating hepatic extraction was derived using linear regression analysis, where:

$$\text{Hepatic extraction} = 1.092 - (0.0000308 \times \text{AUC}_{0-30 \text{ minutes}})$$

There was good correlation between the clearance half-time from the cardiac time-activity curve and hepatic extraction. The best correlation was between the fast phase half-time clearance and hepatic extrac-

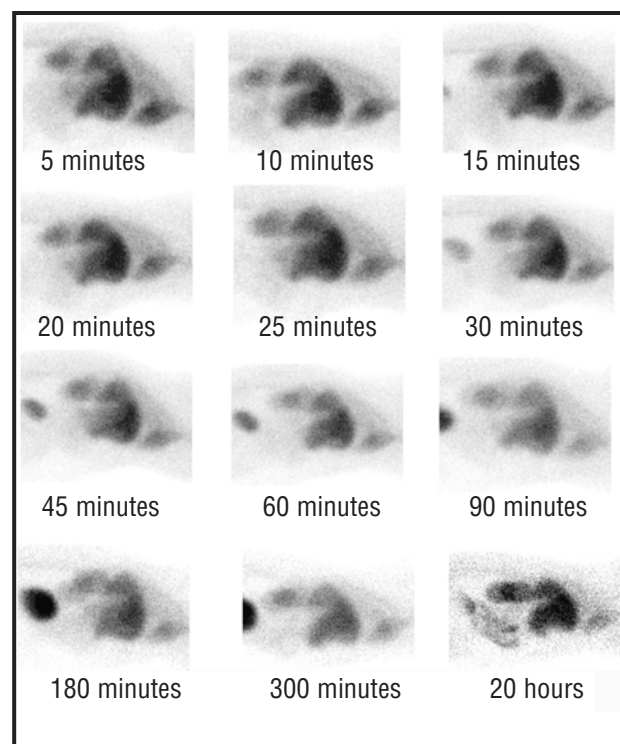


Figure 12.15: Right lateral images from a cat following injection of ^{99m}Tc -mebrofenin

There is poor uptake of the radiopharmaceutical by the hepatic parenchyma and the time to peak liver radioactivity is delayed indicating poor hepatic cellular dysfunction. There is retention of the radiopharmaceutical by the hepatic parenchyma indicative of intrahepatic cholestasis. There is intestinal radioactivity seen at 20 hours indicating a patent biliary tract. This pattern is consistent with severe hepatocellular disease.

tion ($r^2 = 0.88$). This is a simple and accurate way to quantify hepatic function using images for the hepatobiliary scan.

3. Hepatic Excretion

Hepatic excretion is a measure of the movement of the hepatobiliary radiopharmaceutical from the hepatocytes into the biliary tree. The liver should excrete ^{99m}Tc -mebrofenin into the biliary tract so that the gallbladder and the intestine are seen within 1 hour (Figure 12.12). An ROI is placed over a peripheral portion of the liver, and the changes in liver radioactivity versus time are recorded graphically. Hepatic excretion is a first-order process and the

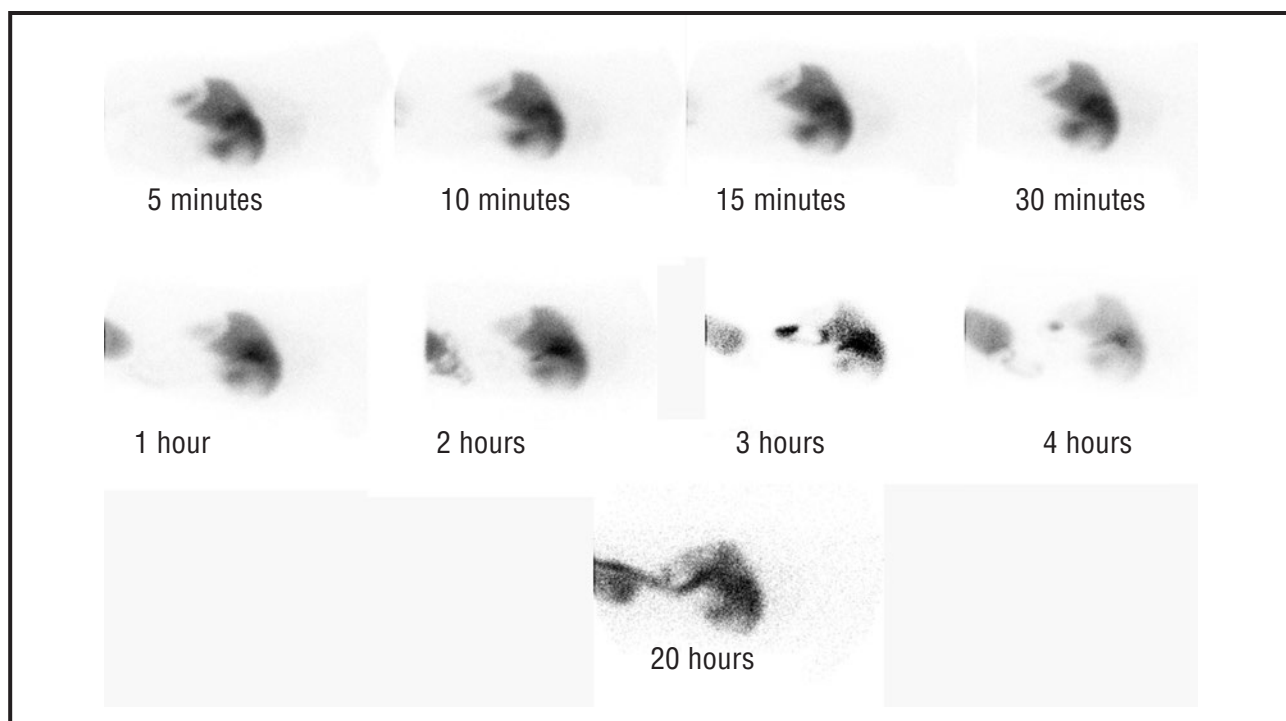


Figure 12.16: Right lateral images of a canine liver at various times following injection of ^{99m}Tc -mebrofenin

There is poor uptake of the radiopharmaceutical by the hepatic parenchyma, and the time to peak liver radioactivity is delayed indicating poor hepatic parenchymal cell function. Note that the liver is enlarged and the borders are rounded. There is retention of the radiopharmaceutical by the hepatic parenchyma indicative of intrahepatic cholestasis. There is intestinal radioactivity seen at 2 hours indicating a patent biliary tract. The gray scale of the 3-, 4-, and 20-hour images has been adjusted to account for the lower number of counts. This pattern is consistent with severe hepatocellular disease.

hepatic excretion curve can be fitted using the following formula:

$$\text{Hepatic radioactivity} = Ae^{-\lambda t}$$

where A is the y intercept and λ represents the excretion coefficient and t is time in minutes. The half-time clearance can then be calculated by the following formula:

$$\text{Half-time clearance} = \ln(2)/\lambda$$

The normal half-time clearance in dogs is 19 minutes (Figure 12.13).^{1,3,23} In cases of intrahepatic cholestasis, this value will increase relative to the severity of the disease (Figure 12.14).

4. Biliary Kinetics

Biliary kinetics is assessed by the temporal passage of the radiopharmaceutical through the biliary tree. The times required for visualizing the gallbladder and small intestine are noted, both of which should occur at less than 1 hour in a normal dog.² In addition, gallbladder ejection fraction can be determined following injection of cholecystokinin and a specific rate of gallbladder emptying documented.^{3,43} In the normal dog, the mean ejection fraction is $60\% \pm 18\%$ (mean $\pm$ Std Dev) with a rate of 10% per minute.³ These values were obtained following infusion of a synthetic octapeptide of cholecystokinin but the ingestion of a fatty meal could also be used. The use of cholecystokinin is more reproducible, predictable, and faster to act than the fatty meal.

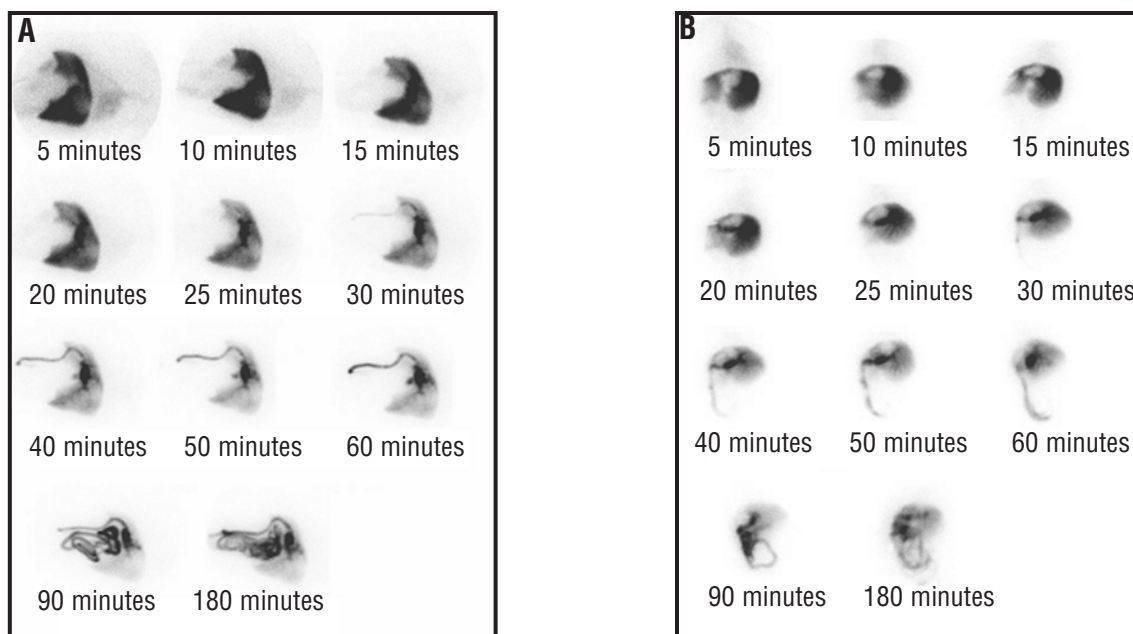


Figure 12.17: Right lateral (A) and ventral (B) images of a dog obtained at specific time points following injection of ^{99m}Tc -mebrofenin

There is a mild decrease in the radiopharmaceutical uptake by the hepatic parenchyma. Cardiac blood pool radioactivity persists and is seen 10 minutes following injection, indicating mild hepatic parenchymal cell dysfunction. The clearance of the radiopharmaceutical from the hepatic parenchyma is delayed consistent with mild intrahepatic cholestasis. There is intestinal radioactivity seen at 30 minutes indicating a patent biliary tract. The gallbladder is seen as the photopenic void to the right of midline and ventral. There is accumulation of the radiopharmaceutical in the hepatic duct adjacent to the gallbladder. These changes are consistent with chronic cholecystitis.

5. Drug Influences on Biliary Transit Times

Opioids are commonly used for pain management and sometimes as sedative agents. Opioids can prolong the transit time of the hepatobiliary radiopharmaceutical to the intestine. Opioids (morphine and butorphanol) cause varying degrees of smooth muscle constriction at the sphincter of Oddi thus inhibiting the passage of bile from the bile duct into the duodenum. The influence of these drugs on biliary transit times in dogs and cats has not been experimentally validated, but caution should be exercised when using these drugs to sedate animals for hepatobiliary studies. General anesthesia will also prolong biliary transit times. In an awake dog or cat, the hepatobiliary radiopharmaceutical is seen within the intestine by 1 hour. Intestinal radioactivity is rarely seen within an hour if the dog is under general anesthesia.

Abnormalities of Hepatobiliary Scintigraphy

Patterns of scintigraphic abnormalities can be distinguished based on the morphology, the uptake, and the excretion pattern of the radiotracer by the liver. In addition the sequence of visualization of the biliary tree, gallbladder, and intestine plays a significant role in the final interpretation and conclusions reached regarding intra- or extrahepatic biliary disease.

Diffuse Hepatocellular Disease

The liver may appear enlarged with rounded margins. Hepatic parenchymal uptake may appear mottled. Diffuse hepatocellular disease is characterized by an overall decrease in hepatic function. The most prominent feature is poor hepatic uptake of the radiopharmaceutical, causing prolongation of the

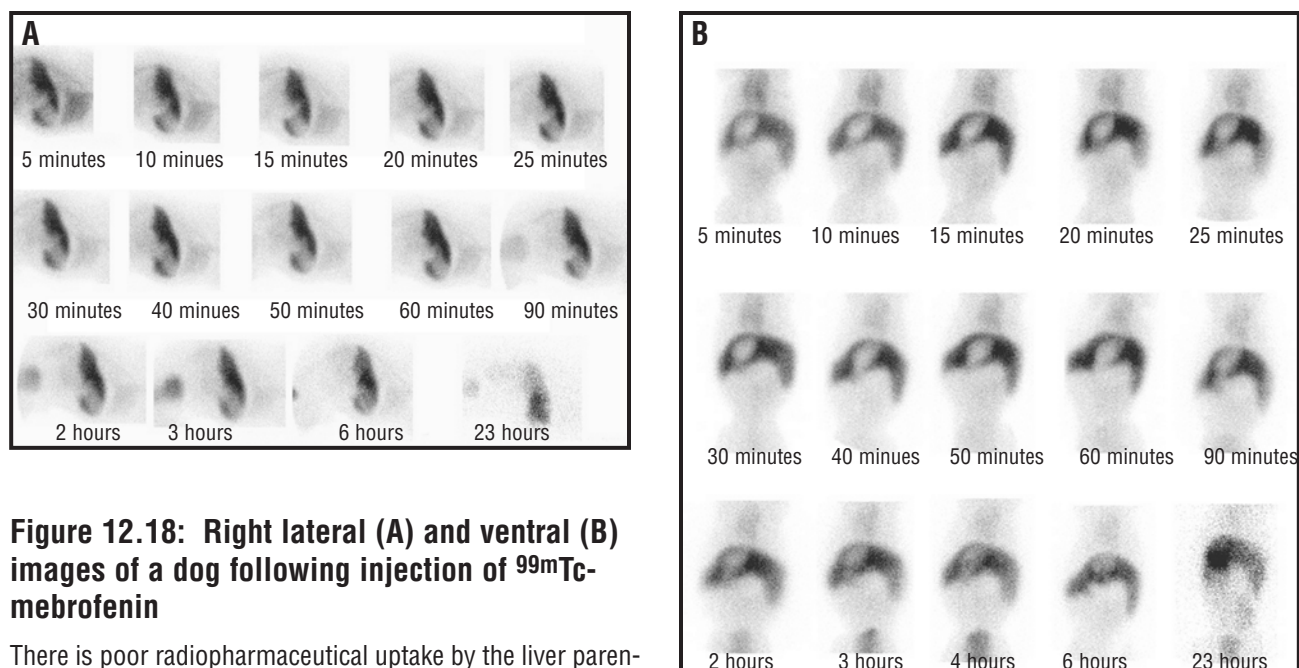


Figure 12.18: Right lateral (A) and ventral (B) images of a dog following injection of ^{99m}Tc -mebrofenin

There is poor radiopharmaceutical uptake by the liver parenchyma, and cardiac blood pool radioactivity is seen at 23 hours following injection indicating severe hepatocellular dysfunction. The clearance of the radiopharmaceutical from the liver is delayed indicative of severe intrahepatic cholestasis. The gallbladder is seen as the photopenic void to the right of midline and ventral. The gallbladder is slow to fill and is first identified at 23 hours. None of the radiopharmaceutical is seen within the small intestine. This pattern is consistent with chronic extrahepatic biliary obstruction with secondary hepatocellular dysfunction.

blood pool radioactivity as evidenced by the persistent visualization of the heart and extrahepatic soft tissues. In the normal dog, hepatic uptake is rapid and after 5 minutes only the liver and the biliary tree have radioactivity significant enough to be clearly seen on the hepatobiliary images. In dogs with persistent blood pool radioactivity, the HEF would be expected to be less than 80%. In severe cases, there may also be intrahepatic cholestasis resulting in decreased excretion of the radiopharmaceutical into the biliary tree. The kidney and urinary bladder are seen as alternate routes of excretion. Radioactivity that reaches the biliary tree should then proceed into the intestine. Sometimes the excretion of the radiopharmaceutical will be so slow that intestinal radioactivity may not be seen until the following morning. The presence of the radiopharmaceutical within the colon is conspicuous by the next morning if the biliary tree is patent (Figures 12.15 and 12.16).

Acute Cholecystitis

In cases of acute cholecystitis, the liver may be

normal size and shape. The area of the gallbladder may be seen as a photopenic void to the right of midline on the ventral image and in the cranial ventral liver region on the right lateral image. There will be normal hepatic uptake of ^{99m}Tc -IDA, with the liver reaching maximum radioactivity between 5 and 10 minutes postinjection. The radiopharmaceutical clears the blood pool rapidly, with the heart just faintly seen at 5 minutes. The liver parenchyma excretes the radiopharmaceutical into the biliary tree, and liver radioactivity decreases by half every 19 minutes. A normal transit time to the small intestine will be noted. The biliary duct adjacent to the gallbladder may be dilated to retain a portion of the radiopharmaceutical. There will be an obstruction of the cystic duct (functional or structural) that will result in persistent nonvisualization of the gallbladder for up to 4 hours following ^{99m}Tc -IDA. The degree of gallbladder distension is based on the size of the photopenic defect. Because these animals may have normal hepatic function, the majority of the liver is cleared of the radiopharmaceutical by 45 minutes, and a second injection of the radiopharmaceutical is

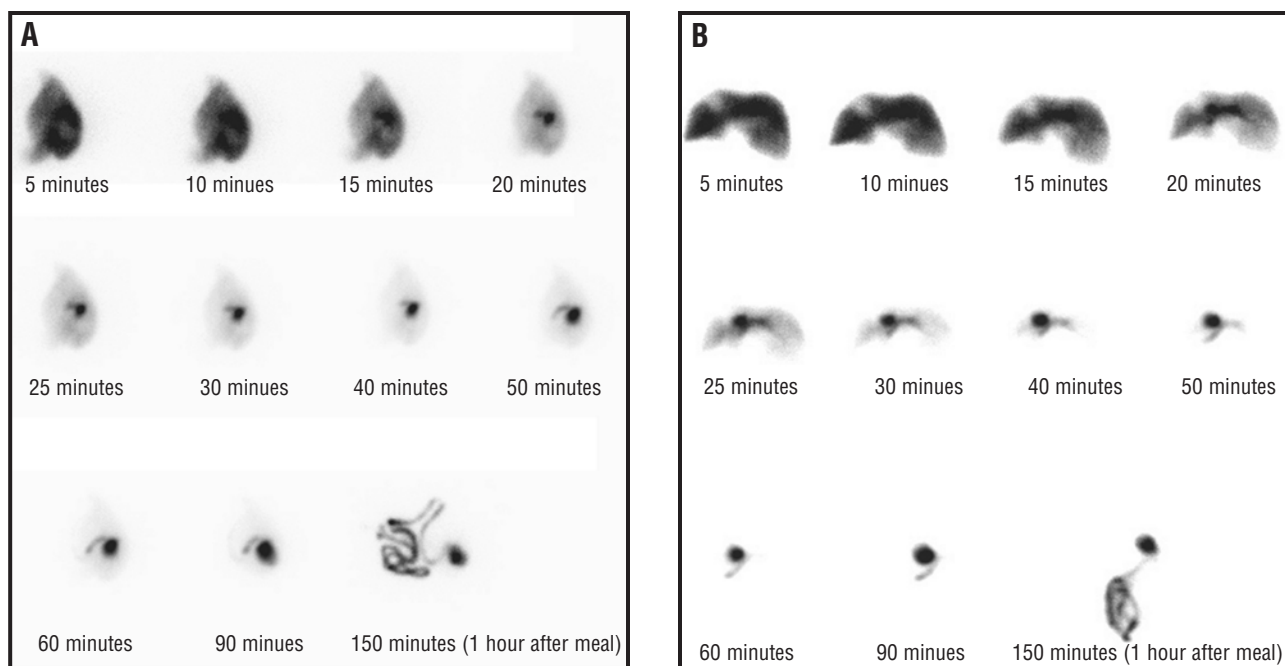


Figure 12.19: Right lateral (A) and ventral (B) images from a dog following injection of ^{99m}Tc -mebrofenin

There is normal uptake of the radiopharmaceutical by the liver parenchyma, and the cardiac blood pool radioactivity has cleared by 5 minutes. The clearance of the radiopharmaceutical from the liver parenchyma is slightly delayed indicative of mild intrahepatic cholestasis. The gallbladder is slow to fill. The radiopharmaceutical accumulates in the gall bladder neck and eventually fills the gallbladder by 90 minutes. The radiopharmaceutical can be seen in the common bile duct at 50, 60, and 90 minutes but does not enter the small intestine until a fatty meal has been fed to the dog. This pattern is consistent with a partial bile duct obstruction.

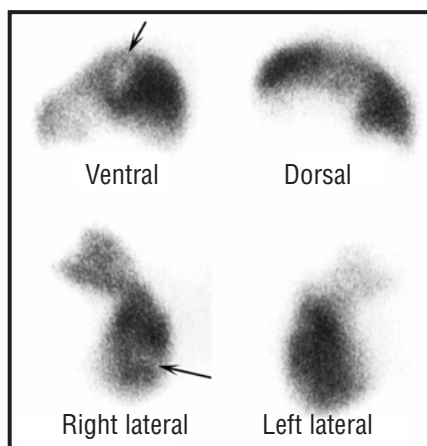


Figure 12.20: Ventral, dorsal and both lateral images of a normal dog 20 minutes following injection of ^{99m}Tc -Sulfur colloid

The arrow points to the region of the gallbladder.

necessary to judge persistent non-visualization of the gallbladder. In humans, a “rim” of increased radioactivity in the region of the gallbladder fossa has also been described. This rim of abnormal radioactivity may be due to increased blood flow into the area secondary to the inflammation or a focal area of edema causing delayed clearance from the adjacent hepatic parenchyma. Also, if a perforation of the gallbladder has occurred, intraperitoneal accumulation of the radiopharmaceutical will be seen.

Chronic Cholecystitis or Partial Obstruction of the Cystic Duct

In cases of chronic cholecystitis, the liver is usually normal in size and shape. The area of the gallbladder may be seen as photopenic. Hepatic uptake is variable ranging from normal to slightly decreased. Hepatic excretion of the radiopharmaceutical into

Table 12.4: Indications for Liver–Spleen Scintigraphy

Evaluate liver morphology.
Evaluate hepatic arterial and portal blood flow (see chapter 13 for the calculation of the hepatic perfusion index [HPI]).
Initial dynamic imaging is required to obtain this information.
Noninvasive means of determining the size and shape of the liver.
Evaluate for the presence of space-occupying intrahepatic lesions: primary hepatic tumors, metastatic tumors, abscesses, granulomas, cysts, hematomas, infarction, cirrhosis, and certain extrinsic masses.
The spleen is evaluated for mass lesions and blood supply.
Radiocolloid images are not affected by peritoneal fluid and can be used to assess the liver and spleen when radiography is uninformative.

Table 12.5 Imaging Parameters for Liver–Spleen Scintigraphy**Radiopharmaceutical**^{99m}Tc-Technetium sulfur colloid (^{99m}Tc-SC)**Dose**

Species	mCi	MBq
Dog	2 - 5	74 - 185
Cat	1 - 4	37 -148

Acquisition Parameters

Animal preparation	None.
Static frame acquisition	Count-based acquisitions (500,000 counts per image).
Matrix	256 × 256 × 16.
Collimator	Low-energy, all-purpose or high-resolution.
Time to image	20 minutes postinjection.
Positioning	Animal recumbent over the camera.
Views	Right lateral view of the abdomen (include lung within field of view).
	Left lateral view of the abdomen.
	Dorsal view of the abdomen.
	Ventral view of the abdomen.
	Left ventrolateral oblique view of the spleen (liver shielded by lead).

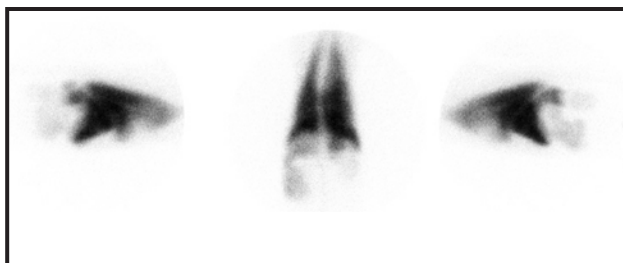


Figure 12.21: Ventral, dorsal and opposite lateral images of a normal feline lung 20 minutes following injection of ^{99m}Tc -sulfur colloid

Note the pulmonary radioactivity that is typical in normal cats.

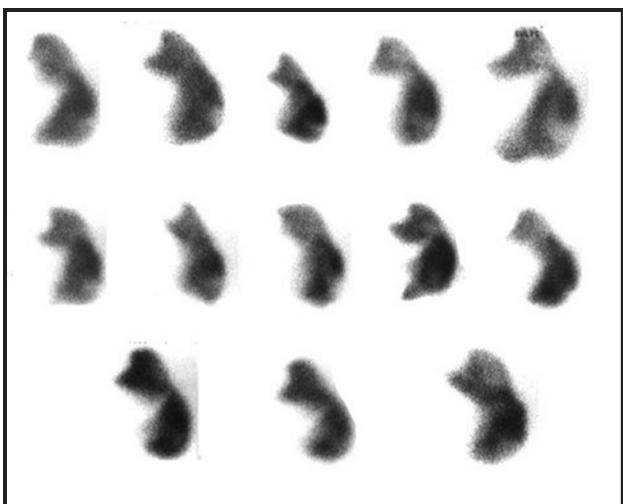


Figure 12.22: Right lateral images of the liver acquired 20 minutes following injection of ^{99m}Tc -sulfur colloid in 13 normal dogs

Note the variation in liver shape and the distribution pattern of the radiopharmaceutical within the liver.

the biliary system is also variable. In cases of mild severity, the clearance half time can range from normal (20 minutes) to mild intrahepatic cholestasis (Figure 12.17). The time to visualization of the intestine can be normal (<1 hour) to slightly delayed. The gallbladder is not seen at 1 hour, but later images show gallbladder radioactivity by 4 hours. A second radiopharmaceutical injection may be necessary to document gallbladder filling.

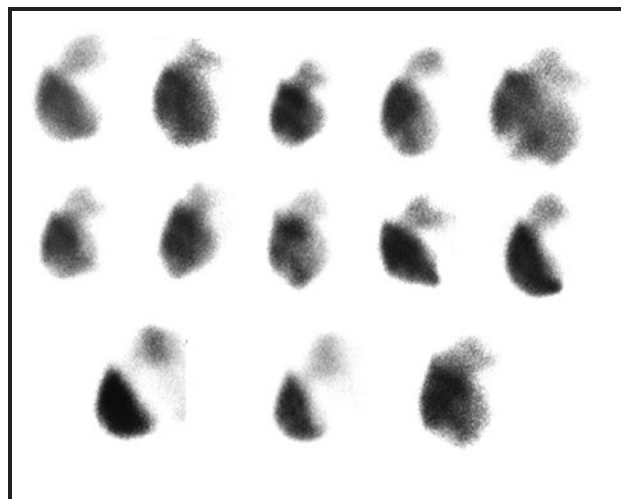


Figure 12.23: Left lateral images of the liver acquired 20 minutes following injection of ^{99m}Tc -sulfur colloid in 13 normal dogs

Note the variation in liver shape and the distribution pattern of the radiopharmaceutical within the liver.

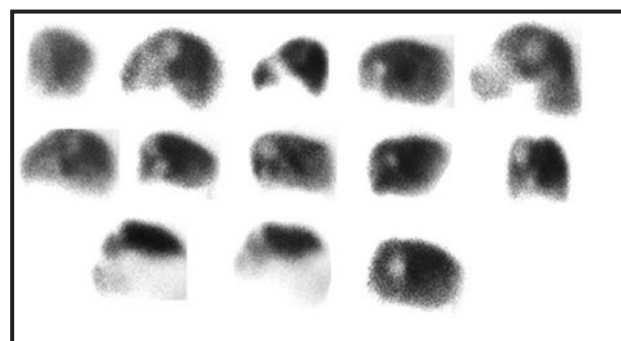


Figure 12.24: Ventral images of the liver acquired 20 minutes following injection of ^{99m}Tc -sulfur colloid in 13 normal dogs

Note the variation in liver shape and the distribution pattern of the radiopharmaceutical within the liver.

Cholestasis

Cholestasis is the retention of bile within the hepatobiliary system resulting in the accumulation of bile products in the serum. Cholestasis can be classified as intrahepatic or extrahepatic. Intrahepatic cholestasis is the retention of bile within the liver. Cholestasis can occur at the level of the hepatocyte, bile canaliculi, or the intrahepatic ducts. Intrahepatic

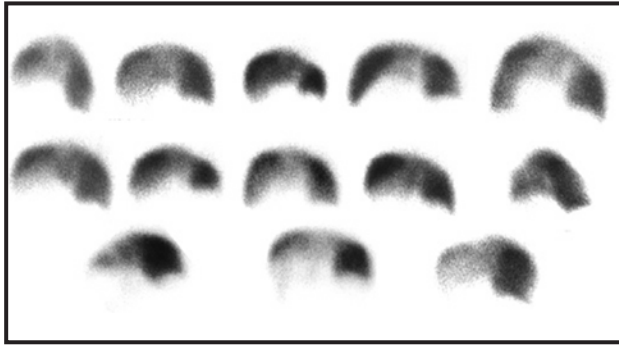


Figure 12.25: Dorsal images of the liver acquired 20 minutes following injection of ^{99m}Tc -sulfur colloid in 13 normal dogs.

Note the variation in liver shape and the distribution pattern of the radiopharmaceutical within the liver.

cholestasis can be due to either primary liver disease or secondary to chronic extrahepatic obstruction. Intrahepatic cholestasis is seen as prolonged hepatic retention of the ^{99m}Tc -IDA (clearance half-time of greater than 20 minutes). Intrahepatic cholestasis can be secondary to hepatocyte swelling and inhibition of normal bile flow. A variety of insults to the liver can result in inhibition or contraction of the canalicular walls and microvilli resulting in atony and dilation of the canaliculi causing intrahepatic cholestasis. After the ^{99m}Tc -IDA reaches the biliary ductal system, it will flow into the gallbladder and duodenum in an animal with intrahepatic cholestasis and a patent extrahepatic biliary duct. Often it will take greater than 4 to 6 hours for sufficient quantities of the hepatobiliary radiopharmaceutical to be seen in the intestine; and, therefore, it is recommended that an image be acquired the following morning if the intestine is not seen by the end of the first day.

Extrahepatic cholestasis is due to bile stasis within the extrahepatic biliary tree, often at the level of the sphincter of Oddi. Chronic extrahepatic cholestasis may be difficult to differentiate from diffuse intrahepatic cholestasis during the first 4 to 6 hours of imaging. With acute extrahepatic obstruction there is normal to decreased hepatic uptake depending on the serum bilirubin levels as marked elevations in plasma bilirubin concentration will inhibit hepatic uptake of the radiopharmaceutical. Chronic extrahepatic obstructions can also result in increased intraductal pressure to the point that it inhibits the

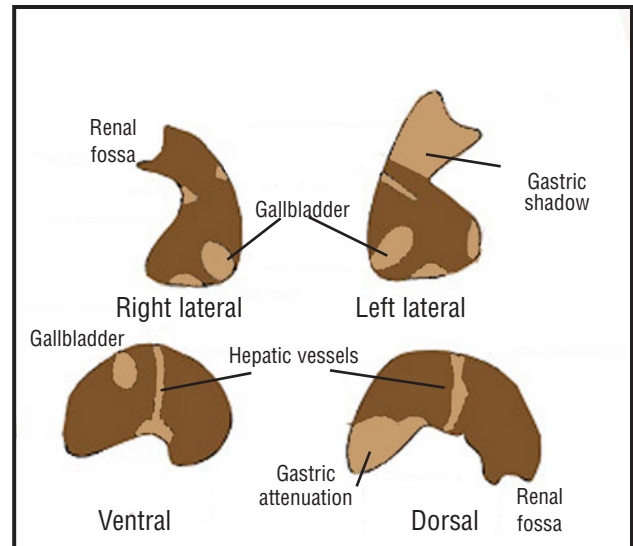


Figure 12.26: Schematic drawing of a normal canine liver showing the pattern of ^{99m}Tc -sulfur colloid uptake as seen in Figures 12.22 to 12.25

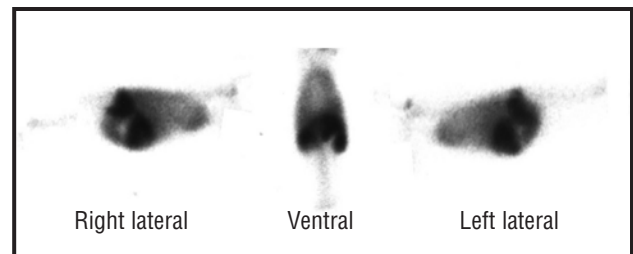


Figure 12.27: Static ventral and lateral images obtained 20 minutes after the injection of 185 MBq (5 mCi) of ^{99m}Tc -sulfur colloid

This is a dog with a congenital, extrahepatic portosystemic shunt. The liver is small and there is diffuse pulmonary radioactivity, which causes the mononuclear phagocytic population to reside in the lungs as opposed to the liver.

excretion of the radiopharmaceutical into the biliary tree and the images show prolonged retention of the radiopharmaceutical within the liver parenchyma (Figure 12.18). The appearance is similar to diffuse severe intrahepatic disease unless one can visualize part of the biliary tree. Imaging beyond 6 hours may be necessary for the radiopharmaceutical to be seen in the biliary ducts. Biliary ducts may appear dilated, but this is a difficult scintigraphic interpretation because the apparent size of the biliary duct is also

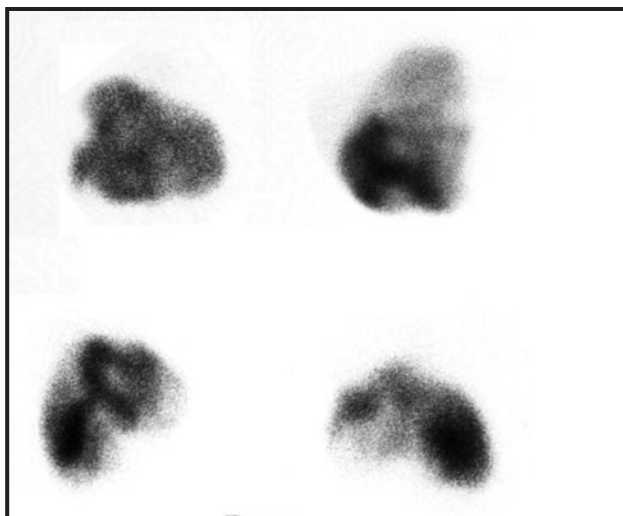


Figure 12.28: Ventral and lateral images of the liver, acquired 20 minutes following injection of ^{99m}Tc -sulfur colloid in a dog with hepatic metastasis

Note the numerous photopenic defects throughout the liver parenchyma.

influenced by the amount of radioactivity within the duct and distance from the camera. To further complicate interpretation, the ^{99m}Tc -IDA accumulates within dilated extrahepatic biliary ducts, and it is hard to differentiate between an obstructed duct and a dilated nonobstructed or partially obstructed duct. The administration of a fatty meal will stimulate the movement of the ^{99m}Tc -IDA into the duodenum if the duct is not obstructed (Figure 12.19). If radioactivity has reached the biliary ducts but is not seen within the intestine by the following morning and remains with the biliary ducts following administration of a fatty meal, then an obstructed bile duct can be assumed.

Liver – Spleen (Mononuclear Phagocyte Colloidal) Scintigraphy

The liver and spleen can be imaged following injection of radiocolloids.^{2,5,6,8,13,29} These radiocolloids are small particles ranging in size from 100 to 1,000 μm and are removed from circulation by the mononuclear phagocytes of the liver, spleen, lung and

bone marrow.³² The uptake of the ^{99m}Tc -sulfur colloid within the liver should be uniform (Figure 12.20). Morphologic changes in size and shape of the liver can be appreciated. Intrahepatic masses are seen as discrete photopenic voids. The use of this mononuclear phagocytic imaging to evaluate the presence of hepatic or splenic parenchymal abnormalities is primarily of historical significance, as alternate imaging modalities (ultrasound and computed tomography) are currently used to evaluate the internal parenchyma of the liver. The indications for liver-spleen radiocolloid scintigraphy are summarized in Table 12.4. The imaging parameters specific to liver-spleen scintigraphy are summarized in Table 12.5.

Mechanism of Localization

Commercial preparations of ^{99m}Tc -sulfur colloid (^{99m}Tc -SC) have a mean particle size of 300 μm and are rapidly removed from circulation by the mononuclear phagocytic system (MPS) following intravenous injection. Localization of ^{99m}Tc -SC within the liver is due to phagocytosis by the Kupffer cells. Factors that influence phagocytosis of ^{99m}Tc -SC include blood flow, Kupffer cell numbers and appropriate cellular function, and physical characteristics of the particle, such as size, number, and charge.^{29,32} The human and canine livers normally remove 80% of ^{99m}Tc -SC within 20 minutes. The remainder localizes within the MPS of the spleen (15%) and bone marrow (5%).

Distribution of the MPS varies between species. Normally, the distribution of the mononuclear phagocyte population in dogs is similar to that in humans. However, in cats and horses, there is a large population of mononuclear phagocytes located in the lungs. The labeled sulfur colloid will localize in the lung in the cat and horse. If a cat is injected with ^{99m}Tc -SC, a significant portion of the radiopharmaceutical localizes within the lung (Figure 12.21). Kupffer cells are uniformly distributed within the liver, therefore the distribution of ^{99m}Tc -SC defines normal liver anatomy. Diseases that destroy, replace, or displace Kupffer cells may be identified by a reduced concentration of the ^{99m}Tc -SC as compared with normal surrounding structures.

Principles of Interpretation

The liver scintigraphic image is evaluated for size, shape, and distribution of the radiopharmaceutical

within the liver. Liver size can be estimated by comparing the liver to a lead ruler placed over the liver or a radioactive ruler (^{57}Co) placed within the image field. A method has also been developed by which the liver volume can be estimated by measuring the liver area as determined by computer-assisted ROI placement.¹³ Both methods have been shown to be reliable predictors of liver weight.

Normal liver shape varies considerably with body conformation. The ventral and dorsal images show the greatest variation. In addition, normal structures, such as the gallbladder, porta hepatis, intrahepatic vessels, interlobar fissures and attenuation by the stomach and intestine, result in photopenic regions and can mimic pathologic space-occupying lesions. Animals with large amounts of intra-abdominal fat often have a wedge-shaped defect along the ventral liver margin due to fat in the falciform ligament separating liver lobes. When interpreting a radiocolloid scan, normal variations must be considered. Figures 12.22, 12.23, 12.24, and 12.25 are a series of lateral, dorsal, and ventral views obtained from 13 normal dogs. Note the variation in liver shape and the pattern of uptake.

Figure 12.26 is a schematic drawing of the canine liver developed from the observed distribution of $^{99\text{m}}\text{Tc}$ -SC in normal dogs. Photopenic defects along the visceral margin are the result of attenuation by overlying abdominal viscera. Linear photopenic defects seen near the midline on the ventral and dorsal views are caused by a combination of vessels, interlobular fissures, and attenuation by the vertebral column and sternum. In addition, interlobar fissures in the area of the porta hepatis and caudal vena cava can result in wedged-shaped defects.

Diseases that can decrease the number of Kupffer cells will result in a greater percentage of extrahepatic uptake of the radiopharmaceutical. These diseases include portosystemic shunts, chronic hepatic cirrhosis, glycogen storage disorders, amyloidosis, endotoxemia, and other causes of microheptica.^{2,6} Figure 12.27, from a dog with a portosystemic shunt, was obtained 20 minutes following injection of 111 MBq (3 mCi) of $^{99\text{m}}\text{Tc}$ -SC. Note the uptake of the $^{99\text{m}}\text{Tc}$ -SC by the lung. In some dogs, pulmonary uptake of the $^{99\text{m}}\text{Tc}$ -SC can exceed that of the liver radioactivity.

Liver-spleen scintigraphy was once used for the

detection of intrahepatic masses. A mass lesion within the liver will displace or replace the Kupffer cells and result in areas of decreased intensity (Figure 12.28). Detection of liver masses may require the lesion to be greater than 1.5 to 2.0 cm. In an experimental animal study, overall sensitivity of radiocolloid imaging for detecting liver tumors was 60% and all lesions greater than 3 cm were detected. SPE[C]T improves this sensitivity but offers no advantage over computed tomography. The major limitation of radiocolloid imaging is the nonspecific nature of the findings; therefore the results of the scintigraphy must be correlated with findings from other diagnostic tests.

Summary

The use of hepatobiliary scintigraphy is widely applicable in veterinary medicine, both as an aid to evaluation of patients suspected to have cholestatic disease, as well as determination of hepatic function. Once a single study has been done, follow-up studies can be used to evaluate response to therapy. $^{99\text{m}}\text{Tc}$ -SC scintigraphy is largely a procedure of the past and was reviewed in this chapter for historical interest.

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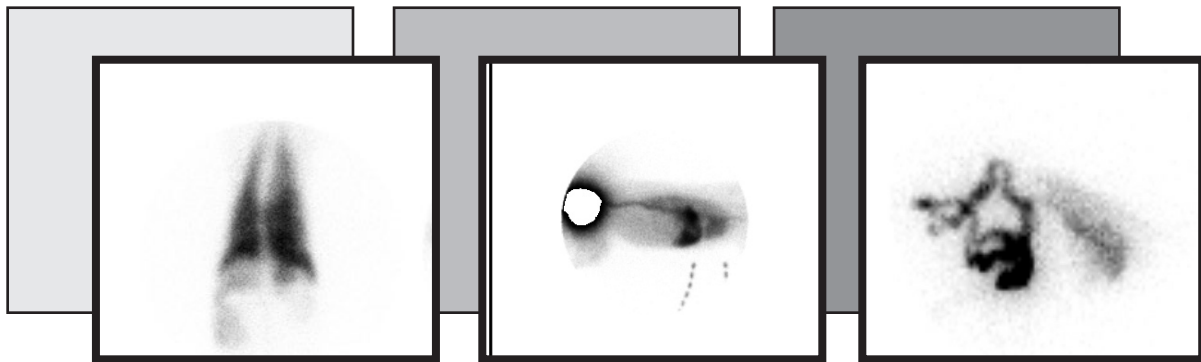
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Scintigraphic Detection of Portosystemic Shunts

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Introduction

Portosystemic shunts are abnormal vascular communications between the portal vein and the systemic venous circulation.¹⁻¹⁰ Portosystemic shunts may be classified as congenital or acquired.¹¹ Congenital portosystemic shunts usually occur as single macrovascular connections between the main portal vein or a portal tributary and the caudal vena cava or other systemic vein, such as the azygos vein.

Congenital portosystemic shunts are anatomically divided into intrahepatic and extrahepatic. Congenital intrahepatic portosystemic shunts occur mainly in large breed dogs and are described according to their position in the liver as involving the left, central, or right divisional branches of the main portal vein as it enters the porta hepatis.^{12,13} Left divisional branch shunts are usually associated with a patent ductus venosus and are seen in Irish wolfhounds. Congenital extrahepatic portosystemic shunts connect a major tributary of the portal vein, such as the splenic or left gastric vein, with the caudal vena cava. Occasionally, the shunting vessel drains into the azygos vein or other systemic venous structure.¹⁴ Congenital extrahepatic portosystemic shunts usually affect small breeds, particularly the Yorkshire Terrier, Miniature Schnauzer, Miniature Poodle, Shih Tzu, Lhasa Apso, Bichon Frise, and Cairn Terrier.¹⁵

Acquired portosystemic shunts develop in response to chronic portal hypertension.¹⁴ Portal hypertension develops as a result of hepatic fibrosis or cirrhosis.¹⁶ Acquired portosystemic shunts take the form of multiple, small tortuous extrahepatic shunt vessels that are found in the omentum or retroperitoneum near the left kidney, esophagus, or rectum.^{11,14} These acquired extrahepatic portosystemic shunts will drain directly or indirectly into the caudal vena cava.

Diagnosis of macroscopic portosystemic shunts is often based on diagnostic imaging. Methods include survey radiographs, radiographic contrast procedures, ultrasound, (including Doppler color-flow and pulsed-wave Doppler sonography) or scintigraphy.^{3,8-10,17-20} Survey radiographs will document microhepatia, ascites, or mineralized cystic calculi in dogs and cats. Ultrasound can document the aberrant shunt vessel and has been used as a screening method for evaluation of dogs with congenital portosystemic

shunts.^{3,9} Changes in portal venous and caudal vena caval Doppler waveforms and color flow patterns have been described.¹⁰ Nonmineralized cystic calculi, renomegaly, and a small liver with a reduced number and diameter of intrahepatic vessels are common findings in ultrasound, suggestive of portosystemic shunts.³ In dogs and cats with acquired portosystemic shunts secondary to portal hypertension, there is often ascites and the liver will have increased echogenicity with irregular margins. Color-flow Doppler imaging can be used to document multiple small shunting vessels in and around the renal vessels or the caudal abdominal retroperitoneum.³ Ultrasound evaluation of the patient with a suspected portosystemic shunt can be time-consuming and is operator (experience) dependent.

Contrast mesenteric portovenograms provide reliable anatomic information but are invasive and require anesthesia, selective catheter placement, contrast medium administration, and fluoroscopic imaging.^{21,22} In a recent report, it was shown that patient positioning appeared to play a role in the sensitivity of mesenteric portovenograms in identifying anomalous shunt vessels in dogs with confirmed congenital macroscopic portosystemic shunts.²³ In this report, left lateral recumbency was the most sensitive position for visualizing the portosystemic shunt vessel.

Scintigraphy has been used to evaluate dogs and cats for portosystemic shunting since the early 1980s. One of the first radiopharmaceuticals used to diagnose portosystemic shunts was ^{99m}Tc-sulfur colloid. ^{99m}Tc-sulfur colloid is a small colloidal particle that will localize in the mononuclear phagocytes of the reticuloendothelial system.²⁴ In the normal dog, the radiopharmaceutical will localize in the liver, spleen, and bone marrow within 20 minutes following injection.²⁵ In normal dogs, pulmonary radioactivity usually peaks during the first pass of the radionuclide through the pulmonary circulation, drops to a lower level of radioactivity, and then gradually increases slightly over time. In dogs with portosystemic shunts, a significant portion of the radiopharmaceutical will localize in the lung (Figure 13.1).^{26,27} This technique appeared to be specific for the diagnosis portosystemic shunts; however, it was found that pulmonary radioactivity was not specific for portosystemic shunts and was seen in dogs with other causes of hepatic insufficiency.²⁶ Dogs with other causes of hepatic disease such as cirrhosis or other

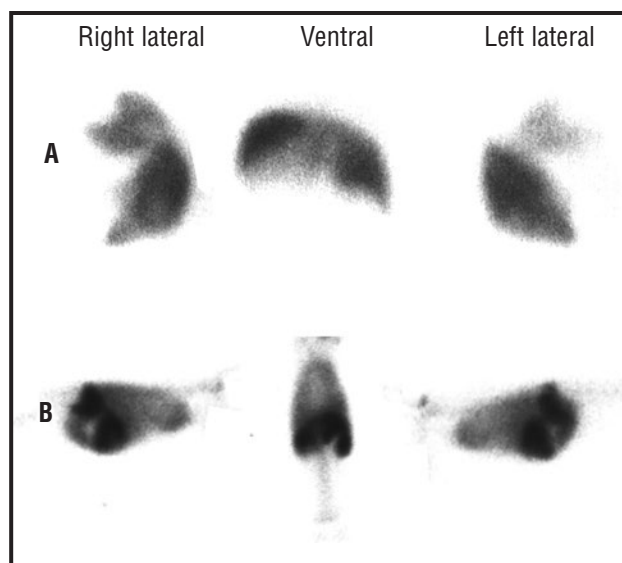


Figure 13.1: Static ventral images of a canine thorax and abdomen obtained 10 minutes after the injection of 185 MBq (5 mCi) of ^{99m}Tc -sulfur colloid

A, Normal dog with normal hepatic uptake and the absence of pulmonary uptake. **B**, A dog with a portosystemic shunt where there is pulmonary uptake.

types of diffuse hepatic disease will have decreased hepatic uptake and increased uptake in lung, spleen, and bone marrow. Yet there is a strong association of decreased hepatic localization of ^{99m}Tc -sulfur colloid and portosystemic shunts. Koblik and Hornof (1995) reported on a series of 101 dogs with congenital ($n = 61$) and acquired ($n = 40$) portosystemic shunts.²⁸ In this study, the ^{99m}Tc -sulfur colloid was used to evaluate the mononuclear phagocytic system. The research showed that the plasma clearance rate constant, relative liver uptake, and the hepatic-extrahepatic (lung and spleen) uptake ratios were decreased compared with a group of 26 control dogs ($p < 0.001$, Table 13.1).²⁸ ^{99m}Tc -sulfur colloid cannot be used in the cat for the diagnosis of portosystemic shunt because lung uptake is seen in normal cats (Figure 13.2). There is a resident population of mononuclear phagocytes present in the feline lungs resulting in high uptake of the ^{99m}Tc -sulfur colloid. Horses and other ungulates also have a high resident pulmonary population of intravascular macrophages resulting in increased uptake of the ^{99m}Tc -sulfur colloid and again precluding this technique in these species.

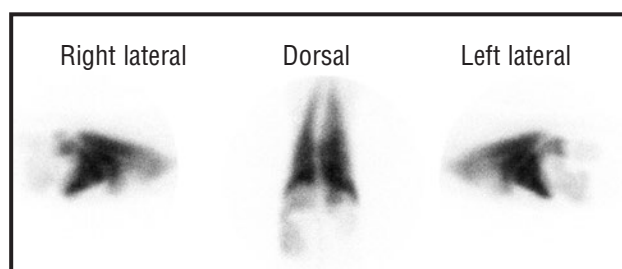


Figure 13.2: Normal pulmonary uptake seen in cats injected with ^{99m}Tc -sulfur colloid

These images were obtained 10 minutes after intravenous injection of 74 MBq (2 mCi) of ^{99m}Tc -sulfur colloid.

Table 13.1: Plasma Clearance and Mononuclear Phagocytic Uptake Values In Normal Dogs and Dogs With Portosystemic Shunts

Group*	Kp	% Liver	% Spleen	% Lung	HEHU
Control	0.78 ± 0.25	88.6 ± 4.4	9.1 ± 4.2	2.3 ± 1.2	9.1 ± 4.1
All PSS	0.28 ± 0.11	52.5 ± 17.2	31.2 ± 15.1	16.3 ± 13.4	1.53 ± 1.57
Single PSS	0.29 ± 0.13	50.0 ± 17.4	35.5 ± 14.1	14.4 ± 15.1	1.3 ± 1.0
Multiple PSS	0.26 ± 0.06	56.23 ± 16.6	24.6 ± 14.6	19.2 ± 13.1	1.9 ± 2.1

*Studies were acquired using ^{99m}Tc -sulfur colloid. Kp = plasma clearance rate constant (min^{-1}) obtained from least squares single exponential fit of hepatic time radioactivity data (after processing of curve data); HEHU = hepatic-extrahepatic (lung and spleen) uptake ratio, PSS = portosystemic shunt. Mean values $\pm$ standard deviation values are reported.²⁸

Hepatic Perfusion Index

The next scintigraphic technique developed to identify animals with portosystemic shunts evaluated the hepatic arterial and portal venous blood flow to the liver based on first-pass scintigraphic studies of the liver.^{26,29} These studies require dynamic acquisition following bolus injection of a radiopharmaceutical, usually ^{99m}Tc -sulfur colloid. Regions of interest are placed over the liver and kidney. Time-activity curves of the liver and kidney are created from the dynamic acquisition. The liver time-activity curve has two distinct phases or slopes (Figure 13.3). The relative volume of hepatic arterial and portal venous blood flow to the liver is determined from the arterial and venous slopes on the hepatic time-activity curve. The first slope represents hepatic arterial flow and is seen simultaneously with the initial peak of the renal time-activity curve. The second slope (portal venous phase) is seen 5 to 10 seconds later, after the portion of the radiopharmaceutical that entered the cranial mesenteric artery has passed through the intestinal capillary bed and entered the portal vein and subsequently the liver. A normal dog will have similar slopes for the arterial and portal phases. The slopes of each phase can be determined by fitting a line to each portion of the hepatic uptake curve ($y = mx + b$, where m = slope and b = y-intercept). The two slopes are then divided to create a ratio called the hepatic perfusion index.

The normal hepatic perfusion index is less than 2:1 (normal: 0.9 ± 0.4 , Figure 13.3). In an animal with a portosystemic shunt, there will be reduced portal flow relative to the arterial blood flow. Therefore the hepatic perfusion index will increase to values greater than 2 (Figure 13.4). This test lacks specificity however in that any disease that either increases hepatic arterial flow (hepatic neoplasia) or decreases hepatic portal venous flow (hepatic cirrhosis) will cause an increase in the hepatic perfusion index.

Per-Rectal (Transcolonic) Scintigraphy

Images of the portal venous system can be made following administration a radionuclide into the colon.^{18,19,30-36} Radionuclides that have been used for per-rectal portal scintigraphy include ^{201}Tl thallium, ^{123}I -iodoamphetamine, and sodium ^{99m}Tc -pertechnetate.

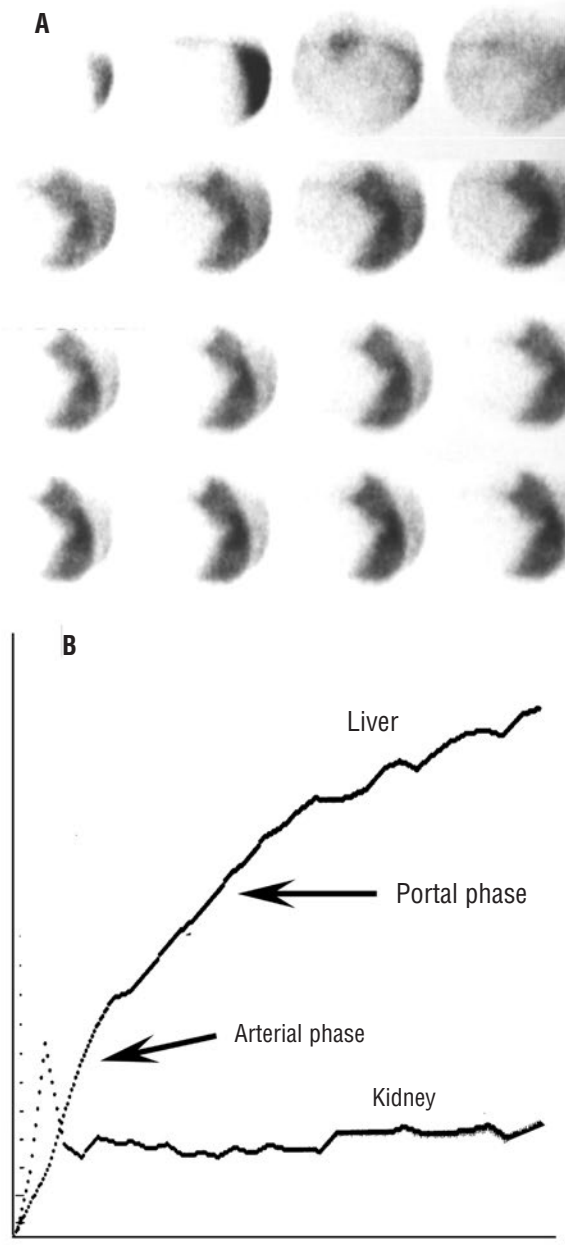


Figure 13.3: Normal ^{99m}Tc -sulfur colloid flow study following intravenous administration of the radiopharmaceutical

A, Dynamic images (2 seconds per frame) were obtained for 3 minutes. B, Hepatic and renal time-activity curves obtained following intravenous injection of ^{99m}Tc -sulfur colloid. The renal curve is used to help judge the start of the arterial phase of the hepatic uptake curve. A ratio of the slopes of the arterial and portal phases is then calculated. This ratio is called the hepatic perfusion index and is less than 2:1 (0.9 ± 0.4) in normal dogs.

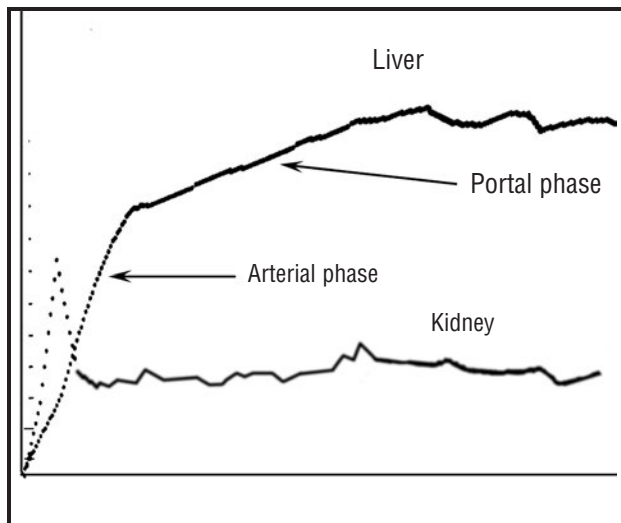


Figure 13.4: Hepatic and renal time-activity curves obtained following intravenous injection of ^{99m}Tc -sulfur colloid

In this dog with a portosystemic shunt, there is a marked reduction in the slope of the portal phase, thereby causing an increase in the hepatic perfusion index (greater than 2:1).

tate. In veterinary medicine, the most commonly used radionuclide for per-rectal portal scintigraphy is sodium pertechnetate.

Sodium ^{99m}Tc -pertechnetate is absorbed into the portal venous system by an active transport mechanism in the distal colon and rectum.³⁰ A transport protein, located along the luminal surface of the epithelial cells in the distal colon, will actively secrete bicarbonate (HCO_3^-). The bicarbonate is pumped out of the cell in exchange for the Cl^- anion found along the mucosal surface. Because pertechnetate has a valence and an ionic radius similar to chloride, it is absorbed by the same mechanism. In the proximal colon (ascending and transverse portions), a large amount of fluid from the chyme is reabsorbed. The luminal sides of the intestinal epithelial cells of the proximal colon are bound together by a band of specialized proteins forming a tight junction called the zonulae occludens. There is active transport of sodium and chloride ions into the cell at these tight junctions. The electrical gradient created by the positively charged sodium being transported into the epithelial cell is partially responsible for this absorption

process. Water will then follow an osmotic gradient and will be reabsorbed in the proximal large intestine. This later mechanism of Cl^- uptake by the large intestine is presumed not to play a significant role in the absorption of the sodium pertechnetate just based on the location at which this process occurs (proximal large intestine). Once absorbed across the intestinal epithelium, pertechnetate is considered an inert radionuclide that travels with the blood flowing through the portal venous system into the liver in a normal dog or cat. As the pertechnetate is inert relative to the heart/lung, it is assumed that there is no active uptake or retention of the radionuclide by these organs but the liver will retain a small percentage of the administered dose. Following per-rectal administration, the distribution of the pertechnetate within the portal blood flow is recorded in a dynamic acquisition using the gamma camera.

Per-rectal absorption of sodium pertechnetate in the normal dog is $15.26 \pm 6.88\%$ (mean $\pm$ SD) at 2 minutes.³⁷ The absorbed sodium pertechnetate is eliminated by the kidneys with some gastrointestinal excretion based on salivary and gastric excretions. The unabsorbed pertechnetate passes from the descending colonic and rectal lumen during the next bowel movement. Per-rectal portal scintigraphy is a safe, noninvasive, sensitive, and specific screening test for the evaluation of small animals suspected of having macrovascular portosystemic shunts.^{3,18,19}

Imaging Protocols

The indications for per-rectal portal scintigraphy are found in Table 13.2. The acquisition parameters for the per-rectal portal scintigraphy for evaluating dogs and cats are summarized in Table 13.3.

The patient is positioned in right lateral recumbency over the gamma camera. This position is preferred because the majority of the liver is on the right side. To the authors' knowledge, positional influences (ie, right and left recumbency) on the outcome of the per-rectal portal scintigraphy have not been reported in the literature, nor have the authors experienced them. It is imperative that the liver and the heart be correctly identified for accurate interpretation of a study and the drawing of regions of interest for time-activity curve generation. Correct identification of the liver and the heart can be difficult in small patients or in patients with poor colonic absorption

Table 13.2: Indications for Per-Rectal Portal Scintigraphy

Utilization as a noninvasive screening procedure for the detection of acquired or congenital portosystemic shunts.
Determine the severity of the shunt based on shunt fraction (limited value).
Evaluate the efficacy of surgical ligation postoperatively.
Monitor the effects of gradual occlusive devices (ameroiod constrictors).
Monitor for acquired extrahepatic portosystemic shunt formation in small animals with hepatic failure or postoperatively after surgical ligation of a single, congenital portosystemic shunt.

Table 13.3: Imaging Parameters for Per-Rectal Portal Scintigraphy**Radionuclide**

Sodium ^{99m}Tc -pertechnetate ($\text{Na}^{99m}\text{TcO}_4$).

Dose

Species	mCi	MBq
Dog	5-20	185-740
Cat	5-10	185-370

Acquisition Parameters

Patient preparation	None required. Dogs should be walked prior to the study to decrease chances of placing the radioactivity into a fecal material, thereby precluding absorption of the radionuclide.
Acquisition mode	Dynamic frame mode, acquired at 1 frame per second for 120 seconds (2 minutes). If the dog is a small breed or a cat is being imaged, a 1.5 or 2.0 digital zoom should be considered when setting up the acquisition parameters. The study is reframed to 2 or 4 seconds per frame when complete. A single composite image can be created for hand drawing the regions of interest around the heart or liver.
Matrix	128 × 128 × 16.
Collimator	Low-energy, all-purpose. A converging collimator or pinhole can be considered if the patient is extremely small (<1 kg).
Time to image	Acquisition begins just prior to or simultaneous with the injection of the radionuclide bolus.
Positioning	Patient is placed in right lateral recumbency on the imaging table (gamma camera under the table facing the patient) OR on the gamma camera face (absorbent paper is used to protect from contamination).
Views	Dynamic data set obtained as a series of right lateral images.

of the radionuclide. Magnification of the image by converging or pinhole collimators or the use of analog or digital zoom will help in organ identification. Externally placed radioactive markers can be used to identify the position of the liver and heart. One marker is positioned ventral to the xiphoid process of the caudal sternum for marking hepatic position, and the other marker is placed ventral to the apex beat of the heart. External markers are especially helpful in cases of poor radionuclide absorption by the colon/rectum. Prior to the start of the study, a lead shield should be placed between the pelvis of the dog and the gamma camera to block the large bloom of radioactivity that will be associated with the bolus deposited within the rectum/descending colon. If the colonic radioactivity is included within the image field, then the image display will set the gray scale to the maximum pixel density of the colon, thereby obscuring the much lower count density of the absorbed radionuclide and its passage through the cranial abdomen and thorax. The high intensity of the colonic radioactivity can also lead to dead time count losses by the gamma camera.

A lubricated red rubber feeding tube is placed into the distal colon. The catheter is inserted to the level of the pelvic inlet (iliac crest). A three-way stopcock is used to connect a 6 or 10 mL air filled syringe to the feeding tube. Prior to attaching the syringe containing the radionuclide, a bolus of air should be given to ensure the catheter tip has not been placed into feces and the flow from the catheter tip is easy and unobstructed. After reloading the syringe with air and setting the three way stop cock into the proper position, a shielded syringe containing the radionuclide (volume of 0.5 to 1.5 mL) is attached to the open port. The dynamic data set is begun, and the radionuclide is then pushed into the red rubber catheter. The radioactivity is deposited into the descending colon using the bolus of air.

Principles of Interpretation

Caudal Abdominal Vascular Anatomy

In normal dogs, the venous drainage of the ascending, transverse and descending colon and cranial rectum are via branches of the caudal mesenteric vein.^{5,33} The venous drainage of the anal sac, external anal sphincter, and the wall of the anal canal are

via the caudal rectal vein. The caudal rectal vein anastomoses with the cranial rectal vein via the rectal venous plexus.³⁸ The caudal rectal vein is an indirect tributary of the caudal vena cava and the cranial rectal vein is an indirect tributary of the portal vein. Because the caudal rectal vein communicates with the caudal vena cava (albeit indirectly), it is possible for sodium pertechnetate placed into the rectum to be absorbed into the systemic circulation, thereby creating a false positive. To the authors' knowledge, this has never been documented in dogs, cats, or pigs but the authors have seen small animal cases that would be interpreted as positive for a portosystemic shunt in which no shunt was found at surgery or necropsy. The number of supposed false-positive cases appears to be very small. The caudal rectal vein is the most likely cause of a true false-positive study. A false positive study has been reported in the calves³⁹ and has also been seen in foals (GBD, unpublished data, 2001).

Image Interpretation

The images of the dynamic acquisition are reviewed to determine the temporal sequence of the arrival of the pertechnetate into the liver or heart (Figure 13.5). The images of the dynamic acquisition can be summed to create a high count density composite image. Relative distribution of the radionuclide within the liver and heart is determined from the composite image along with the size, shape, and position of the liver. Regions of interest (ROIs) are hand drawn around the liver and the heart. These ROIs are used to create hepatic and cardiac time-activity curves. In studies with poor radionuclide absorption, these ROIs can be overlaid on the dynamic images to help determine at which organ (the liver or the heart) the radionuclide first arrived. Quantitative analysis is based on an integral count of the radioactivity within the liver and heart during the first-pass transit of the radionuclide through the portal and systemic venous system. The shunt fraction is based on the total heart counts seen within a certain time period (8 to 16 seconds) divided by the total counts within the heart and liver ROIs.^{18,40}

Absorption of the sodium pertechnetate occurs within 10 to 15 seconds following per-rectal administration. In some animals, a scintigraphic portovenogram is clearly seen, but more often, there is insufficient radioactivity absorbed to identify the portal vein as a

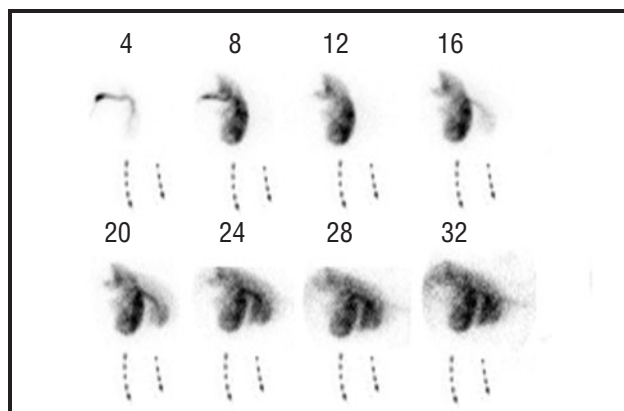


Figure 13.5: Normal per-rectal portal scintigraphy study in a dog

The study was acquired with the dog in right lateral recumbency and is formatted to 4 seconds per frame. The portal vein is easily visualized within the midabdomen on the first frame. There is normal distribution of the radionuclide in the liver (uniform with a normal hepatic size and shape); and then, after three frames (16 seconds) radioactivity is detected in the heart and thorax. The following frames show recirculation of the radionuclide. Time interval is shown above each image.

distinct structure. Because of the poor absorption and low count density of images, images are acquired in 4-second intervals. Faster frame rate provides better temporal resolution but poorer spatial resolution due to the low count density. Many camera users acquire images at 1-second intervals and then reframe them into courser frame rates.

If the colon is not shielded with lead, then the bloom from the deposition of the radionuclide will obscure the caudal and mid abdomen. The difference in image quality achieved by using a colon lead shield is shown in Figure 13.6. If the abdomen is obscured by the colonic radioactivity, the presence or absence of a portosystemic shunts is determined by visual inspection of the images for the time of arrival of the radionuclide into either the liver or heart. In Figure 13.6A there is an area of high radioactivity noted in the first image. This radioactivity is within the descending colon. The portal vein cannot be seen due to the bloom and the altered gray scale of the image. Note in this figure, that even though the portal vein is not seen, it is apparent that the radioactivity arrives

in the liver prior to arrival in the heart. The liver is seen 8 to 12 seconds (2 to 3 frames) before radioactivity is seen within the heart in a normal study. The same dog was imaged 2 days later using the same technique except a lead shield was used this time to block the colonic radioactivity (Figure 13.6B). Note the marked improvement in image quality. If colonic radioactivity is obscuring the image, then another method to improve the image is to mask the areas of increased count density (> 30 counts per pixel). The initial dynamic study can then be displayed after setting all pixels with a count density of > 30 to 0 (Figure 13.7). Replaying the study will then show the normal gray scale appearance of the absorption of the radio-pharmaceutical and vascular delivery over time.

The presence or absence of a portosystemic shunt is usually evident from the summed images of the dynamic acquisition. In a normal dog, the liver will receive all of the portal blood flow and will therefore appear more intense relative to the heart on the summed image (Figure 13.8). In Figure 13.8A, note the normal size, shape, and margins of the liver. These are in contrast to animals with portosystemic shunts in which the majority of portal blood bypasses the liver. The liver will be small and difficult to see on the summed image, often seen as a low intensity area just cranial to the photopenic void of the stomach. (Figure 13.8B).

Portosystemic Shunts

In animals with portosystemic shunts, the radionuclide absorbed from the colon bypasses the liver and arrives in the heart first. The liver is typically seen 10 to 12 seconds following the heart in affected animals. The radionuclide reaches the liver from the systemic arterial side. The additional 6 to 12 seconds is the time needed for the radionuclide to pass through the central circulation of the right side of the heart, pulmonary circulation, left side of the heart, and systemic circulation to the celiac artery and subsequently, to the hepatic arteries. In lower magnitude shunts, the arrival of the radioactivity may be seen in both the liver and heart simultaneously. If the study is performed at 1 second per frame and reframed into 2 seconds per frame, there may be visualization of the heart prior to the liver. When the studies are reformatted to longer times of 4 seconds per frame, there is the potential for simultaneous delivery of the radionuclide to both the liver and heart at the same

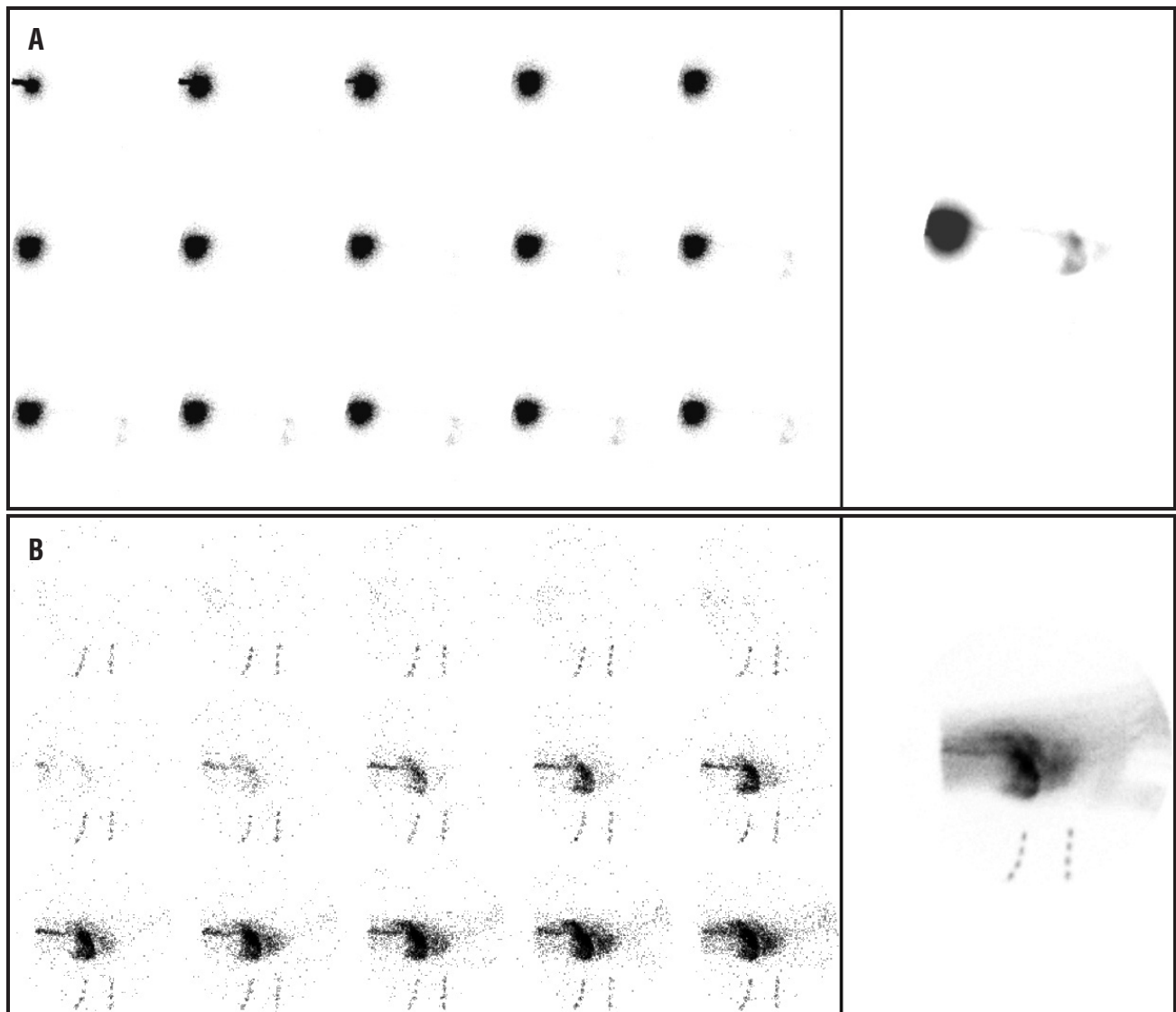


Figure 13.6: Per-rectal portal scintigraphy in a normal dog

The images to the left of the vertical line represent the dynamic images acquired at 4 seconds per frame. The image to the right of the line is a composite image made by summing the images from the entire dynamic acquisition. **A**, Images were acquired without lead blocking the area of the colon. **B**, Same study in the same dog obtained two days later. A lead shield has been positioned to block the colonic radioactivity from the field of view. In **A**, the areas of the liver and heart are difficult to see due to the wide gray scale range needed to include the colonic radioactivity. Note how much easier it is to see the portal vein, liver, and heart with the colonic radioactivity blocked as seen in **B**.

time, particularly in small animals.

The liver normally receives 70% of its total blood flow from the portal venous circulation and only 30% of its blood flow from the hepatic artery (branch of the celiac artery).^{38,41} In cases of portosystemic shunts, the hepatic arteries provide the majority of

the total hepatic blood flow. The majority of portal blood will bypass the liver and enter directly into the systemic circulation. The images in Figure 13:9 include the dynamic study and summed images from a dog with a portosystemic shunt. On the summed image, the heart has more radioactivity than the liver.

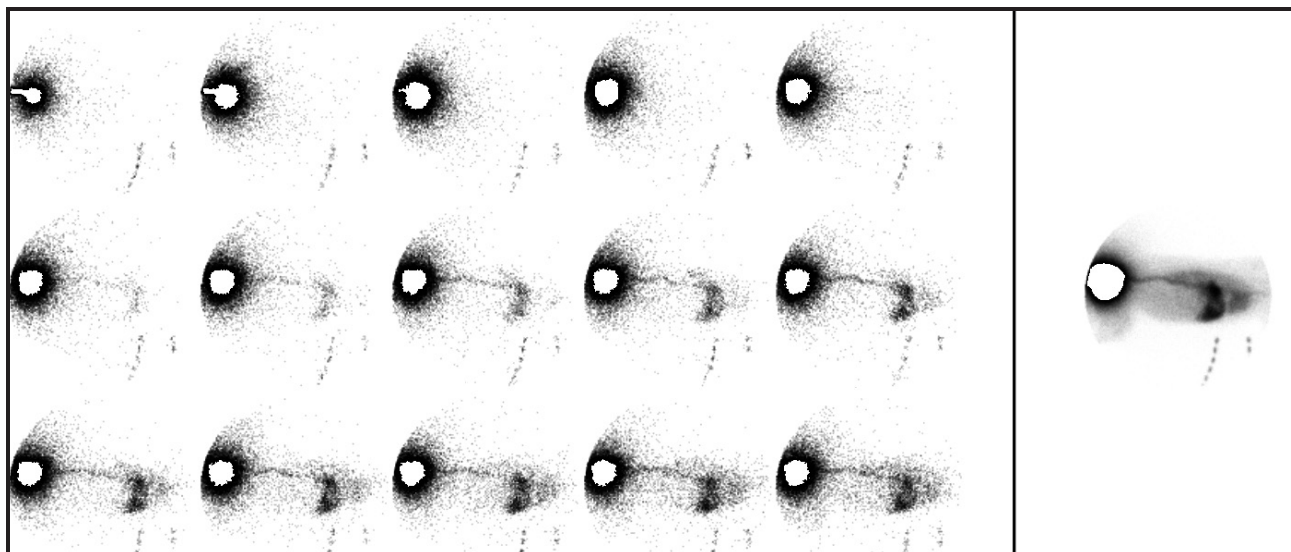


Figure 13.7: Reprocessed dynamic study from Figure 13.6A

All pixels with a count density of greater than 30 were reset to 0. The appearance of the radiopharmaceutical in the portal vessel and the normal vascular delivery to the liver and then to the heart is evident.

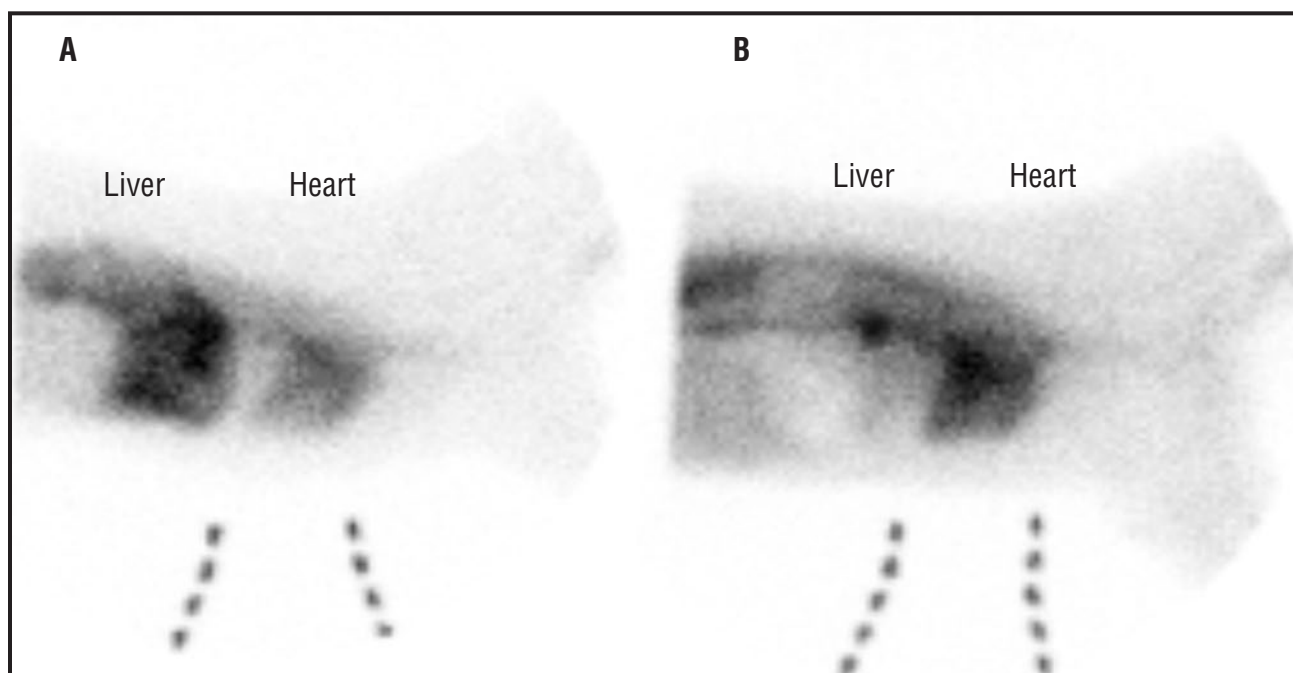


Figure 13.8: Composite image created by summing images from the dynamic acquisition of a normal dog (A) and a dog with a portosystemic shunt (B)

A, In the composite image from the normal dog, the liver has higher intensity than the heart and lungs. Note the size, shape, and margins of the liver. **B**, Composite image from a dynamic acquisition of a dog with a macroscopic portosystemic shunt. Note the portal vein and the relative increased intensity of the heart when compared with the liver. The area of the shunt is represented by the focal accumulation of the radionuclide near the porta hepatis. The liver margins are somewhat ill-defined and smaller than those in the normal dog imaged in Figure 13.7.

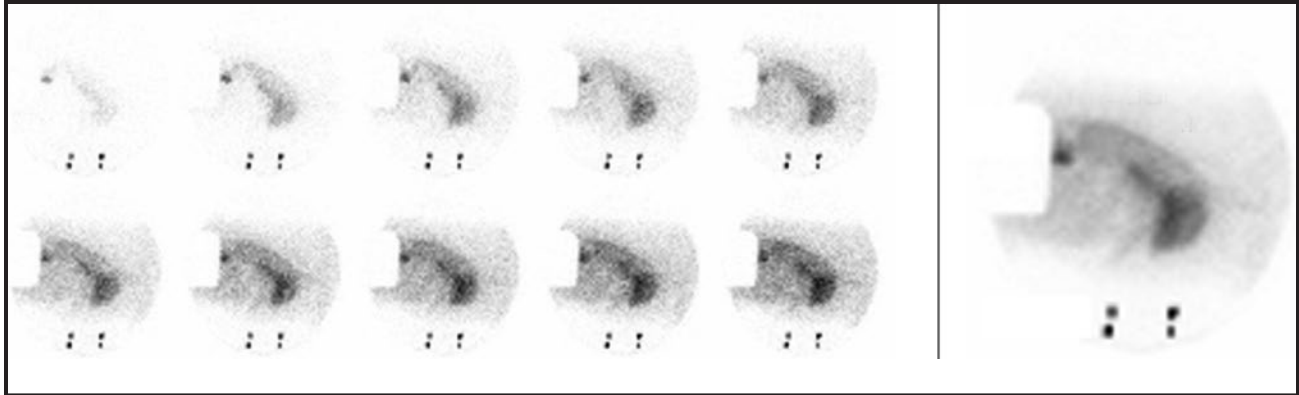


Figure 13.9: Per-rectal Portal Scintigraphy in a dog with a macroscopic portosystemic shunt

The images to the left of the vertical line represent the dynamic images acquired at 4 seconds per frame. The image to the right of the line is a composite image made by summing the images from the entire dynamic acquisition. In this study a discrete portal vascular structure is not seen. The caudal vena cava is seen, but the shunt vessel leading into to the caudal vena cava is not. In most per-rectal studies a discrete portal vein is not seen.

In a large-magnitude shunt, the liver may be hard to identify because of its small size and lack of portal blood flow. Shunt vessel visualization is highly variable and may only be possible when the study has been reformatted and summed (Figure 13.10). However, anatomic characterization of the type of congenital or acquired shunt is not usually possible.

Dogs with microvascular dysplasia will appear normal. The radionuclide will be distributed throughout the liver parenchyma and will bypass the hepatic sinusoids through the thousands of microscopic intrahepatic shunts giving one the impression of normal perfusion of the liver (Figure 13.11). There may be a difference in the hepatic transit time between normal dogs and dogs with microvascular dysplasia; however, this has yet to be proven. The incidence of microvascular dysplasia is very low, which prevents a comprehensive study of the imaging characteristics of the disease.

Dogs with acquired portosystemic shunts typically have multiple small vessels, which are rarely seen on per-rectal portal studies. Acquired shunts develop as a response to portal hypertension. The portal hypertension can also result in poor absorption of the radionuclide from the colon, therefore the images are of even lower count density than usual, which further compromises the ability to see portal vessels (Figure 13.12).

1. Time-Activity Curve Generation and Evaluation

Time-activity curves can be useful to determine the temporal sequence of the arrival of the radioactivity bolus in the liver and heart. Regions of interest are hand drawn around the liver and the heart. These ROIs are applied to the dynamic data set, and time activity plots are created. The y-axis represents increasing radioactivity within the liver or heart and the x-axis is the time following the per-rectal administration. In the normal animal, the radioactivity is first detected in the liver so the liver curve deviates from baseline first, then 8 to 12 seconds later radioactivity is noted in the heart and there is an upslope of the heart curve. It takes 8 to 12 seconds for the radionuclide to pass through the hepatic sinusoids to the central vein, drain into the hepatic vein and into the caudal vena cava, eventually arriving in the heart (Figure 13.13). In a dog with a portosystemic shunt, the position of the liver and heart curves are reversed (Figure 13.14).

Quantitative analysis of the portal scintigram is done as a measure of the percentage of portal blood that bypasses the liver. The shunt fraction is calculated from the integral counts in the heart and liver during the 12-second period of normal liver transit. The total number of counts for the heart is divided by the sum of the total counts for the heart and liver and is reported as a percentage.

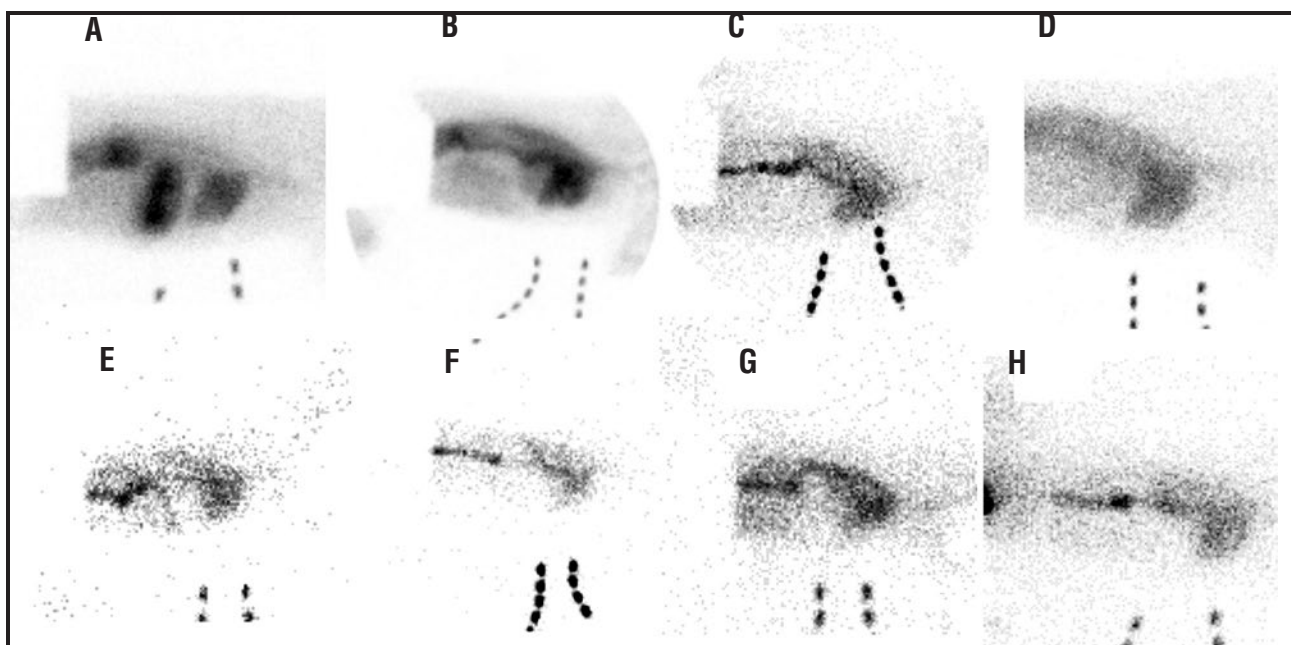


Figure 13.10: Per-rectal scintigrams from eight different animals

The above are summed images of various frames enhancing the visualization of the portal vein and shunt. The diagnosis was confirmed by animals surgery. **A**, No portosystemic shunt. **B**, Intrahepatic shunt of the left divisional branch. **C**, Intrahepatic shunt of the right divisional branch. **D**, Multiple acquired extrahepatic shunts. **E**, Gastroduodenal shunt. **F**, Left gastric portosystemic shunt. **G**, Portoazygos shunt. **H**, Gastrosplenic shunt.

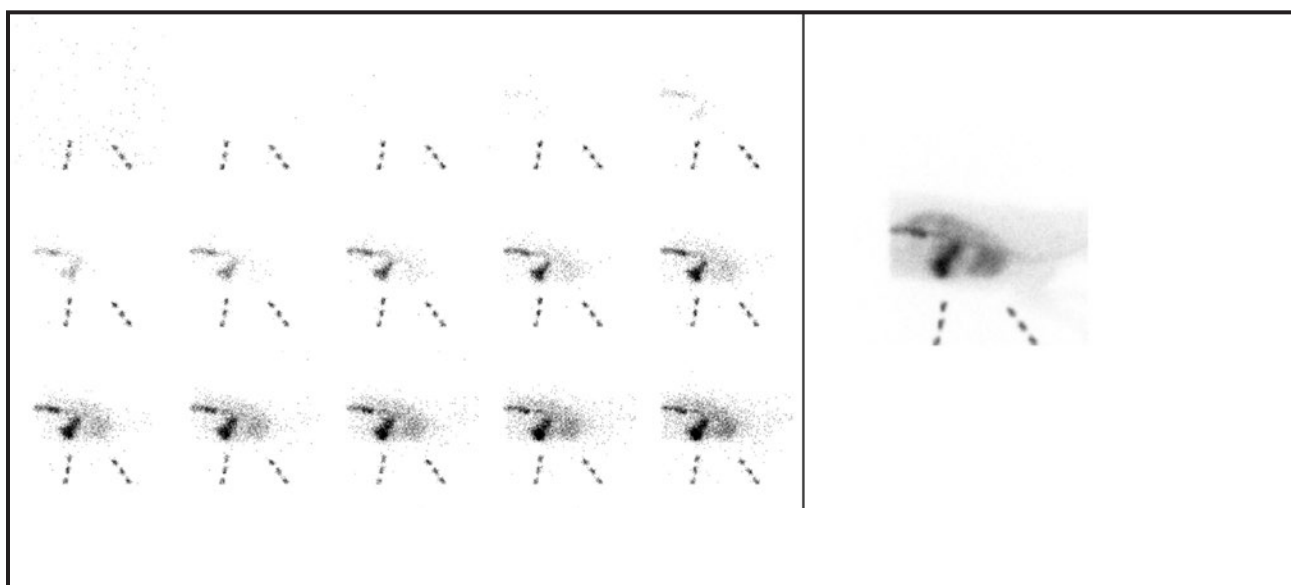


Figure 13.11: Per-rectal portal scintigraphy in a dog with a microvascular dysplasia

The images to the left of the vertical line represent the dynamic images acquired at 4 seconds per frame. The image to the right of the line is a composite image made by summing the images from the entire dynamic acquisition. This study was interpreted as no macroscopic shunt that is the typical pattern seen with microvascular dysplasia. This was confirmed on histology.

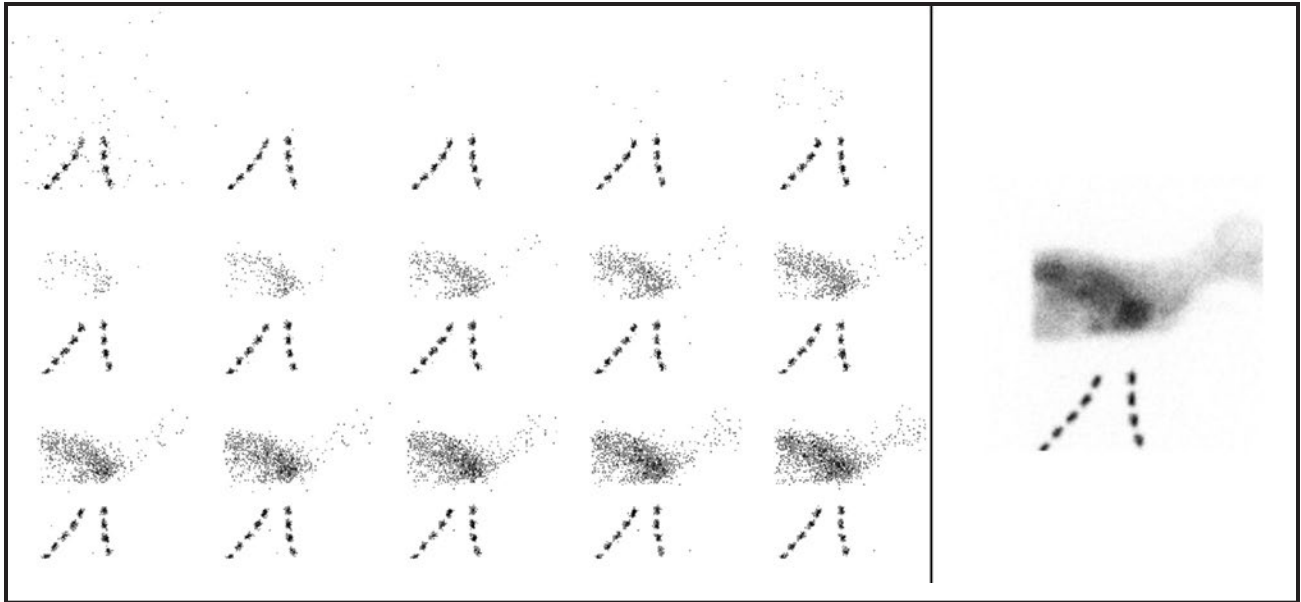


Figure 13.12: Per-rectal portal scintigraphy in a dog with a multiple acquired shunts

The images to the left of the vertical line represent the dynamic images acquired at 4 seconds per frame. The image to the right of the line is a composite image made by summing the images from the entire dynamic acquisition. The shunts cannot be seen, but the diagnosis of the portosystemic shunt is made by the arrival of the radionuclide in the heart before arrival in the liver. In the authors' experience, multiple acquired shunts are not usually seen on per-rectal portal scintigrams.

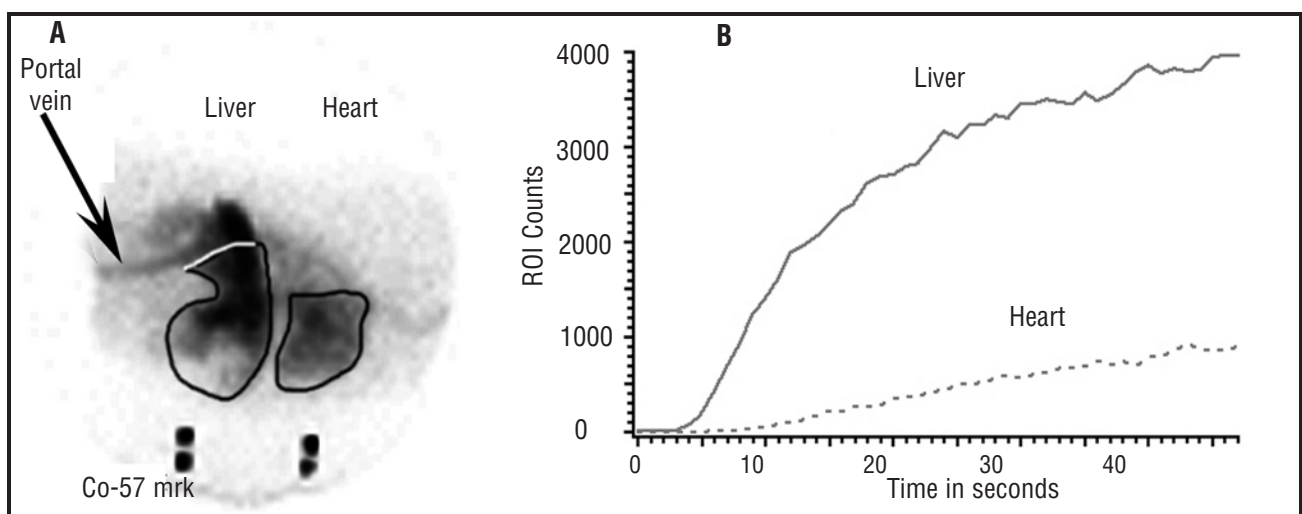


Figure 13.13: Per-rectal portal scintigraphy of a normal dog

A, Hand-drawn ROIs are placed around the liver and heart. **B**, A time-activity curve is generated by applying the ROIs to the dynamic acquisition. Note the rise of the radioactivity within the liver first. After 12 seconds the time-activity curve of the heart starts to show an increase in total counts consistent with normal passage of the radionuclide through the liver into the systemic circulation (caudal vena cava) and then into the heart. The total number of counts during the first 12 seconds of the study after the initial rise in the liver radioactivity is used to calculate the shunt fraction. In this dog, the shunt fraction was 4%. See text for equation.

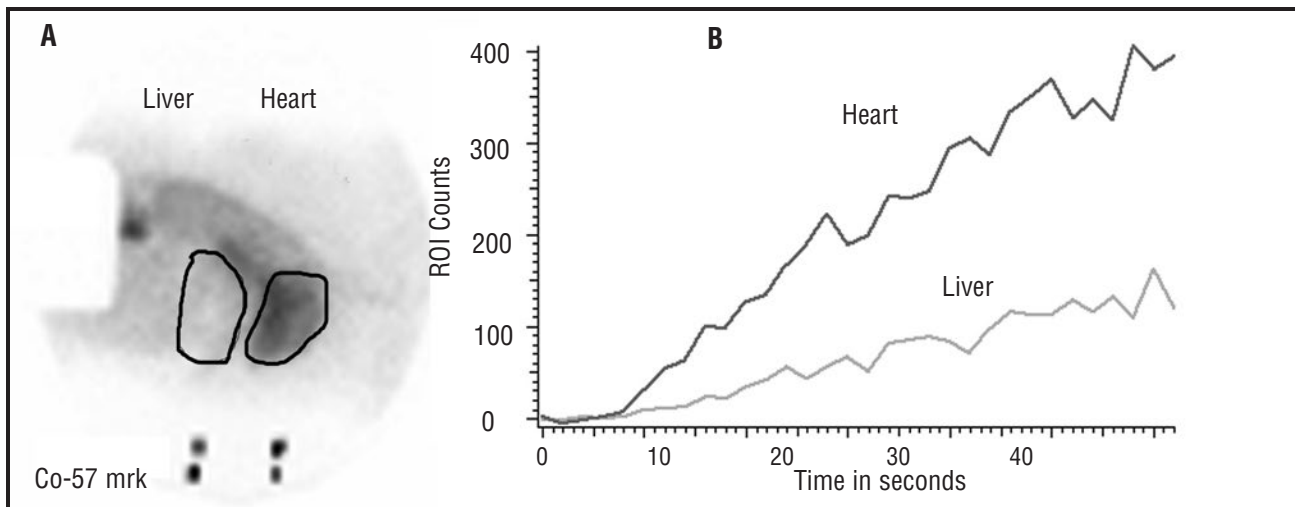


Figure 13.14: Per-rectal portal scintigraphy of a dog with a portosystemic shunt

A, Hand drawn ROIs are placed around the liver and heart. **B**, A time-activity curve is generated by applying the ROIs to the dynamic acquisition. Note the rise of the radioactivity within the heart first. After 12 seconds, the time-activity curve of the liver starts to show an increase in total counts consistent with abnormal passage of the radionuclide through the heart, recirculating in the systemic circulation (aorta) and then into the liver. The total number of counts during the first 12 seconds of the study after the initial rise in the heart radioactivity (defined as T_0) is used to calculate the shunt fraction. In this dog, the shunt fraction was 82%. See text for equation.

$$\text{Shunt Fraction} = \frac{\frac{(\Sigma \text{Heart ROI})}{12 \text{ sec}}}{\left(\frac{(\Sigma \text{Heart ROI} + \Sigma \text{Liver ROI})}{12 \text{ sec}} \right)} \times 100$$

Normal dogs should have a shunt fraction of less than 5%. If there is poor or slow absorption of the radionuclide, the shunt fraction may be as high as 15% to 20% in normal dogs and cats. Most cases of congenital portosystemic shunts whether intra- or extrahepatic will have shunt fractions greater than 60%. The mean shunt fraction value for congenital portosystemic shunts ($n = 87$) was determined to be 84% at the University of Tennessee. These values were not significantly different based on the type or the location of the shunt (Table 13.4).

The quantification of the shunt fraction will overestimate the severity of the blood volume that bypasses the liver. In experimental studies comparing direct portal injection of ^{99m}Tc -macroaggregated albumin and ^{123}I -iodoamphetamine it was shown that true shunt fractions that are greater than 70% are overestimated when using per-rectal sodium pertechnetate studies.³² The exact reason for this disparity has not been determined, but is probably due to difference

in blood flow rates and possible upstream pressure gradients through the liver versus through the shunt vessel to the caudal vena cava or azygos vein. The rate of portal blood flow is slower than the systemic venous blood flow rate, and during a fixed time interval the heart may receive a greater quantity of blood flow per unit of time than the liver would.

A limitation of portal scintigraphy is that often characterization of the shunt is not possible. It has been reported that large portosystemic anastomotic vessels may be demonstrated by per-rectal portal scintigraphy⁴² but it has been the authors' experience that the spatial resolution and count density are insufficient to consistently identify the intra or extrahepatic position of the portosystemic shunt or the exact anatomic type of shunt vessel. Ventral or dorsal images obtained after the initial study will not provide accurate localization information regarding the anatomy of the shunt vessel or localization to the left or right in the case of single intra- or extrahepatic portosystemic shunts.

2. Nondiagnostic Studies

If the liver and heart cannot be readily visualized because of poor absorption at the end of the dynamic

Table 13.4: Mean Shunt Fraction Values (calculated over 12 seconds) Based on Shunt Location

Shunt Location	Number of Dogs (n = 87)	Shunt Fraction (12 seconds)
Left Gastric	12	86.0%
Gastroduodenal	3	90.0%
Gastrosplenic	7	85.0%
Single Intrahepatic	8	80.0%
Multiple Extrahepatic	12	75.5%
Portoazygos	11	78.0%
Portocaval	34	82.8%

acquisition, one can try acquiring a single right lateral static image (60 seconds, $128 \times 128 \times 16$). If the heart is seen but the liver is not readily apparent on the static image, then the animal most likely has portosystemic shunt, but this should be confirmed by replaying the reformatted dynamic images. If the liver and heart are not visualized, then the study is nondiagnostic. In cases of very low counts in the liver and the heart, an image of the colon can confirm if there is radioactivity within the patient. If the radionuclide is confined to a small portion of the colon, then the radionuclide may have been deposited into feces and is thus unavailable for absorption. If the radionuclide has the shape and position of the entire colon, then the patient's colon may be fluid filled from diarrhea or from a previous enema. Diarrhea can prevent normal uptake of the sodium pertechnetate. The secretory capacity of the large and small intestinal crypts is voluminous. The primary secretory cells are found within the crypts of the large and small intestinal villi. Under normal unstimulated conditions there are two active chloride channels found on the apical (luminal) surface of these epithelial cells. These channels are sensitive to increases in cellular concentrations of calcium ions and can also be opened via cAMP-dependent protein kinase A. This results in the secretion of the Cl^- into the luminal space. This creates both an electrical and chemical gradient for Na^+ secretion. This also creates an osmotic gradient for net movement of water into the intestinal lumen. Although the exact mechanism for the lack of pertechnetate uptake is

not known, it is speculated that the net chloride flux is into the lumen and not into the intestinal epithelial cell and thereby into the portal vasculature. This is supported by the poor absorption of pertechnetate when the gastrointestinal cleansing agent, GoLyteLy was used prior to per-rectal portal studies.⁴³ This agent induces a secretory diarrhea and resulted in poor radionuclide absorption. Waiting for the diarrhea to resolve or repeating the study at a later time usually results in a diagnostic quality study.

As the exact mechanisms of absorption are not known, the diagnostic quality of the per-rectal studies is variable and is most dependent on adequate absorption of the sodium pertechnetate ions. In a recent review of per-rectal portal studies performed at the University of Tennessee during a 2-year period of time, 3.6% of the scans were considered undiagnostic; and 25.8% were considered poor quality, with the remainder given a classification of average to excellent.

3. Diagnostic Utility of Shunt Fraction Calculations

In a recent review of the data from dogs that had undergone surgical correction of portosystemic shunts at the University of Tennessee, the shunt fraction values were found to have no prognostic or predictive significance as to how a dog would respond to surgical intervention. The mean shunt fraction of the 110 congenital portosystemic shunts cases was 83% versus a mean shunt fraction of 76% from 13 animals with acquired portosystemic shunts, ($p > 0.05$). The

data was further divided into survival groups post surgery and it was found that there was no significant difference in the shunt fractions noted between dogs alive at discharge ($n = 75$; mean shunt fraction = 82.8%), alive at 6 months postdischarge ($n = 18$, mean shunt fraction = 77.0%) and animals that died prior to discharge ($n = 19$, shunt fraction = 80.0%). Additionally, no correlations were found between the shunt fraction and serum ammonia levels, age of the animal, serum BUN levels, total protein, albumin, preligation intraportal pressure, or postligation intraportal pressure at the time of surgery.

Shunt fractions values have been shown to decrease over time in serial imaging studies done in dogs and cats where a gradual occlusive ameroid constrictor was used for shunt closure.⁴⁴ In this group of dogs, the decreasing shunt fraction was shown to correlate with improvement in clinical signs.

4. Variants: Non Uniform Radionuclide Distribution Within the Liver: Portal Streamlining

Nonuniform distribution of the radionuclide within the hepatic portal venous tributaries within the liver of normal dogs has been seen following per-rectal portal scintigraphy. In 35/51 dogs (68.9%), a heterogeneous pattern of distribution within the liver was reported.⁴⁵ Three common patterns for focal distribution of the radionuclide within the liver were seen, including dorsal hepatic distribution, central hepatic distribution (porta hepatis), and ventral hepatic distribution. The focal dorsal distributions are more likely to influence quantitative analysis of the images and calculation of the shunt fraction. Often the liver ROI is drawn around the liver ventral to the porta hepatis so as to exclude the possibility of a shunt vessel being within the liver ROI. Most shunt vessels will be dorsal to the level of the caudal vena cava; and this area is not typically included in the liver ROI so that radioactivity within the shunt vessel is not be assigned to the liver counts. If a normal animal has streamlining into the right divisional branch and the dorsal liver is not included in the hepatic ROI, a false-positive diagnosis could be made. Because of this potential pitfall, it is recommended that the initial evaluation of the images be made from the dynamic acquisition in a cine loop format. Focal distributions have a hepatic transit time similar to that for uniform distributions and arrive in the liver first and then in the heart. 8 to 12 seconds later. This

would be different from the temporal sequence in animals with a portosystemic shunt where the transit time should be very fast (less than 2 seconds). Once the transit time through the liver is visually assessed, then the region of interest is drawn around the liver. The focal area of accumulation should be included in the liver ROI if the radionuclide takes 8 to 12 seconds to pass through this area prior to thoracic vascular distribution.

Blood flow within the portal vein is not homogenous, but has the characteristic of being streamlined. These discrete channels of streamline flow permit different parts of the liver to receive blood from distinct visceral sources. Streamlining occurs when laminar blood flow prevents adequate mixing of the radionuclide within the portal vein so there is unequal distribution of the radionuclide in the tributaries of the portal vein. If this occurs, the radionuclide will flow into one of the main streamline flow branches of the portal vein. There are three portal venous branches that have been anatomically described. The right divisional branch of the portal vein supplies portal venous blood to the caudate, right lateral, and right medial hepatic lobes. The central divisional branch supplies portal venous blood to the lobes and areas associated with the porta hepatis, including the quadrate hepatic lobe. The left divisional branch of the portal vein (the direct continuation of the portal vein after the right divisional and central divisional branches have bifurcated from the main portal vein) supplies the left lateral and medial hepatic lobes and has a predominantly ventral distribution (see Figure 13.15). If the radioactivity is confined primarily to the left divisional branch, then the radioactivity will be confined to the left hepatic lobes, so that from a lateral view the radioactivity has a ventral distribution. If the radioactivity is confined primarily to the central divisional branch then the radioactivity will be confined to the central hepatic lobes and porta hepatis, so that from a lateral view the radioactivity has a central hepatic distribution. If the radioactivity is confined primarily to the right divisional branch, the radioactivity will be confined to the right hepatic lobes, and from a lateral view the radioactivity has a dorsal hepatic distribution. In Figure 13.16 are summed images from different dogs that showed the three basic patterns of portal streamlining of the pertechnetate portal venous distribution within the liver. To scintigraphic evidence of a portosystemic

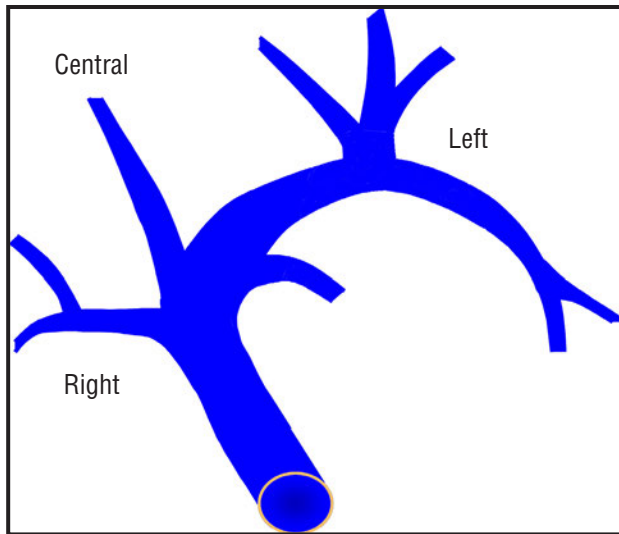


Figure 13.15: The hepatic portal vein and the three divisional branches

The drawing is viewed from the caudal aspect.

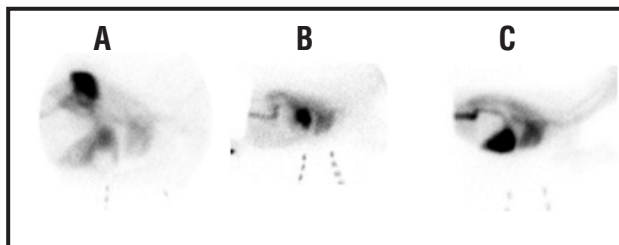


Figure 13.16: Composite images of variations of hepatic distribution based on a per-rectal portal study

A, Dorsal distribution of radioactivity corresponding with right divisional branch portal streaming. **B**, Central distribution of radioactivity corresponding with central divisional branch portal streaming. **C**, Ventral distribution of radioactivity corresponding with left divisional branch portal streaming.

shunt was seen in any of these dogs, and all scintigraphic studies and shunt fractions were considered normal.

Trans-splenic Portal Scintigraphy

The portal venous system can be imaged following injection of contrast medium into the splenic

parenchyma. The contrast medium will move from the splenic venous sinusoids into the splenic vein, which then combines with the mesenteric branches to form the portal vein. Although this technique is less invasive than mesenteric portovenography, it has not gained the same level of acceptance. The volume of contrast medium and the rate at which it has to be injected limit the quality of radiographic transsplenic contrast studies. The first trans-splenic scintigraphic study was described in 1994. Portosystemic shunts were diagnosed and quantified following injection of ^{99m}Tc -macroaggregated albumin into the splenic parenchyma.⁴⁶ In normal dogs the radiopharmaceutical localized exclusively in the liver, while in dogs with portosystemic shunts, the radiopharmaceutical passed through the abnormal vascular connection and localized in the lung via capillary blockade. A shunt index can be calculated by determining the radioactivity within the lungs divided by the radioactivity in the lungs plus liver. The average shunt index in dogs with portosystemic shunts was found to be 0.94 compared with 0.01 in normal dogs.⁴⁶

Trans-splenic portal scintigraphy using pertechnetate has recently been described.^{37,47} The advantages over per-rectal scintigraphy include: (1) a lower radionuclide dosage, (2) reduced personnel exposure, (3) consistent visualization of the portal venous system, (4) higher count density images, and (5) improved statistical quality of the quantitative analysis. The indications and acquisition parameters for transsplenic portal scintigraphy are given in Tables 13.5 and 13.6, respectively.

Procedure

A 22-gauge, 1.5-inch needle is placed into the splenic parenchyma using ultrasound guidance. A dynamic frame-mode image acquisition (4 frames per second for 180 seconds) is started, and a dose of 54.5 MBq (1.5 mCi) of sodium pertechnetate in a 0.2 mL volume is injected. The syringe and needle are then removed from the field of view. Even though the acquisition is for three minutes, the most important information is contained in the first passage of the radionuclide, and this occurs within several seconds following injection of the radionuclide into the splenic parenchyma. It is critical to start the acquisition and make sure it is running for several seconds before making the injection because the transit time from the spleen to the liver or heart can be less than 1 second.

Table 13.5: Indications for Trans-splenic Portal Scintigraphy

Utilization as a noninvasive screening procedure for the detection of acquired or congenital portosystemic shunts.
Determine the morphology of the shunt (multiple versus single).
Quantify Liver function (using ^{99m}Tc -Mebrofenin).
Determine the severity of the shunt based on the calculated shunt fraction.
Determine where the shunt terminates (caudal vena cava, azygos vein, or internal thoracic vein).
Monitor the effects of gradual occlusive devices (ameroïd constrictors).
Monitor for acquired extrahepatic portosystemic shunt formation.

Table 13.6: Imaging Parameters for Trans-splenic Portal Scintigraphy

Radionuclide	Dose		
	Species	mCi	MBq
Sodium ^{99m}Tc -pertechnetate or ^{99m}Tc -mebrofenin	Dog	2	74
	Cat	2	74

Acquisition Parameters

Patient preparation	Sedation or anesthesia is recommended. Ultrasound is needed to ensure needle placement into the spleen.
Acquisition mode	Dynamic frame mode, acquired at 4 frames per second for 180 seconds (3 minutes). If the dog is a small breed or a cat is being imaged, a 1.5 or 2.0 digital zoom should be considered when setting up the acquisition parameters. A single composite image can be created for hand drawing the ROIs around the heart or liver.
Matrix	128 × 128 × 16.
Collimator	Low-energy, all-purpose. A converging collimator or pinhole can be considered if the patient is extremely small.
Time to image	Acquisition begins 1 second prior to injection of the radiopharmaceutical.
Positioning	Patient is placed in right lateral recumbency on the imaging table (gamma camera under the table facing the patient) OR on the gamma camera face (using absorbent paper to protect from contamination).
Views	Dynamic data set obtained as a series of right lateral images or dorsal images.

1. Normal

In the normal dog, the radionuclide is rapidly absorbed from the spleen into the splenic vein into the left gastric vein, and then into the main portal vein, (Figure 13.17). A frame rate of 4 frames per second is used so that the rapid passage of the radionuclide from the spleen into the portal venous system can be temporally resolved. The absorption from the spleen is variable, but at least 42% of the injected dose will enter the portal venous system within 2 minutes following injection. In the normal dog, the transit time from the liver to the heart is 7.03 ± 2.3 (mean $\pm$ SD) seconds.³⁷ Shunt fractions can be determined as with the per-rectal studies; but because radioactivity arrives in a discrete bolus, a shorter integral count of 7 seconds is used to calculate the shunt fraction. The shunt fraction for normal dogs is 2.64 ± 1.3 .³⁷

2. Portosystemic Shunts

In dogs and cats with portosystemic shunts, the shunt vessels are clearly seen (Figure 13.18). Animals with multiple extrahepatic shunts can be easily differentiated from dogs with a single intra- or extrahepatic shunt (Figures 13.19 and 13.20).⁴⁷ The shunt vessel is routinely seen using the trans-splenic administration.

The major potential shortcoming of the trans-splenic technique is the identification of portosystemic shunts located caudal to the entrance of the splenic vein into the portal vein. The authors have observed the radionuclide bolus traveling caudally before entering the portal vein, indicating hepatofugal venous flow. The portal hemodynamics cranial to the shunt have recently been documented by intra-operative ultrasound in a series of dogs. Hepatofugal portal flow was detected cranial to the shunt indicating that false-negative studies may be avoided.⁴⁸ At the time of this writing, the transsplenic technique has been used successfully to diagnose over 80 dogs and cats with surgically confirmed intra- and extra-hepatic portosystemic shunts. The improvement in study quality with a reduced radiation dose to the patient and personnel will most likely make the trans-splenic technique the study methodology of choice for portal scintigraphy.

Trans-splenic Injection of ^{99m}Tc -Mebrofenin

^{99m}Tc -mebrofenin is currently being tested as an alternative to sodium pertechnetate for trans-splenic portal scintigraphy. ^{99m}Tc -mebrofenin has a high first-pass extraction by the liver.⁴⁹ In normal dogs

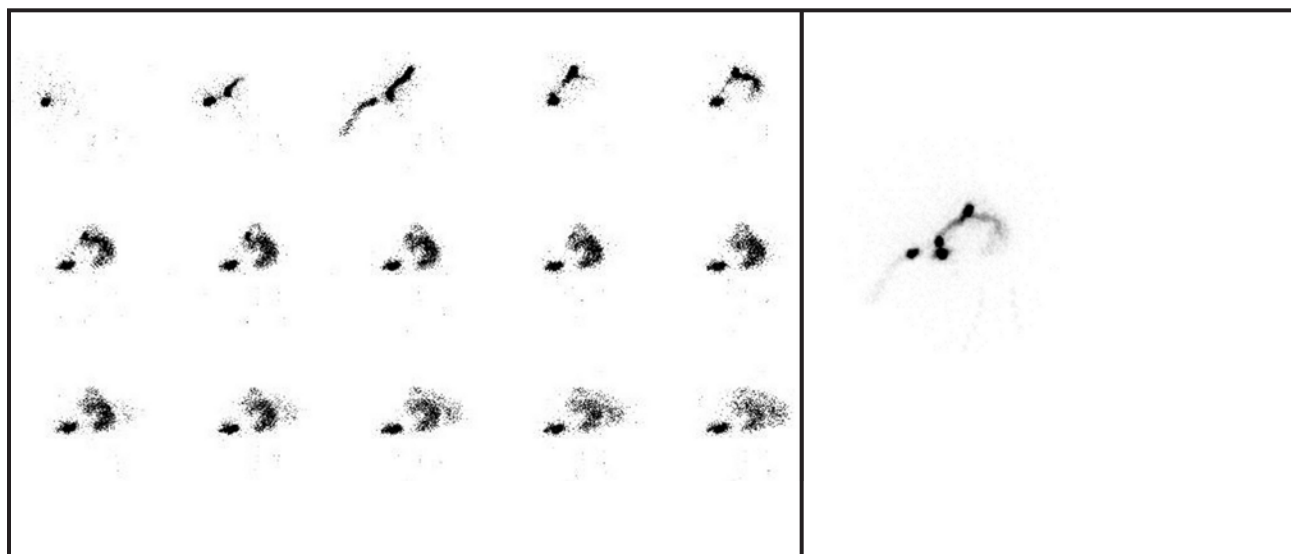


Figure 13.17: Trans-splenic portal scintigraphy study using sodium ^{99m}Tc -pertechnetate in a normal dog

The study was acquired with the dog in right lateral recumbency and reformatted at 1 frame per second. The portal vein is easily visualized within the midabdomen on the first frame. There is normal distribution of the radionuclide in the liver (uniform with a normal size and shape); and then, after 8 frames (8 seconds), radioactivity is detected in the heart and thorax.

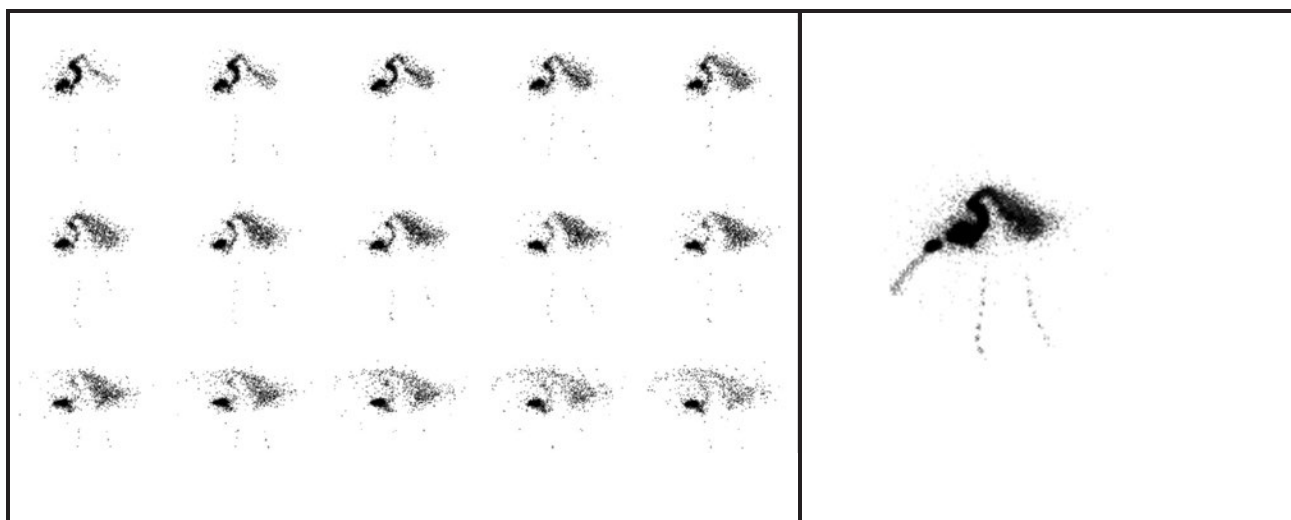


Figure 13.18: Trans-splenic portal scintigraphy study using sodium ^{99m}Tc -pertechnetate in a dog with a single extrahepatic shunt

The study was acquired with the dog in right lateral recumbency and is reformatted at 2 frames per second. The portal vein is easily visualized within the midabdomen on the first frame. The shunt can be seen curving dorsally then ventrally entering the caudal vena cava. At surgery the shunt vessel penetrated the left diaphragm.

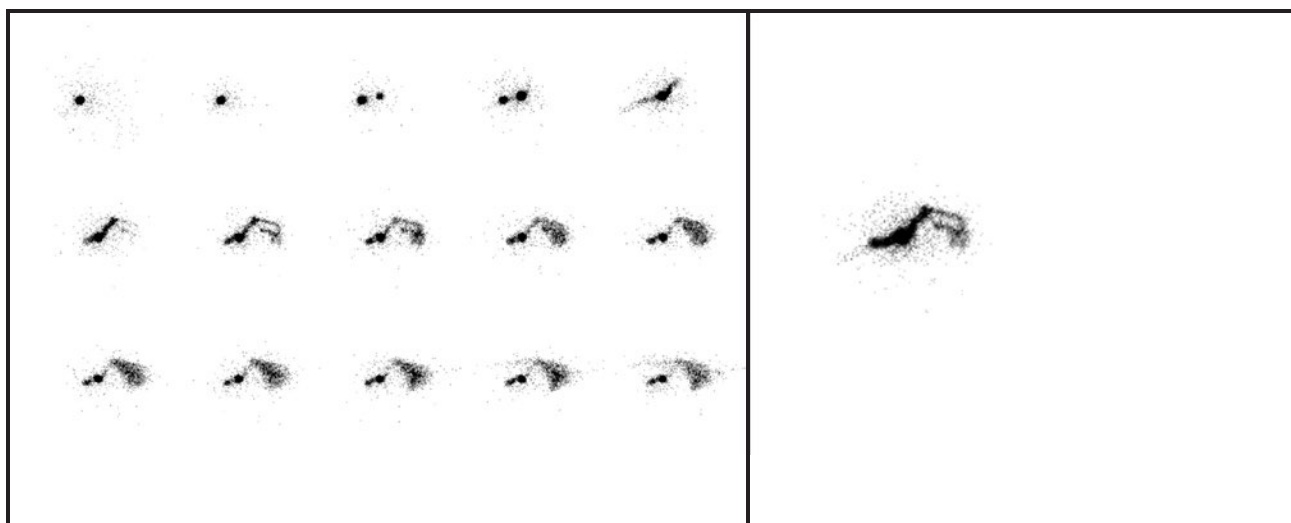


Figure 13.19: Trans-splenic portal scintigraphy study using sodium ^{99m}Tc -pertechnetate in a dog with portocaval and portoazygos shunts

The study was acquired with the dog in right lateral recumbency and reformatted at 2 frames per second. The portal vein is easily visualized within the mid-abdomen on the sixth frame. Two shunt vessels are seen, one entering the caudal vena cava and the other extending dorsally to the azygos vein.

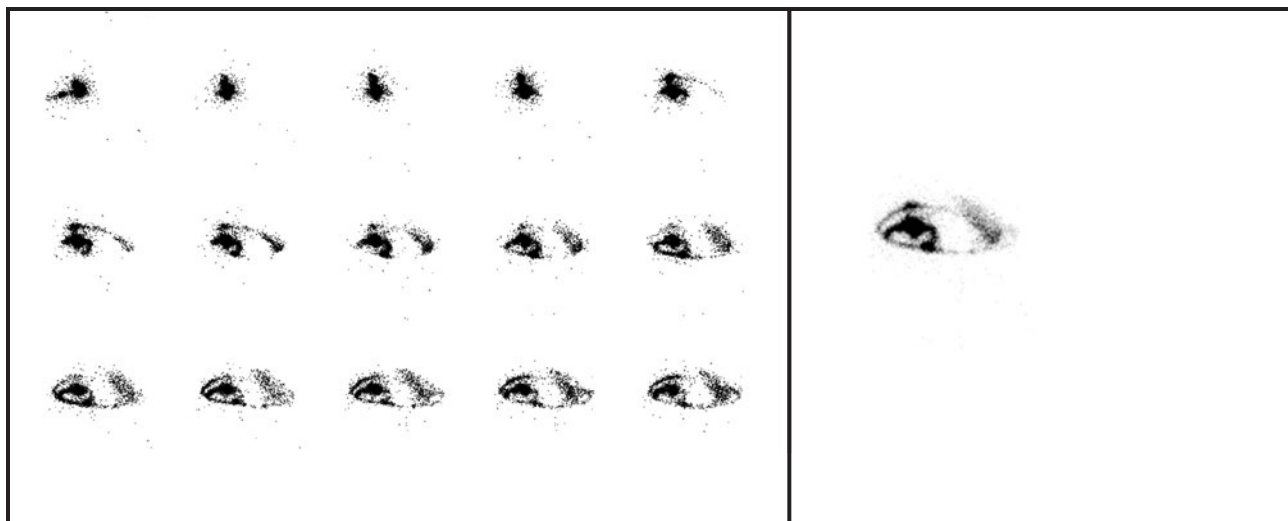


Figure 13.20: Trans-splenic portal scintigraphy study using sodium ^{99m}Tc -pertechnetate in a dog with acquired, multiple, extrahepatic portosystemic shunts

The study was acquired with the dog in right lateral recumbency and reformatted at 2 frames per second. The first shunt is seen dorsal and caudal to the spleen. Other shunts are seen ventrally, one entering the internal thoracic vein and the other curving dorsally toward caudal the vena cava. The large, central photopenic area represents to the liver.

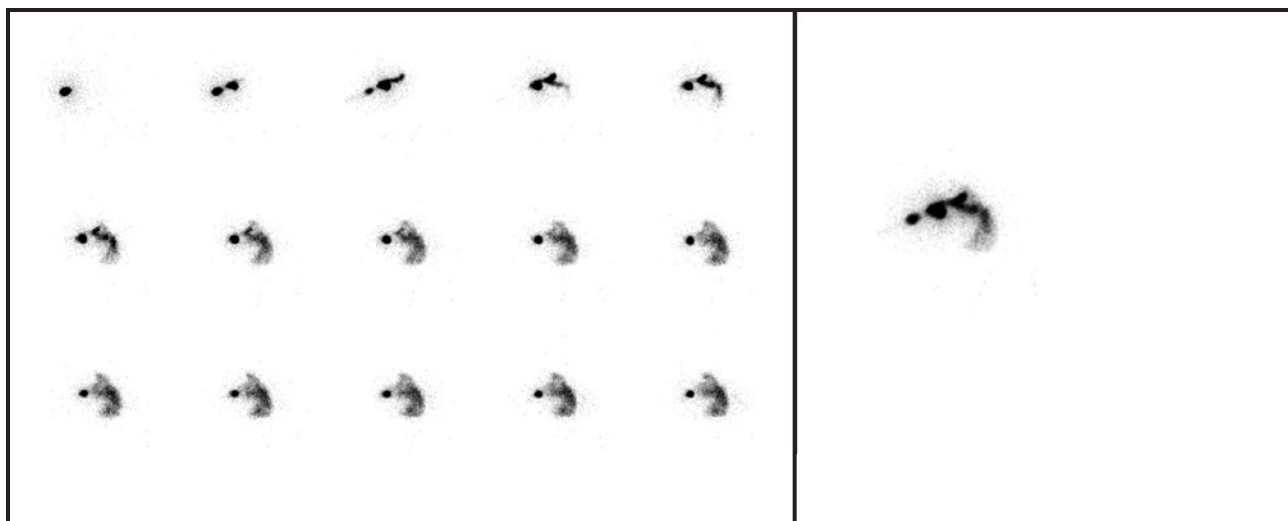


Figure 13.21: Trans-splenic portal scintigraphy study using ^{99m}Tc -mebrofenin in a normal dog

The study was acquired with the dog in right lateral recumbency and reformatted at 2 frames per second. The portal vein is easily visualized within the midabdomen on the first frame. There is normal distribution of the radionuclide in the liver (uniform with a normal size and shape). Note there is virtually no radioactivity seen in the heart because the liver extracted the ^{99m}Tc -mebrofenin on the first-pass.

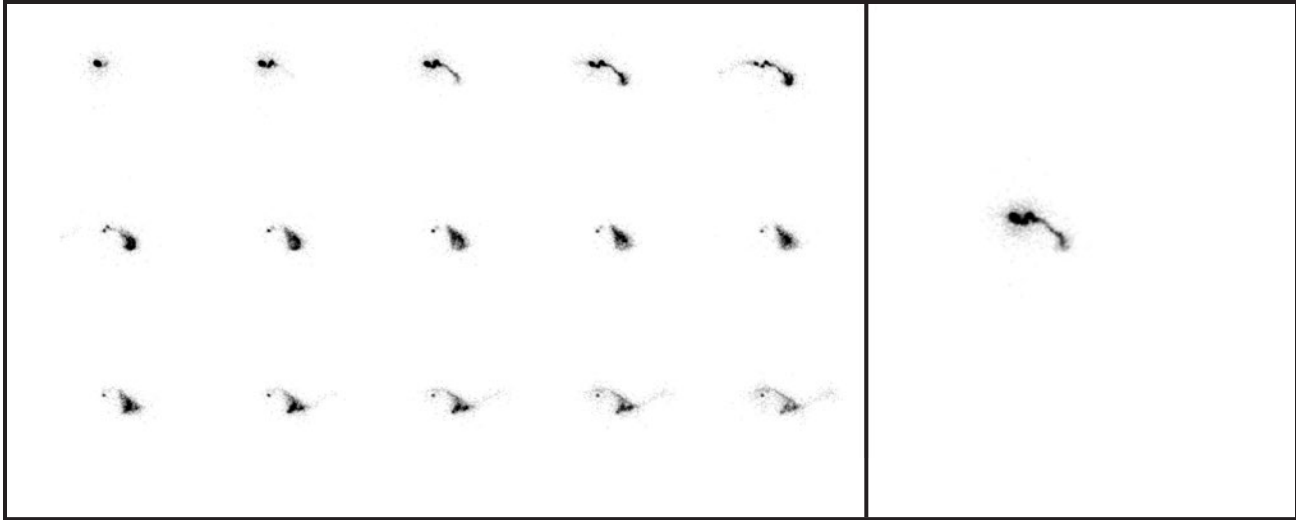


Figure 13.22: Trans-splenic portal scintigraphy study using ^{99m}Tc -mebrofenin in a dog with a congenital, single, extrahepatic portosystemic shunt

The study was done with the dog in right lateral recumbency and reformatted at 2 frames per second. The portal vein is easily visualized within the midabdomen on the first frame. The portosystemic shunt vessel can be entering the caudal vena cava and bypasses the liver completely.

the radiopharmaceutical clears the spleen similar to pertechnetate giving excellent images of the portal vein (Figure 13.21). Unlike pertechnetate, ^{99m}Tc -mebrofenin does not pass through the liver via the hepatic venous system into the caudal vena cava and into the thorax. The radiopharmaceutical is retained by the liver and is gradually cleared into the biliary system with a clearance half-time of 19 minutes.⁵⁰ Dogs with portosystemic shunts have a conspicuously different pattern from normal dogs. The radiopharmaceutical bypasses the liver and is first seen in the heart (Figure 13.22). Over the next several minutes, the liver will accumulate the ^{99m}Tc -mebrofenin from the hepatic arterial delivery of the radiopharmaceutical. Liver function can be determined from the rate of clearance of the ^{99m}Tc -mebrofenin from the blood pool.^{51,52} Transsplenic portal scintigraphy using ^{99m}Tc -mebrofenin will make the diagnosis of portosystemic shunts easy and will also enable quantification of the liver function, which could be helpful for long term prognosis.

shunts. The caveat is that microscopic dysplasias are not seen on a per-rectal or transsplenic portal scintigraphic study. Other imaging modalities, however, would also miss this disorder as the portosystemic shunting is described at the capillary level.

Although a quantitative shunt fraction can be calculated in per-rectal and transsplenic scintigraphy, this should only be interpreted in light of the dynamic imaging study. The shunt fraction should not be used in and of itself for the diagnosis of a portosystemic shunt because of the limitations of these calculations. Transsplenic scintigraphy for the diagnosis of portosystemic shunts, helps to resolve the problems associated with poor count density per-rectal studies that are dependent on the absorption of the radio-tracer from the colon. The technique appears safe and minimally invasive with the possibility of characterizing the anatomy of the portosystemic shunt, as well as evaluating hepatic function when using ^{99m}Tc -mebrofenin.

Summary

Portal scintigraphy provides a rapid, safe, repeatable, and reliable imaging test for evaluating dogs, cats and pot-bellied pigs with macroscopic portosystemic

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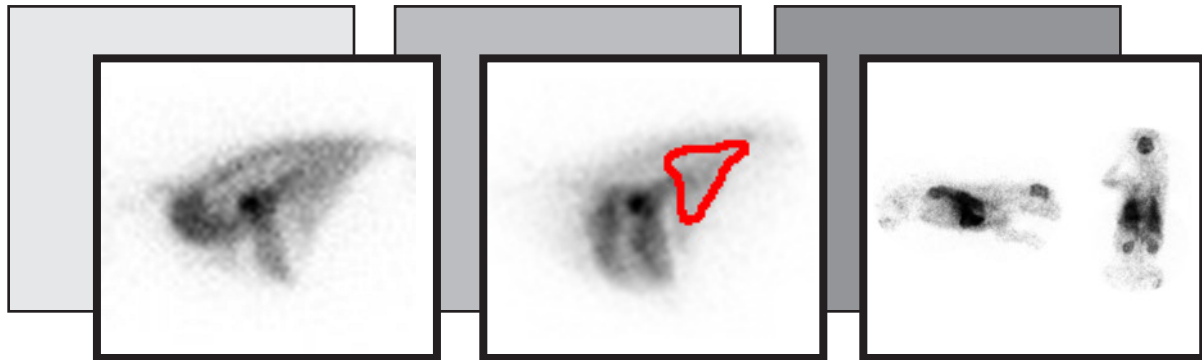
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First Pass Radionuclide Angiocardiology and Cardiac Shunt Analysis

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Introduction

Cardiac applications of nuclear medicine have advantages over other imaging techniques in their ability to noninvasively evaluate cardiac function and determine the direction and magnitude of cardiac shunts.¹⁻⁵ These cardiac procedures require a gamma camera interfaced with a dedicated imaging computer.^{3,6-8} Many imaging computers have the software necessary for acquisition and processing of first pass cardiac studies, but the degree of sophistication varies. Cardiac scintigraphy, despite the obvious advantages and capabilities, is still an underutilized technique in veterinary medicine.

First Pass Radionuclide Angiocardiography

First pass radionuclide angiocardiography (FPRA) is used to evaluate for shunts due to congenital heart defects.⁹⁻¹³ These studies are quick to perform, do not require general anesthesia, and require only peripheral intravenous injections. The information obtained is unique in that the direction and magnitude of the shunt can be estimated.^{13,14} These studies complement echocardiography and thoracic radiographs in helping establish a diagnosis and prognosis.

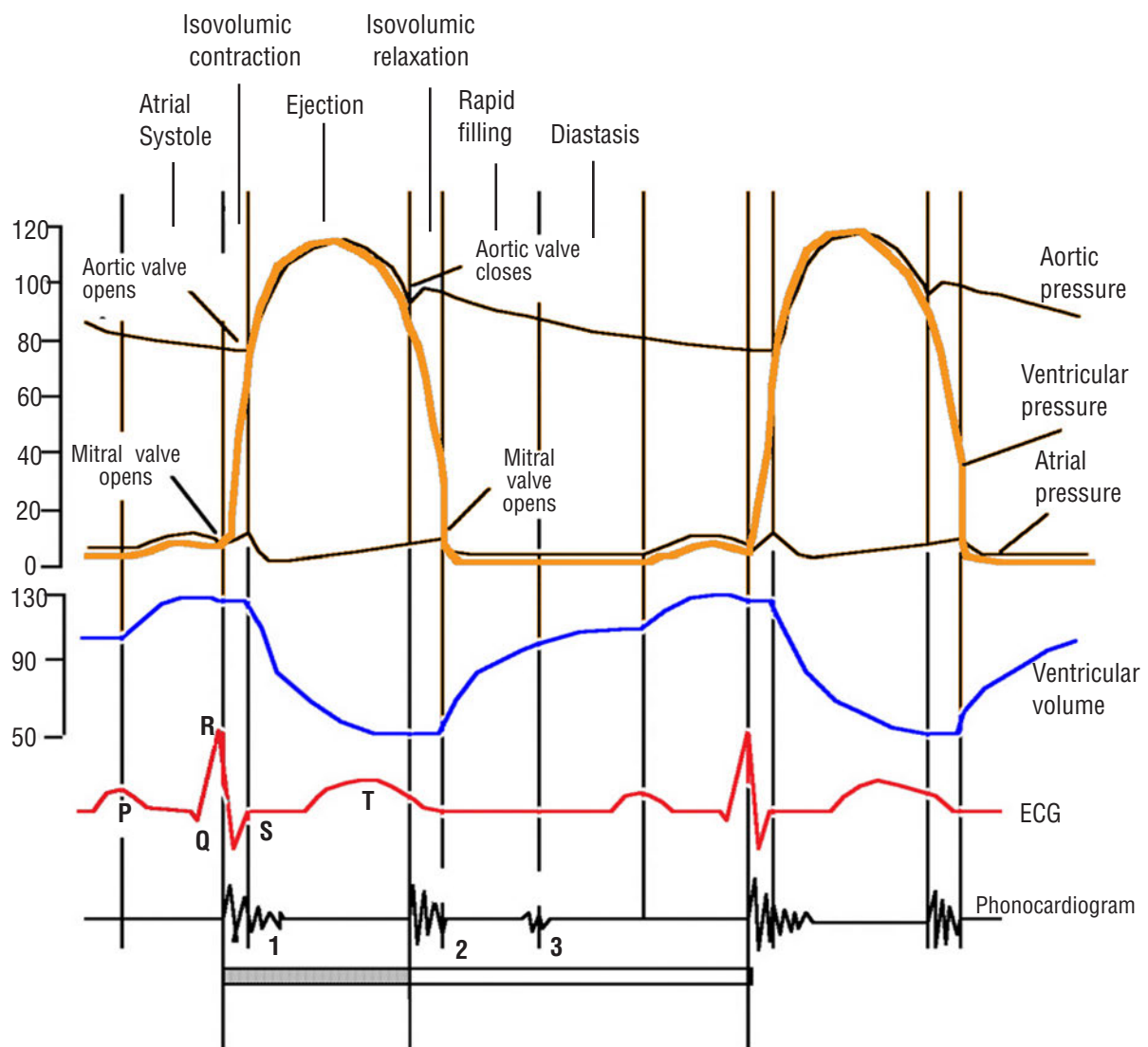


Figure 14.1: Wiggers cycle that shows the atrial, ventricular and aortic pressures (mm Hg) as they match with timing from the heart sounds, the electrocardiogram and ventricular volumes (mL).

These relationships need to be fully understood in order to comprehend the physiologic changes that might occur when interpreting first pass radionuclide angiocardiograms and radionuclide ventriculography.

Table 14.1: Indications for First-Pass Radionuclide Angiocardiology

Diagnosis and quantification of left to right cardiac shunts.
Diagnosis and quantification of right to left cardiac shunts.
Determine the location of shunt (intracardiac versus extracardiac).
Follow-up evaluation of postsurgical correction (patent ductus arteriosus).

Table 14.2 Imaging Parameters for a First-Pass Radionuclide Angiocardigram**Radionuclide**

Sodium ^{99m}Tc -pertechnetate.

^{99m}Tc -DTPA may be used if there is a need for rapid clearance of the radiopharmaceutical from the blood pool. ^{99m}Tc -mebrofenin is another good ^{99m}Tc agent if rapid clearance of the radioactivity is desired for repeated studies on the same day.

Any radiopharmaceutical could be used with the exception of ^{99m}Tc -MAA.

Dose

Species	mCi	MBq
Dog	5-20	185-740
Cat	2-5	74-185
Horse	20-70	740-2,590

Acquisition Parameters

Animal preparation	Sedation (cat, dog, and horse), intravenous catheter, large gauge, short length.
Acquisition parameters	Dynamic frame mode with a minimum 4 frames per second (250 msec per frame); the authors suggest 8 frames per second and reframing the dynamic study into 4 frames per second if necessary.
Matrix	$64 \times 64 \times 16$ or $128 \times 128 \times 16$.
Collimator	Low-energy, all-purpose or low-energy, high-sensitivity if under anesthesia. A diverging collimator should be used for horses if available.
Time of imaging	Dynamic sequence started simultaneously with bolus injection.
Positioning	Dog and cat in left lateral recumbency over the camera; horse standing with the camera positioned along the left side just caudal to the elbow.
View	Left lateral thorax including heart, lung and cranial abdomen.

Anatomy and Physiology

It is imperative that the clinician has a thorough understanding of the normal cardiac anatomy and the possible congenital abnormalities seen in dogs and cats. An understanding of normal cardiac physiology is also necessary for understanding the impact various congenital and acquired abnormalities will have on the blood flow and cardiac output, thereby impacting the first pass study. The Lewis or Wiggers cycle should be reviewed for specifics regarding the mechanical, pressure, and electrical events of the normal cardiac cycle (Figure 14.1). The normal passage of the bolus through the heart will be from the cranial vena cava, right atrium, tricuspid valve, right ventricle, pulmonic valve, pulmonary artery, pulmonary circulation, pulmonary vein, left atrium, mitral valve, left ventricle, aorta, and into the system circulation. The most common congenital defects in the dog include subaortic stenosis, left-to-right patent ductus arteriosus, pulmonic stenosis, ventricular septal defect, tetralogy of Fallot, right-to-left patent ductus arteriosus, and tricuspid dysplasia.

Mechanisms of Localization

Many different radiopharmaceuticals can be used for FPRA. The only requirement is that the radiopharmaceutical must flow passively through the central circulation of the heart and lung.^{1,2,10,13} Radiopharmaceuticals cannot actively concentrate or localize within the heart or lungs. The most commonly used radiopharmaceutical is ^{99m}Tc -pertechnetate. If repeated studies are to be performed on the same day, then a radiopharmaceutical that is rapidly cleared from the blood could be used. ^{99m}Tc -sulfur colloid, ^{99m}Tc -DTPA or ^{99m}Tc -mebrofenin are both cleared quickly from the blood thereby allowing multiple studies in a single day. Most of the radiopharmaceutical used will be eliminated in the urine. If ^{99m}Tc -mebrofenin is used, then its elimination is via hepatic excretion into the intestinal tract. If ^{99m}Tc -pertechnetate is used, then a small quantity will be secreted from the salivary glands and gastric mucosa, both being eliminated in the feces.

The indications for first pass radionuclide angiocardigraphy are summarized in Table 14.1. Routine acquisition parameters for the FPRA are summarized in Table 14.2.

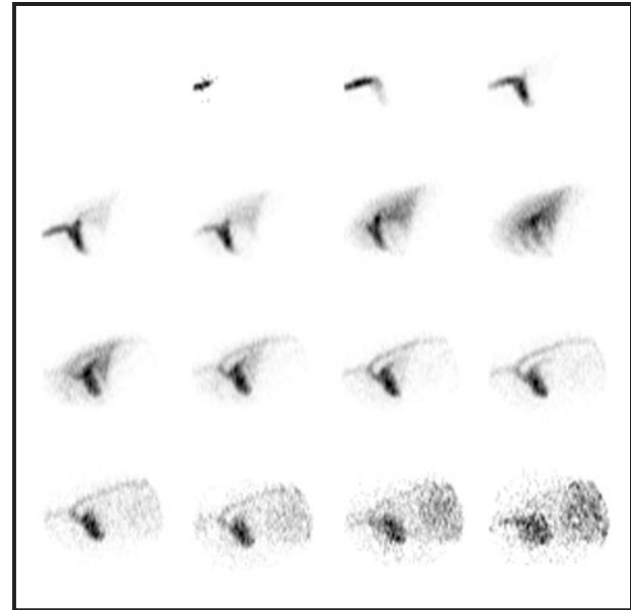


Figure 14.2: First-pass radionuclide angiocardigram in a normal dog

Left lateral images taken at a rate of 4 frames per second. There is normal passage of the radionuclide bolus through the heart and lung. The radionuclide clears from the lung as the bolus of radioactivity transverse the left ventricle and enters the systemic circulation.

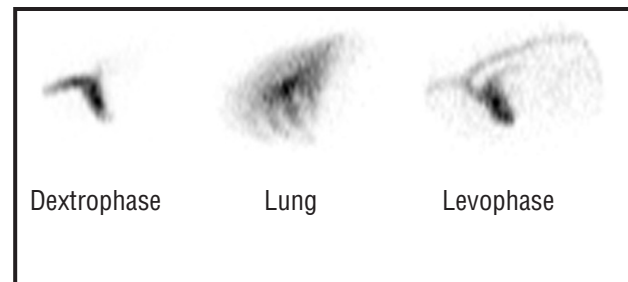


Figure 14.3: Dextrophase, pulmonary phase, and levophase of bolus transit

Summed left lateral images to display the right side of the cardiac radioactivity (dextrophase), pulmonary phase (lung), and left side of the heart and systemic circulation (levophase).

Normal Appearance

A normal FPRA is characterized by the passage of the radiopharmaceutical sequentially through the cranial vena cava, right atrium, right ventricle, pulmonary arteries, lung, pulmonary veins, left atrium,

left ventricle, and finally the aorta (Figure 14.2). The bolus of radioactivity should be discrete and should clear the chambers of the heart and lung following its passage through the pulmonary circulation. The lungs should clear radionuclide sufficiently so that the left side of the heart (left atrium and left ventricle) and the thoracic aorta is clearly seen. The size of the different heart chambers is assessed along with shape and appearance of the aorta and main pulmonary artery. Displaying the dynamic image sequence on the computer monitor in a cinematic motion facilitates analysis of FPRA. The dynamic image sequence is reformatted into three distinct phases. The first phase is the dextrophase that is seen as the radionuclide passes through the right side of the heart. The next phase is the pulmonary phase where the right side of the heart has cleared and the radionuclide is distributed throughout the pulmonary circulation. The last phase is the levophase where the radionuclide bolus has cleared the pulmonary circulation and is seen within the left side of the heart and the aorta (Figure 14.3).

Interpretative Principles

Dextrophase

During the dextrophase, the blood normally passes from the right ventricle into the lung. Both normal dogs and dogs with a left-to-right shunt may appear similar during this phase. Animals with a right-to-left shunt are characterized by the simultaneous appearance of the radioactivity within the right ventricle, main pulmonary artery, and aorta. Radioactivity may also be present within the left ventricle depending on the location of the shunt (Figure 14.4).

Pulmonary Phase

During the pulmonary phase, the radioactive bolus should clear the right ventricle and then become uniformly distributed throughout the pulmonary circulation. There will be greater radioactivity in the caudal and dorsal lung fields because of the greater volume of pulmonary parenchyma and because blood flow to the caudal lung lobes is greater than the remaining lung lobes. Both normal dogs and dogs with a left-to-right shunt may appear similar during the initial portion of this phase. Animals with right-to-left shunts will have less pulmonary radioactivity and

some of radioactivity will be seen within the abdomen via the thoracic and abdominal aorta. If there is persistent radioactivity within the right ventricle during the lung phase, it could be due to: poor injection of the bolus, large volume of the radionuclide, tricuspid dysplasia, pulmonic stenosis, or right ventricular failure.

Levophase

During the levophase, the blood normally passes through the left atrium, left ventricle and aorta. Both normal dogs and dogs with a right-to-left shunt may appear similar during this phase (at least the images of the left atrium and ventricle). An animal with a left-to-right shunt will have prolonged lung radioactivity during the levophase and the pulmonary circulation retains radioactivity. Other causes of prolonged lung radioactivity would include left heart failure, poor injection of the bolus, mitral valve dysplasia and insufficiency, and aortic stenosis (Figure 14.5).

Abnormal First Pass Radionuclide Angiogram

Left-to-Right Shunts

Left-to-right systemic shunts are characterized by prolongation of the radioactivity in the lung as a result of recirculation through the shunt (ventricular septal defect or patent ductus arteriosus), with returning radioactivity to the lung. In a normal animal, the lung should sufficiently clear during the levophase so that the thoracic aorta is unmistakably seen. In animals with left-to-right shunts, the borders of the thoracic aorta are partially or completely obscured. Compare the clearance of the lung phase in Figures 14.2 and 14.6, during the levophase in a normal dog and a dog that has a left-to-right shunt. With careful inspection of the images, the type of shunt can sometimes be diagnosed. The reappearance of the right ventricle during the levophase is characteristic of a large ventricular septal defect (VSD, Figure 14.7). With a large VSD, a significant portion of the shunted blood will distribute throughout the entire right ventricle during the levophase. A small VSD may not be seen because the shunted blood crosses the membranous portion of the interventricular septum in the area of the pulmonary outflow tract of the right

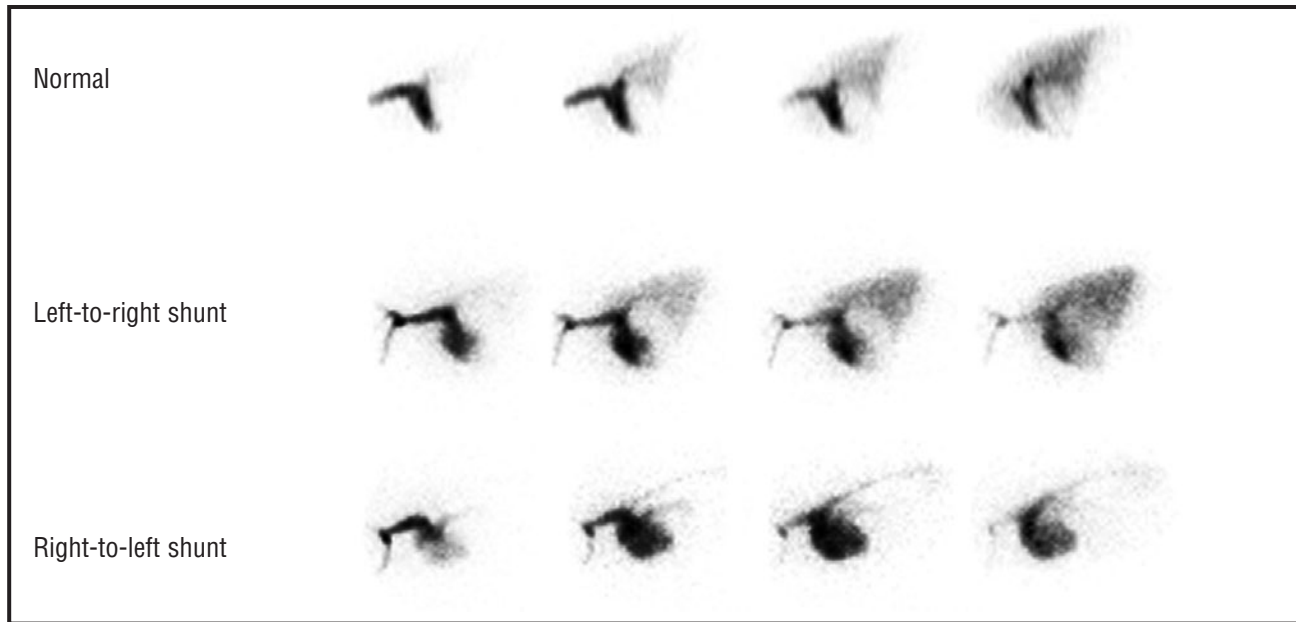


Figure 14.4: Dextrophase and pulmonary phase images of a first-pass radionuclide angiogram in a normal dog, and in dogs with left-to-right and right-to-left shunts

The dextrophase in the normal dog and the dog with left-to-right appear similar. In the dog with the right-to-left shunt, radionuclide delivery to the pulmonary and systemic circulations is simultaneous. In the example above, note the filling of the right and left ventricle in the dog with the right-to-left shunt indicating a VSD.

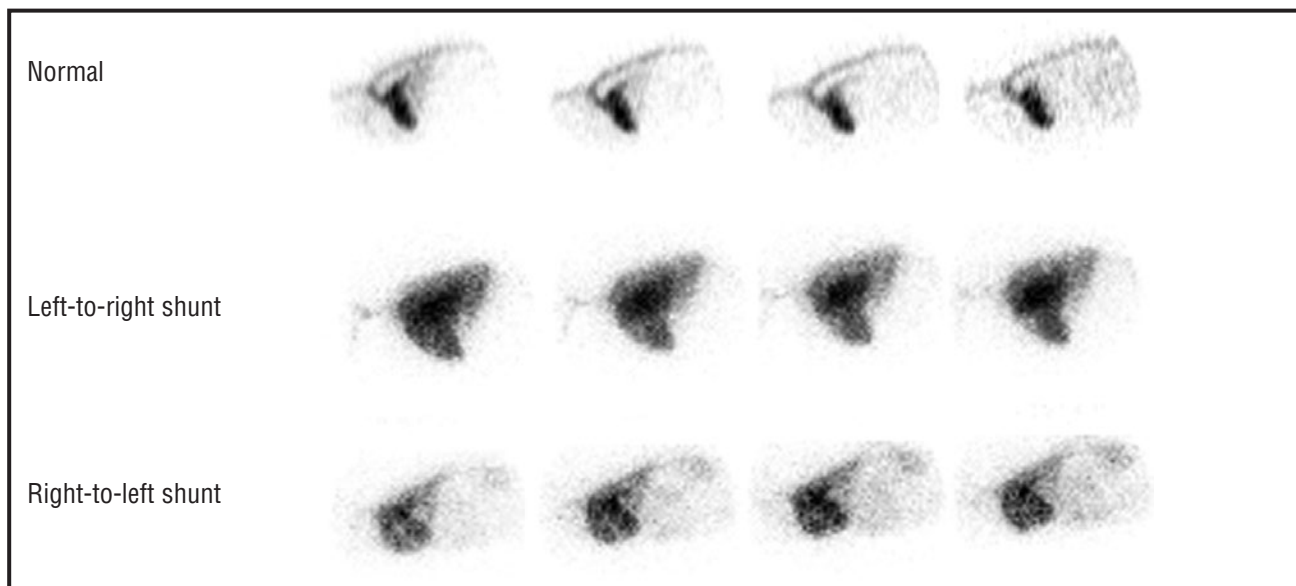


Figure 14.5: Levophase images of a first-pass radionuclide angiogram in a normal dog and in dogs with left-to-right and right-to-left shunts

In the normal dog (top, Normal), notice how distinct the left side of the heart and aorta are. The pulmonary phase has cleared. In the dog with the left-to-right shunt, notice how the pulmonary phase persists consistent with pulmonary recirculation. The left atrium and ventricle are enlarged consistent with volume overload. In the dog with the right-to-left shunt, the radioactivity is present to a greater degree in the abdominal aorta and kidneys from the early delivery of the radioactivity to the systemic circulation and there is less radioactivity in the pulmonary circulation.

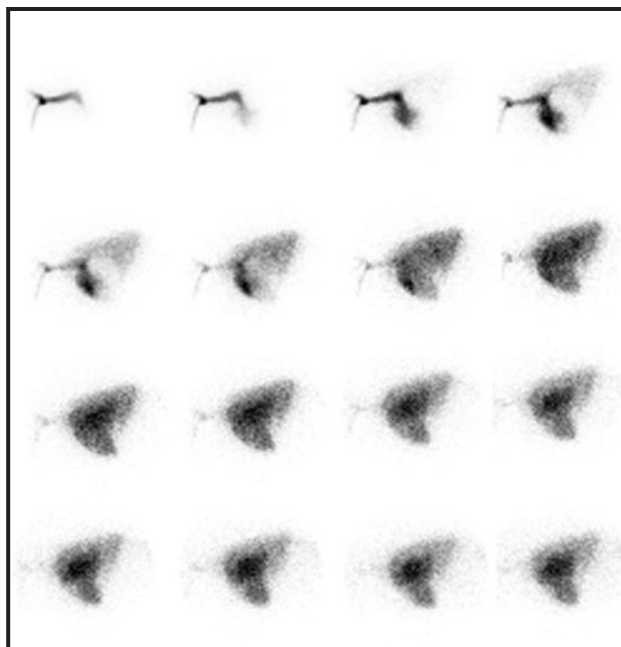


Figure 14.6: First-pass radionuclide angiogram in a dog with a left-to-right patent ductus arteriosus

There is persistence of the pulmonary phase and levophase consistent with recirculation. The left atrium and ventricle are enlarged consistent with volume overload.

ventricle. The shunted radioactivity quickly passes into the pulmonary artery without completely mixing with the entire right ventricular volume. The authors have not seen cases of left-to-right atrial septal defects, but one would also assume a reappearance of the right ventricle during the levophase. A left-to-right patent ductus arteriosus (PDA) will shunt blood from the descending aorta to the main pulmonary artery. In this case, the shunting occurs outside the heart and the right ventricle is not involved in the recirculation and therefore will not be seen during the levophase. (Figure 14.7).

Quantitative Evaluation of Left-to-Right Shunts

The magnitude of a left-to-right shunt may be measured by quantifying radioactivity in the lung during the levophase.^{1,4,9,10,13,15} To create a pulmonary time-activity curve, a composite image of the thorax is made by summing the frames of the dynamic acquisition. This composite image is of high count density, and anatomic features of the thorax are easily recognizable. A region of interest (ROI) is

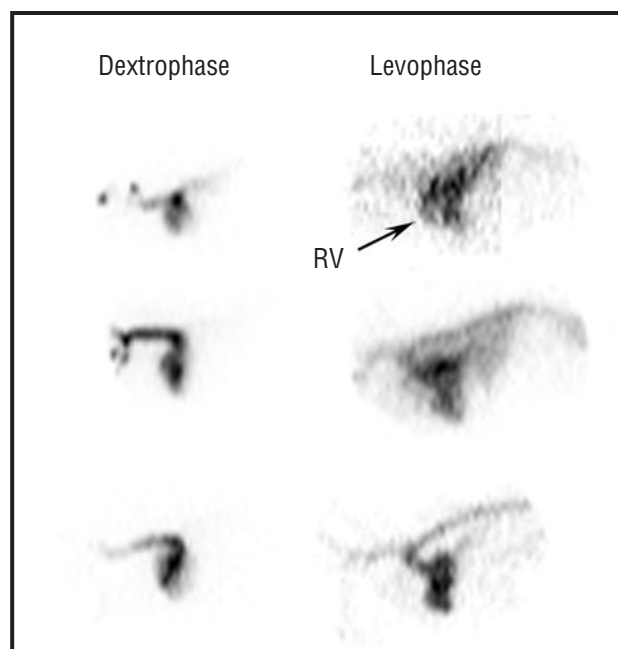


Figure 14.7: First-pass radionuclide angiogram in three dogs

The two images at the top are from a dog with a left-to-right ventricular septal defect. Note the right ventricular radioactivity that reappears during the levophase (arrow). The two images in the middle are from a dog with a left-to-right patent ductus arteriosus, where the right ventricle is not seen during the levophase. The bottom two images are from a normal dog for comparison.

drawn over the caudodorsal lung field taking care to exclude areas where the lung ROI would overlap with the aorta, main pulmonary vessels, or the liver (Figure 14.8). This lung ROI is then overlaid on each image of the dynamic acquisition enabling the generation of a pulmonary time-activity curve. A sharp, narrow peak of radioactivity that drops to a low level as the radioactive bolus clears the pulmonary circulation characterizes a normal pulmonary time-activity curve. Gradually the time-activity curve will rise to a basal level as the radionuclide equilibrates in the blood pool (Figure 14.9). Residual radioactivity in the normal lung following the bolus passage represents systemic arterial radioactivity in the lung (bronchial branch of the bronchoesophageal artery from the right fifth intercostal artery from the descending aorta) and superimposed thoracic wall radioactivity. A time-activity curve in an animal with a left-to-right shunt is characterized by multiple recirculation peaks (Figure 14.10).

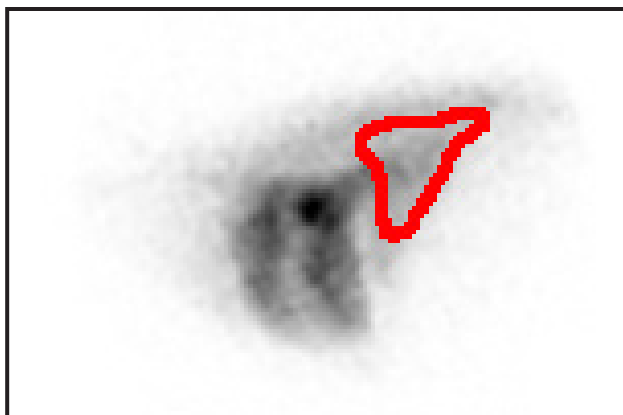


Figure 14.8: Summed image made from the dynamic images of a first-pass radionuclide angiogram

A ROI has been drawn over the lung parenchyma. The ROI should be drawn as large as possible to obtain the best counting statistics and should not overlay the aorta, liver, or heart.

Morphologic Features of Congenital Heart Disease

The most important information derived from the series of images of the first pass radionuclide angiography is the sequence of bolus passage through the central circulation of the heart and lung. However, morphologic features of the heart that may not be seen on survey radiographs may be visualized. First pass radionuclide angiography has an advantage over radiographs in that there is no superimposition of overlying structures and one is evaluating the radioactivity as it passes through the central circulation. Poststenotic dilation of the pulmonary artery (Figure 14.11) or the proximal aorta (Figure 14.12) is easily recognized in cases of pulmonic stenosis or aortic stenosis, respectively.

QP:QS Ratio

The radioactivity in the lung peaks as the bolus passes through the pulmonary vasculature then rapidly decreases to a low level. In animals with left-to-right shunts, blood returns to the lungs immediately following its passage through the left side of the heart so that the pulmonary time-activity curve has a second peak.^{1,2,9} The magnitude of the shunt can be measured by calculating the area under the initial and second peaks. The area under a peak of a time-

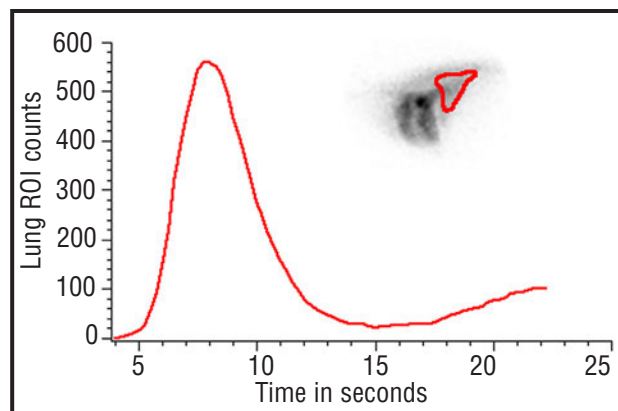


Figure 14.9: Pulmonary time-activity curve in a normal dog

The pulmonary radioactivity increases and then sharply decreases to a low level following radioactive bolus transit during the first pass through the pulmonary circulation.

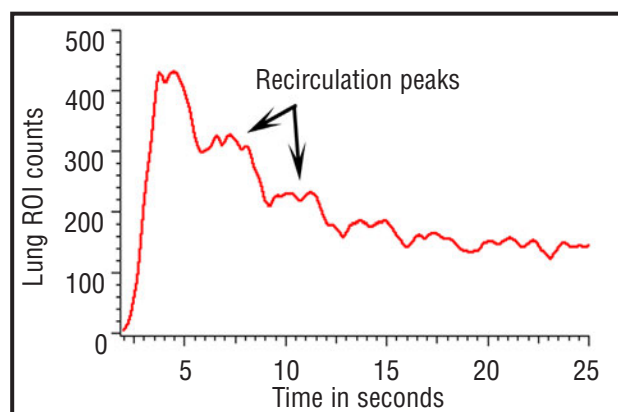


Figure 14.10: Pulmonary time-activity curve in a dog with a left-to-right shunt

Note the multiple recirculation peaks spaced at regular intervals indicating recirculation of the radioactivity through each subsequent pass during the actual left-to-right shunt.

activity curve will be proportional to volume. The passage of a bolus under an ROI creates a specifically shaped curve characterized by a rapid rise and a longer downslope. Mathematically, this curve can be fitted using a gamma variate equation (Figure 14.13). The analysis procedures require the operator to mark the beginning of the pulmonary curve and the last point of the curve before the recirculation peak begins. This usually entails marking the upslope at a point approximately 10% between baseline and

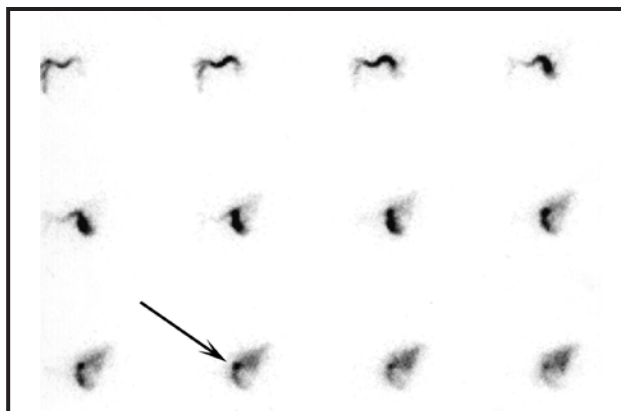


Figure 14.11: Dextrophase and pulmonary phase images from a first pass radionuclide angiogram in a dog with pulmonic stenosis

Note the focal accumulation of the radionuclide in the region of the main pulmonary artery (arrow). This corresponds to an area of poststenotic dilation of the main pulmonary artery.

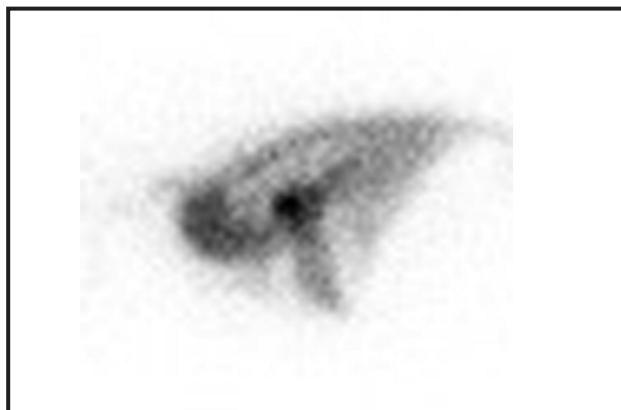


Figure 14.12: Summed image that includes parts of the levophase and pulmonary phase from a first pass radionuclide angiogram in a dog with subaortic stenosis

Note the marked enlargement of the ascending aorta and aortic arch consistent with poststenotic dilation. (Courtesy of Dr. Anne Bahr, Texas A&M University)

peak. The end point is marked distal to the peak at a point 70% to 80% of the peak value (Figure 14.14). The computer uses this portion of the data to fit a curve using a gamma variate formula. The fitted curve should closely approximate the peak of the

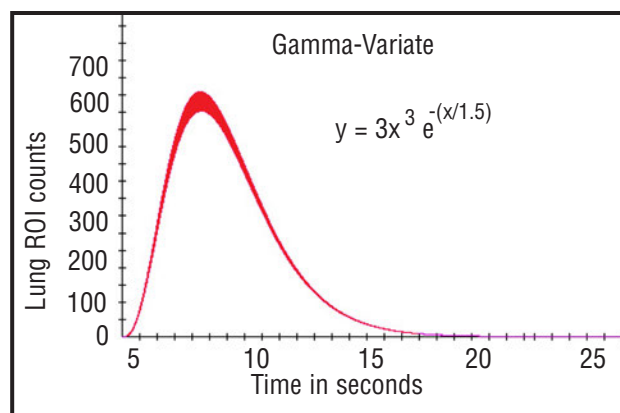


Figure 14.13: Example of a gamma variate curve

Note the rapid rise and slower decline of the curve.

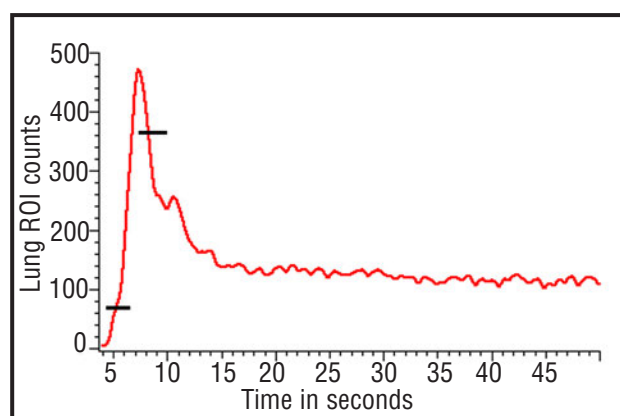


Figure 14.14: A pulmonary time-activity curve showing the start and stop points for the gamma variate fit analysis

first pass of the pulmonary curve. If the fit is not good, the end points can be adjusted so that fitting of the curve is repeated until a good fit is established. The fitted gamma variate curve simulates an ideal bolus passage with the end of the curve going to 0 counts. After a good fit to the first pulmonary peak is obtained, the data from the fitted pulmonary curve is subtracted from the pulmonary time-activity curve on a point-by-point basis. The residual curve represents the systemic curve. During the systemic phase, the radioactivity recorded in the lung ROI should represent systemic arterial blood flow to the lung and the overlying body wall by the arterial supply previously described. The systemic curve is fitted using

the same endpoints as described for the pulmonary curve and a second gamma variate is used to fit the bolus peak of the residual systemic curve.^{10,13} The areas under the two fitted curves are then calculated. If the animal has a left-to-right shunt, the systemic curve will be larger because it will contain the normal systemic blood plus all the blood recirculated through the shunt (Figure 14.15). The magnitude of increase in the systemic curve will be proportional to the size of the shunt. Quantification of the areas under the initial pulmonary curve (Q_p) and the systemic curve (Q_s) provides an assessment of the magnitude of the shunt.

$$QP:QS = Q_p/Q_p - Q_s$$

Where Q_p = area under pulmonary curve; Q_s = area under systemic curve.

The $QP:QS$ ratio can never be less than 1 because there will always be some systemic blood flow which makes the denominator smaller than the numerator. As the size of the shunt increases the denominator in the equation will become smaller ($Q_p - Q_s$) thus increasing the $QP:QS$ ratio. Normal animals should have a pulmonary to systemic flow ratio ($QP:QS$) of 1.0 to 1.2. A $QP:QS > 1.2$ is considered abnormal. The relationship between $QP:QS$ and the percentage of blood flowing through the shunt is shown in Figure 14.16.

Errors in calculation can be made by inexperienced personnel. The analysis procedure works well in large magnitude shunts that have large, easily recognized recirculation peaks. In these cases, the imaging computer readily accomplishes fitting of the pulmonary and systemic curves and the results are generally reproducible. In smaller magnitude shunts, the fitting of the systemic curve becomes more difficult because it may be hard to recognize the beginning points and the endpoints. As a rule of thumb, the width of the pulmonary and systemic curves should be similar (systemic is slightly wider than pulmonary). If the fitted systemic curve is substantially wider than the fitted pulmonary curve, then an error has probably been made in defining its borders and the $Q_p - Q_s$ ratio is probably not valid. Intra-observer variability can be decreased by practicing so that the circulation peaks become easier to recognize.

C2:C1 Ratio

Shunt analysis procedures using $QP:QS$ are not

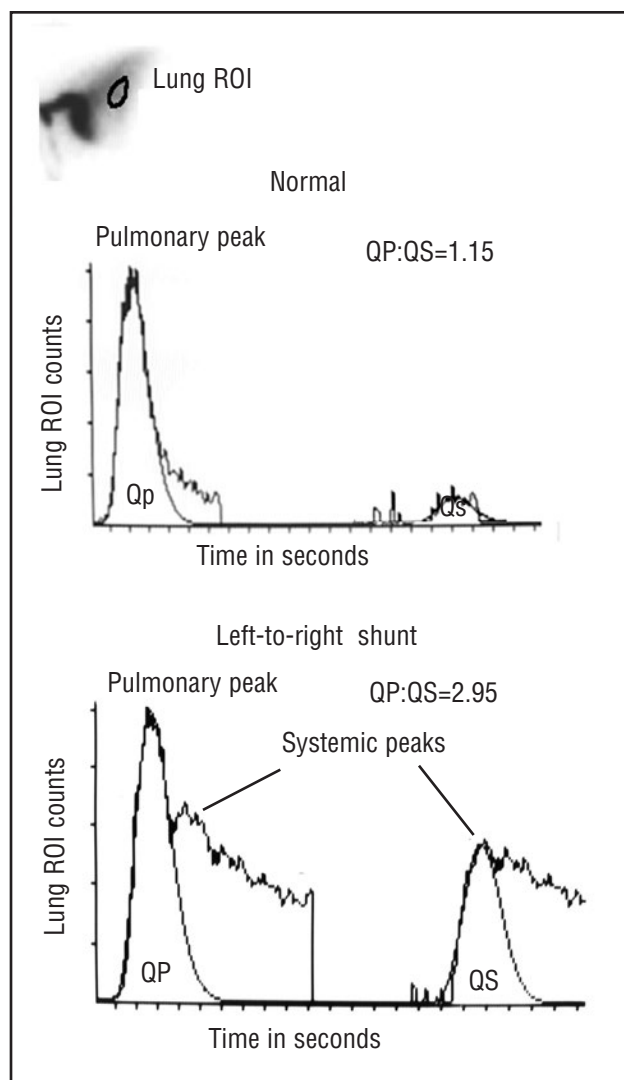


Figure 14.15: Pulmonary time-activity curves in a normal dog and a dog with a left-to-right shunt

In both dogs, a $QP:QS$ analysis has been performed. Note the size difference in the Q_s portion of the time-activity curves. This is due to the recirculation peak in the dog with the left-to-right shunt. The $QP:QS$ ratio was calculated to be 1.15 for the normal dog and 2.95 for the dog with the left-to-right shunt.

always available on all nuclear medicine imaging computers.^{10,13} The gamma variate fitting can be difficult to perform. A simpler alternative procedure is the $C2:C1$ ratio. $C2:C1$ incorporate the ratio of lung counts recorded at specific time intervals during the lung peak and during the washout period. In a normal patient, the lung radioactivity should rapidly

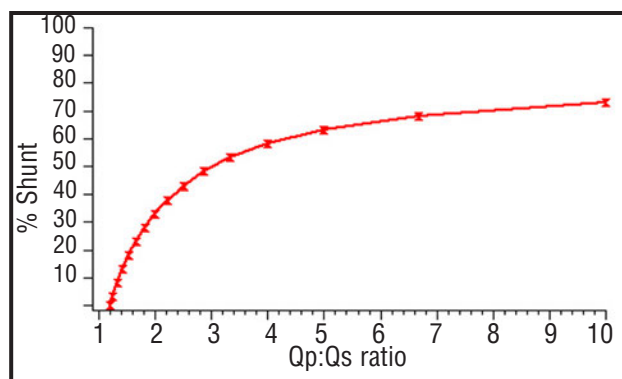


Figure 14.16: Relationship between shunt fraction and QP:QS Ratio

This mathematical model assumes that a normal dog with no shunt would have a QP:QS ratio of 1.2.

clear and the count obtained during this washout period should reflect how well the lung cleared. In the case of a left-to-right shunt, the recirculation of the radionuclide will keep the lung radioactivity at a higher level. In this manner, the ratio (C2:C1) provides an estimate of shunt size. The following time points and counts are determined from the lung radioactivity curve (Figure 14.17).

C1: maximum pulmonary counts (peak of the pulmonary curve):

Tmax: time from initial appearance of bolus until peak counts (C1).

C2: counts related to the time-activity curve taken at 2 x Tmax.

A C2:C1 ratio of less than 0.5 is considered normal. Values above this range are seen with left-to-right shunts. In a series of clinical cases with left-to-right shunts the C2:C1 ratios ranged from 0.23 to 0.75. The graph in Figure 14.18 shows the C2:C1 ratio of normal dogs and dogs with left-to-right shunts. Figure 14.19 is based on the same group of dogs using QP:QS analysis. The separation of the normal and abnormal groups was better when using the QP:QS analysis. In humans, QP:QS correlates well to oximetric studies whereas C2:C1 ratios do not.

Factors Affecting FPRA

Any factor that prolongs the transit of the radioactive bolus through the central circulation can result in an abnormal QP:QS or C2:C1 value. Animals in

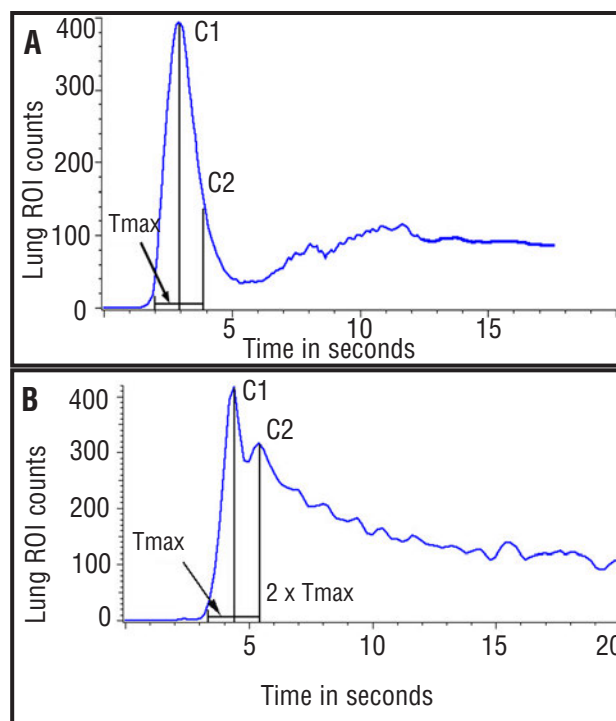


Figure 14.17: Graphs showing the calculation of C1:C2 in a normal dog and a dog with a left-to-right shunt

A, Pulmonary time-activity curve for a normal dog. Tmax is the time from the beginning of the upslope of the pulmonary time-activity curve to the point of maximum pulmonary radioactivity (C1). C2 is the pulmonary radioactivity at 2 times Tmax. **B**, Pulmonary time-activity curve from a dog with a left-to-right shunt. Note the radioactivity at C2 is much higher than that seen in the normal dog.

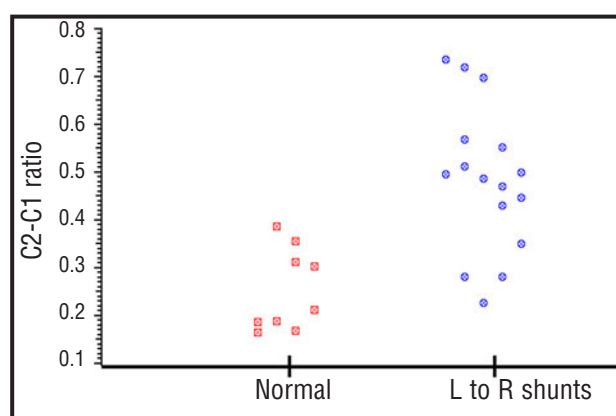


Figure 14.18: A scatter plot showing the C2:C1 values in normal dogs and dogs with left-to-right shunts

Note the overlap of values between the two groups.

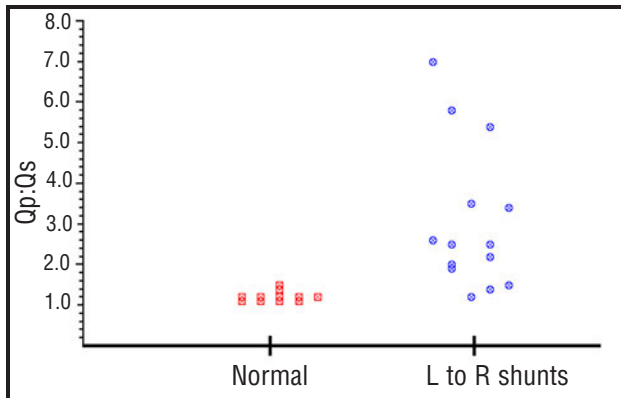


Figure 14.19: Scatter plot showing the QP:QS values in normal dogs and dogs with left-to-right shunts.

Note the QP:QS analysis separates the two populations better than the C2:C1 ratio shown in Figure 14.18.

heart failure will have a prolonged cardiopulmonary transit time that can result in abnormal QP:QS or C2:C1 values. The prolonged transit time results in slow gradual decline in pulmonary radioactivity. The time-activity curve can be used to differentiate between patients in heart failure and those with left-to-right shunts. The presence of a recirculation peak on the time-activity curve is an indication that a left-to-right shunt exists. If there is no second (recirculation) peak but just a slow, gradual drop in pulmonary radioactivity, then heart failure is suspected (Figure 14.20). The heart failure may be secondary to a left-to-right shunt or may be due to other causes.

The FPRA technique assumes that the bolus was delivered in a “tight,” discrete fashion. Most first pass analysis programs require an evaluation of the bolus quality. The tightness of bolus is determined by drawing a region of interest at the level of the cranial vena cava. The ROI is applied to the dynamic data set and a time-activity curve created. A tall peak with a narrow base characterizes a good bolus. A slower infusion delivery of the radiopharmaceutical would have a short peak with a broad base. A biphasic injection would have two peaks. The bolus can be evaluated by the full width at half maximum (FWHM) method. The width of the peak is described in terms of time (milliseconds or seconds) at 50% of the peak value. A good bolus is determined by a FWHM of less than 1 second. The first pass radionuclide angiographic study is not considered valid if the FWHM is greater than 2 seconds.

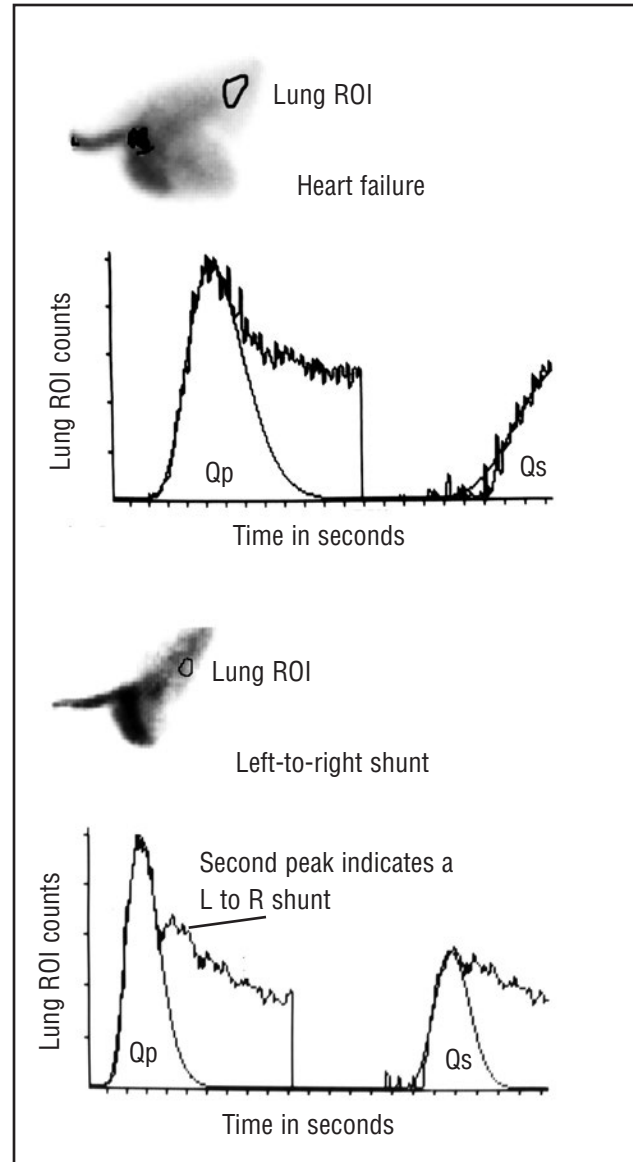


Figure 14.20: QP:QS analyses in a dog in heart failure (upper curve) and a dog with a left-to-right shunt (lower curve)

The dynamic images of these two dogs were similar, both showing persistent pulmonary radioactivity during the levophase. Note that both dogs have an abnormal QP:QS ratio. It is important to look at the pulmonary time-activity curves. The dog in heart failure has a progressive slow decline in pulmonary radioactivity. The dog with the left-to-right shunt has a discrete recirculation peak (arrow). In this example, the dog in heart failure had persistent pulmonary radioactivity during the levophase and an abnormal QP:QS ratio. However, the presence of a left-to-right shunt cannot be confirmed without seeing the recirculation peak on the pulmonary time-activity curve.

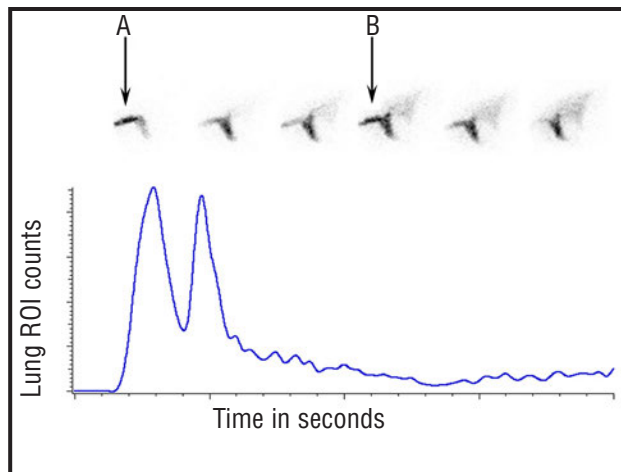


Figure 14.21: Time-activity curve from the cranial vena cava in a normal dog

This is an example of a biphasic bolus. As the bolus passed through the lungs, it would have had the appearance of a recirculation peak and could have rendered a false-positive diagnosis of left-to-right shunt. Bolus quality must be tested during each study.

Poor bolus injections can also give an erroneous indication of the left-to-right shunt. A three-way stopcock should be used to inject the radiopharmaceutical with a large, rapid saline flush. If the volume of the radiopharmaceutical is greater than the volume that can be held by the apparatus (extension tube and stopcock), then the bolus of radionuclide will be split and a biphasic bolus will be created (Figure 14.21). The speed or force which the radionuclide is injected can also influence the quality of the bolus. If injected too slowly, the bolus will be prolonged and the dextrophase, lung phase, and levophase will not be temporally separated. The pulmonary time-activity curve will have a broad base, which can overlap with the systemic peak. If the bolus is injected too forcibly into the cephalic vein, the radioactive bolus will be separated between the cephalic or omobrachial vein and the axillobrachial vein. Because the omobrachial and cephalic veins enter the venous system cranial to the axillobrachial, the bolus may arrive at the heart as two discrete boluses at separate times. Figure 14.22 shows the separation of the bolus at this venous bifurcation. A vigorous injection may also force a portion of the bolus in a retrograde direction into the external jugular vein, also resulting in splitting of the radionuclide and a biphasic bolus. When



Figure 14.22: Example of a split bolus due to a rapid injection

The splitting of the bolus results in either a biphasic bolus or a prolonged bolus. This could artificially create a recirculation peak.

the biphasic bolus traverses the lung, it will appear as a recirculation peak in the time-activity curve.

Shunt Analysis Using Macroaggregated Albumin

Cyanotic heart disease is due to congenital cardiac defects resulting in pulmonary to systemic shunting of blood.¹⁶ The common causes of right-to-left shunts in small animals include tetralogy of Fallot, reverse right-to-left patent ductus arteriosus, or a ventricular septal defect with pulmonary hypertension (Eisenmenger physiology and/or syndrome).¹⁶ All of these conditions can cause significant systemic arterial oxygen desaturation and clinical signs related to tissue hypoxia. As a result, polycythemia develops secondary to the renal release of erythropoietin secondary to hypoxia sensed by the kidneys. Diagnosis of right-to-left cardiac shunts can be difficult and may require invasive cardiac catheterization. Nuclear scintigraphy is a complementary study and is most useful when results are compared with echocardiographic and radiographic evaluations.

Mechanism of Localization

^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) is the radiopharmaceutical used for right-to-left shunt analysis. ^{99m}Tc-MAA is routinely used for pulmonary perfusion scintigraphy. The radiopharmaceutical localizes within the pulmonary capillary bed because of capillary blockade.^{2,14,17} The MAA particles have a mean size of 40 μ m with a range of 10 to 150 μ m. When these particles are injected intravenously, they lodge in the first capillary bed

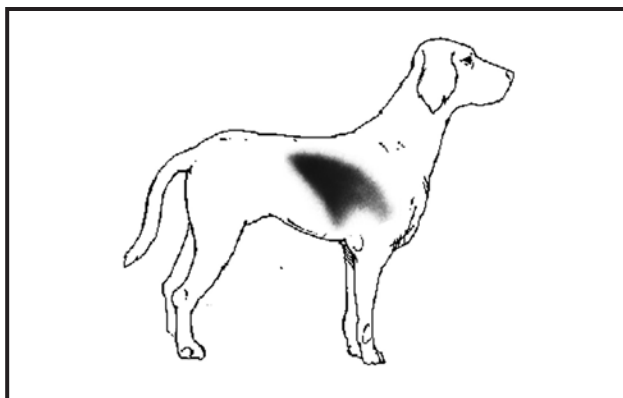


Figure 14.23: Right lateral image of a normal dog (actual image with schematic of dog overlaid) after injection of ^{99m}Tc -MAA

Note the radioactivity is confined to the lung.

encountered. Normally this is the pulmonary capillary bed. The capillary occlusion is temporary, but it is recommended that the number of particles injected be limited so that $< 0.1\%$ of the entire pulmonary capillary bed is occluded. As the label dissociates, the majority of the oxidized $^{99m}\text{TcO}_4^-$ is excreted by the kidneys, with some removal of MAA occurring by pulmonary macrophages. In humans, the recommended number of particles used for lung scintigraphy is 200,000 to 700,000, which represent one-tenth of a standard macroaggregated albumin (MAA) kit. For imaging a right-to-left shunt, the number of particles recommended in humans is 60,000 to 100,000. Specific criteria for use of ^{99m}Tc -MAA in veterinary patients have not been established but the number of particles should not exceed the recommendations used in human imaging.

The indications for using ^{99m}Tc -MAA to evaluate

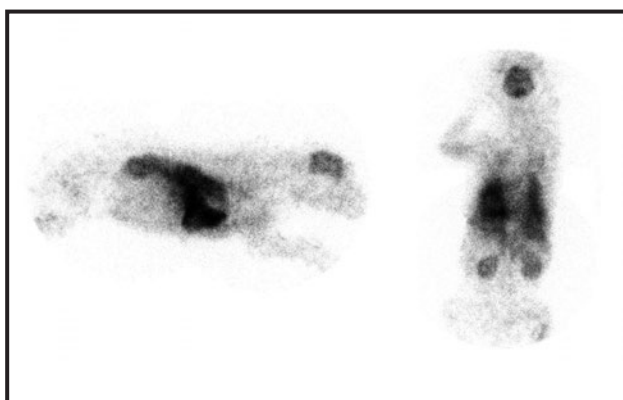


Figure 14.24: Right lateral and dorsal images of a dog after injection of ^{99m}Tc -MAA

This dog had an intracardiac right-to-left shunt. Note that a significant portion of the radioactivity is outside the lung in both the cranial and caudal regions of the dog. The kidneys and brain have higher intensity uptake than other tissues.

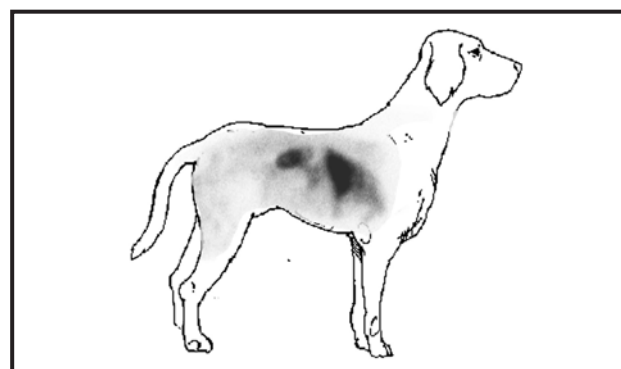


Figure 14.25: Right lateral image of a dog after injection of ^{99m}Tc -MAA

This dog has a right-to-left PDA. Note that the systemic radioactivity is confined to the trunk and rear limbs. Because the shunt occurs distal to the branches of the brachiocephalic trunk and left subclavian artery, none of the shunted blood goes to the front legs, neck, or head.

Table 13.3: Indications for ^{99m}Tc -MAA Shunt Analysis

Diagnosis and quantification of right to left cardiac shunts.
Differentiation of a right-to-left extracardiac (reverse PDA) or from an right-to-left intracardiac shunt (tetralogy of Fallot or Eisenmenger physiology/syndrome).

Table 14.4: Imaging Parameters for ^{99m}Tc -MAA Scintigraphy for the Evaluation and Quantification of Right-to-Left Shunts**Radionuclide** ^{99m}Tc -macroaggregated albumin (MAA).**Dose**

Species	mCi	MBq
Dog	1-3	37-111
Cat	1-3	37-111

Acquisition Parameters

Animal preparation	None.
Acquisition parameters	Static frame mode acquisition that is count limited. Total image counts of 300,000 should be obtained. If counts for the entire animal cannot be obtained in one view, then a time-based acquisition need to be obtained.
Matrix	$256 \times 256 \times 16$.
Collimator	Low-energy, all-purpose.
Time of imaging	Five minutes following intravenous injection.
Positioning	Patient is placed in right lateral recumbency over the gamma camera for the lateral images and in dorsal recumbency for dorsal images.
Views	Right lateral and dorsal images (include the entire animal if possible).

a patient with a right-to-left shunt are summarized in Table 14.3. The routine acquisition parameters for FPRA are summarized in Table 14.4.

Normal Appearance

The normal study should have the appearance of a normal lung scan. The radiopharmaceutical should be uniformly distributed within the pulmonary parenchyma. There should not be radioactivity outside the pulmonary parenchyma (Figure 14.23).

Principles of Interpretation

In patients with a right-to-left cardiac shunt, a portion of the radiopharmaceutical will bypass the pulmonary circulation and lodge in peripheral capillaries. The kidneys and brain will show the most prominent uptake as these organs receive a large percentage of the cardiac output (Figure 14.24). The location of the shunt can also be determined.¹⁸ Because the radiopharmaceutical follows the same path of shunting

blood, a reverse (right-to-left) PDA results in the passage of ^{99m}Tc -MAA into the systemic circulation distal to the brachiocephalic trunk and left subclavian artery. The distribution of the ^{99m}Tc -MAA is limited to the peripheral capillaries of the trunk and rear limbs. The head and thoracic limbs will be void of the ^{99m}Tc -MAA (Figure 14.25). If the location of the shunt is intracardiac, as in a right-to-left VSD, the ^{99m}Tc -MAA will be distributed throughout the entire body. The absence of radiopharmaceutical distribution in the cerebral hemispheres is a good indicator of the presence of right-to-left PDA. The severity of the shunt may be determined by quantifying the pulmonary and extrapulmonary radioactivity from a whole body lateral image.

The percent of shunted blood is calculated from the following formula:

$$\% \text{ Right-to-left Shunt} = \left(\frac{\text{Total Body Counts} - \text{Lung Counts}}{\text{Total Body Counts}} \right) \times 100$$

Summary

The use of first pass studies can be helpful in the complete workup of cardiac patients. Additional lesions may be identified in small animals with congenital heart defects that are complex and in which the anatomy is severely distorted on echocardiographic examination. First-pass studies can also be used for right ventricular function studies and calculation of first pass ejection fraction. Gamma variate fit analysis of first-pass studies will allow for the quantification of a left-to-right shunt. Follow-up procedures can then be done to determine persistence of blood flow or recanalization of a PDA.

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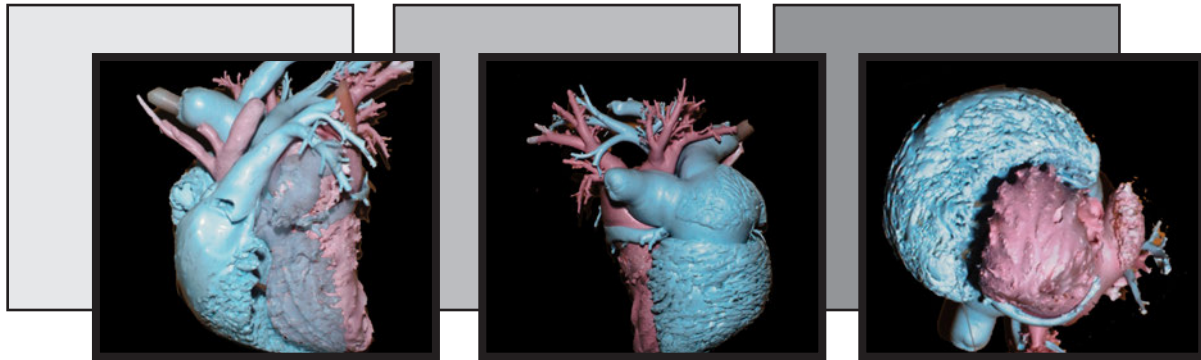
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Gated Radionuclide Ventriculography

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Introduction

The two most common imaging techniques used to evaluate cardiac function noninvasively in humans include echocardiography and gated radionuclide ventriculography (RNV).¹⁻¹⁶ By far the most common method to evaluate cardiac function is the echocardiogram, but RNV has many advantages. Because the RNV images represent a composite of multiple cardiac cycles, the derived indices of ventricular function represent an average function and are not influenced by beat-to-beat variability.^{7,12,14-17} In addition, the images represent cardiac blood pool changes that are independent of image slice position. The RNV study provides data that approximate true global cardiac function. Radionuclide ventriculograms have been used in dogs and cats to evaluate cardiac function in both clinical and research settings.^{1,6,8,12,18-20} Significant correlation has been shown between the indices derived from the RNV and afterload factors, such as hypertension or increased vascular resistance.^{1,8,10} Studies have shown the value of RNV in the evaluation of both left and right ventricular function and assessing the severity of mitral valve regurgitation in dogs with acquired mitral valve endocardiosis.¹⁹

Mechanism of Localization

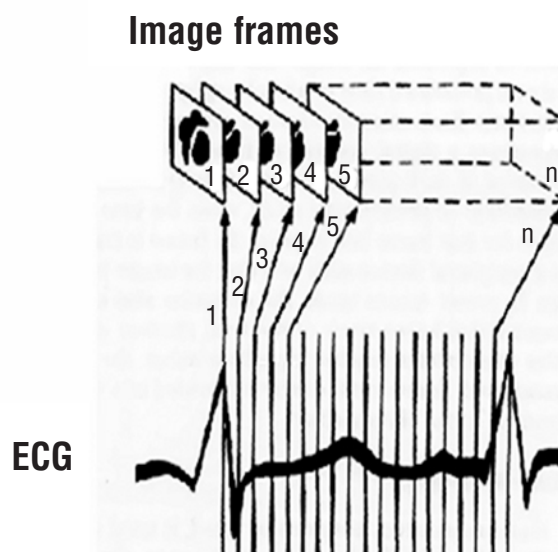
The radiopharmaceutical for the radionuclide ventriculogram is an equilibrium blood pool agent. After injection, the radiopharmaceutical evenly distributes throughout the animal's vascular space.²¹ Following equilibration with the blood pool, the radioactivity within a given quantity of blood is directly related to its volume; therefore, changes in radioactivity within the cardiac ventricles will depict changes in ventricular volume.

The term gated radionuclide ventriculogram refers to the fact the images acquired are synchronized with the electrical signals of the electrocardiograph (ECG).²² The R wave of the ECG acts as an electrical signal and marker for each new cardiac cycle. At the onset of the R wave, a series of images is acquired during the duration of an R-to-R interval (Figure 15.1). The length of the R-to-R interval to be used in the acquisition is selected prior to acquisition of the study. The duration of each frame is determined by dividing the duration of the R-to-R interval by the number of frames obtained. These parameters are chosen in

the setup menu of the acquisition computer. As the length of one R-to-R interval lasts only milliseconds, very few counts would be collected. Because of this, the RNV study collects a series of several hundred cardiac cycles. Each new cardiac cycle with its own set of images is added to the existing images (Figure 15.2). Counts from several hundred cardiac cycles are added sequentially to form a composite set of images representing different phases of an "average" cardiac cycle. The series of images (usually 16 or 32 divisions) represents the length of the cardiac cycle, with each image representing a specific time point during that cardiac cycle (Figure 15.3).

Various camera positions can be used to isolate the cardiac chambers. In humans, the left 35° anterior oblique position of the camera to the patient is used because it provides excellent separation of the left and right ventricles. In dogs, the authors prefer the left lateral view.¹⁹ Figure 15.4 shows equilibrium blood pool images taken at end-diastole. These correlate directly to the images of the silicon casts of the cardiac chamber seen in Figure 15.5. The position of the camera relative to the heart will influence the functional parameters derived from the RNV. The planar camera records the radioactivity from individual cardiac chambers plus any radioactivity

Figure 15.1: Diagram showing the sequence of images acquired following the R wave, which triggers the beginning of the acquisition



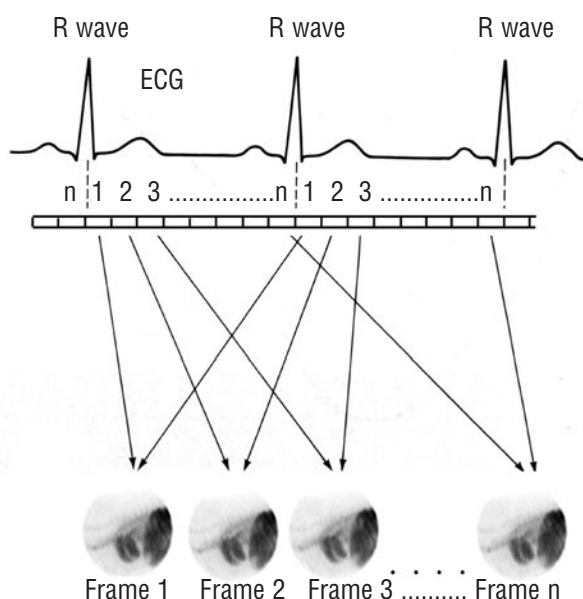


Figure 15.2: Formation of the image series of a gated cardiac acquisition

Sets of images are acquired following the R wave trigger. These images are stored in computer memory or written to the hard disc. The next R wave trigger initiates second sets of images. They are added to the existing images. This process is repeated hundreds of times. The result is a series of images representing the changes in blood pool activity during the cardiac cycle.

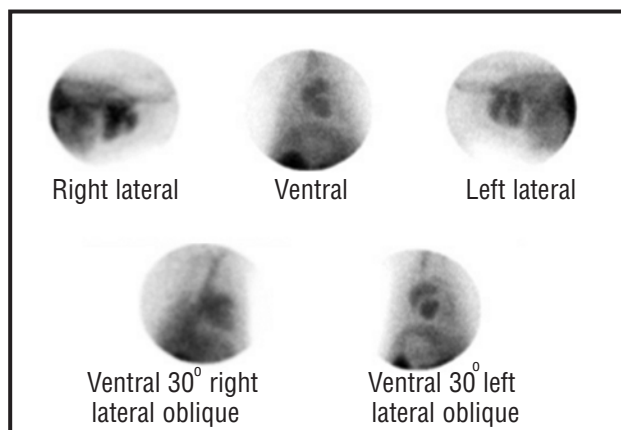


Figure 15.4: Gated radionuclide ventriculogram images taken from various camera positions

The left ventricular borders are easily delineated in the ventral 30° left lateral oblique view and the left lateral view.

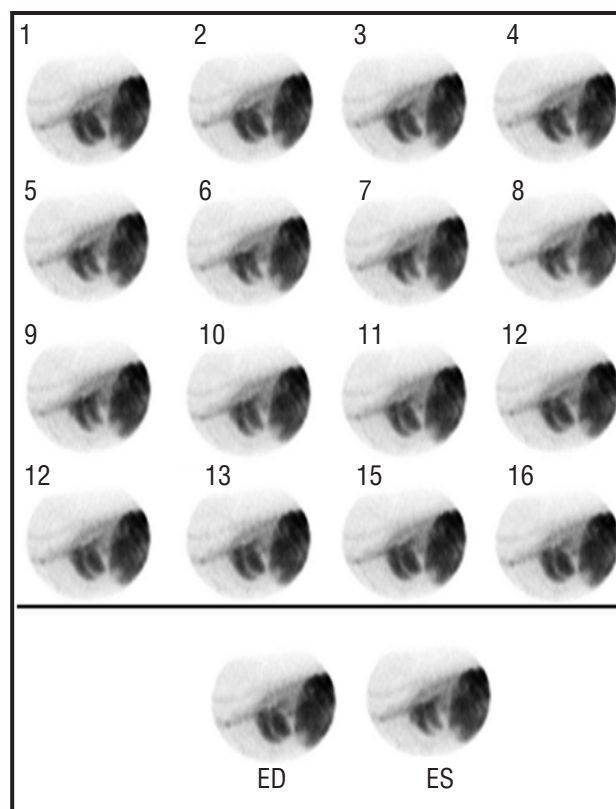


Figure 15.3: Gated radionuclide ventriculogram in a normal dog

The upper 16 images represent changes in blood pool activity during a cardiac cycle. The two images at the bottom are taken at end diastole (ED) and end systole (ES). Note the smaller left ventricular chamber volume at end systole.

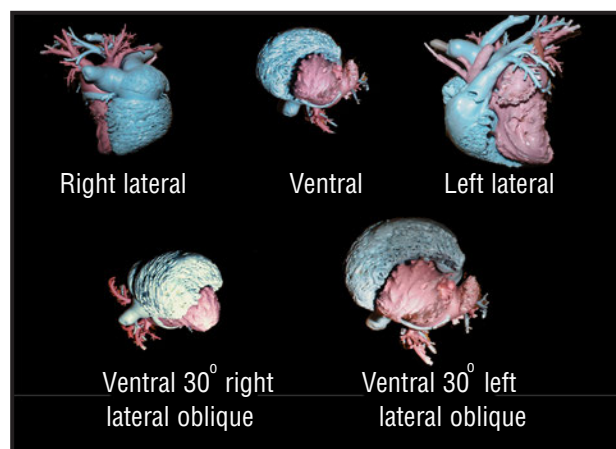


Figure 15.5: Silicon cast images of the canine cardiac chambers

These cast model images are positioned in the same orientation as the images that were acquired in Figure 15.4.

from soft tissues that are superficial and deep in the individual chamber. Ideally, the camera is positioned so that there is maximal separation of the cardiac chambers. For routine clinical RNV studies, the left lateral view is used because positioning is easy and consistent, and nonsedated animals tolerate lateral recumbency for the 5 to 10 minutes required for acquisition. Additionally, there is good visualization of the cardiac chambers. Unfortunately, a portion of the right ventricle overlies the left ventricle when viewed from a lateral position (Figure 15.6). To minimize the contribution of right ventricular radioactivity in the left ventricular region of interest (ROI), a left lateral view is used to increase the distance and the amount of soft tissue between the right ventricle and the camera surface.¹⁹ In the dog, the left oblique position, routinely used in human studies, provides good ventricular separation but also superimposes the atria over the ventricular chambers so that counts recorded are not representative of only the ventricular radioactivity and volumetric changes. The superimposition of the atria over the ventricles dampens the functional parameters by increasing background activity. The overlap of the left ventricle by the left atrium has a greater impact in artificially decreasing the functional indices than does the overlap by the right ventricle because the atria contract out of phase with the ventricles; ie, the atria are maximally distended at systole when the ventricles are at their minimal dimensions. It has been shown that the systolic parameters of the ejection fraction and peak ventricular ejection rate are significantly lower on the ventral 30° left lateral view compared to the left lateral view in the dog.¹⁹

Analysis of the gated radionuclide ventriculogram requires the placement of an ROI over the left ventricle.^{6,7,15-17,22,23} The radioactivity within the ventricle is determined for each frame of the cardiac cycle. A time-activity curve is created representing the changes in left ventricular radioactive during a cardiac cycle. Because changes in radioactivity in the ventricle during the cardiac cycle represent volume changes, the ventricular time-activity curve represents volume changes in the heart during an average cardiac cycle (Figure 15.7). The method of ROI placement can vary and includes automated edge detection, threshold techniques, or manual placement. Because the size of the ventricular lumen changes during the cardiac cycle, the best results are obtained by methods that create a new ROI for each

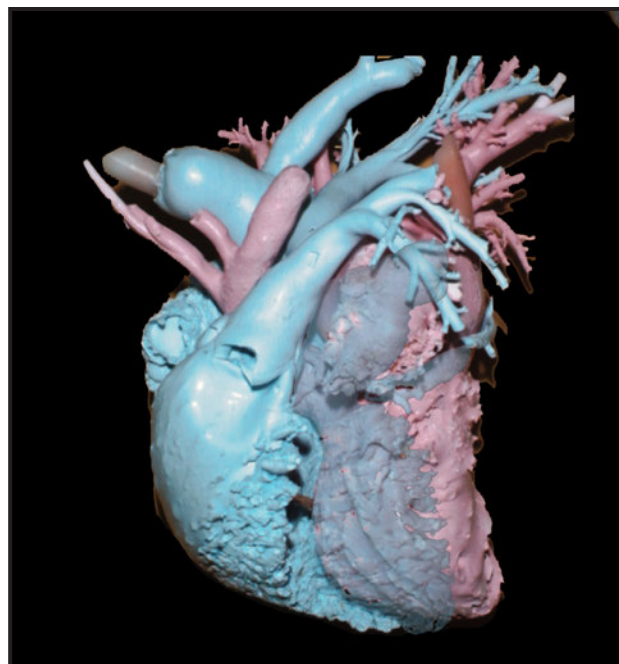


Figure 15.6: Silicon cast image of the canine heart showing the overlap of the right ventricle over the left ventricle as seen in left lateral recumbency

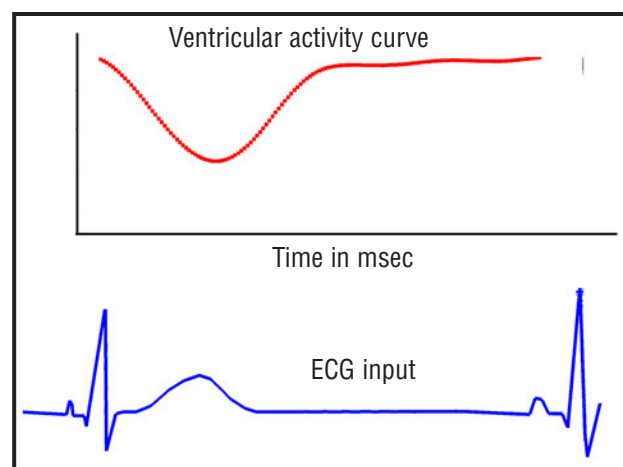


Figure 15.7: Comparison of a ventricular volume curve (top) with the ECG input (bottom)

The volume curve is aligned with the ECG at the bottom. Note the rapid decrease in ventricular volume following the QRS complex. This is due to ventricular contraction. End systole occurs at the time of the T wave. This is followed by ventricular relaxation resulting in ventricular filling. End diastole occurs following atrial contraction (P wave) or can be defined as the onset of the QRS complex on the ECG.

frame as opposed to a fixed ROI that does not change during the cardiac cycle.

Indices of ventricular function are determined from the ventricular time-activity curve. Ejection fraction is the most important and most commonly used index of systolic function obtained from the radionuclide ventriculogram. The ejection fraction is the percentage of the ventricular end diastolic volume (EDV) that is ejected during cardiac contraction. It is determined from the maximum ventricular counts (end diastolic counts after background corrected or net EDV counts) and minimum ventricular counts (end systole counts, ESV counts) (Figure 15.8). The ejection fraction is calculated using the following formula:

$$\text{Ejection fraction} = \frac{[\text{End diastolic counts} - \text{End systolic counts}]}{\text{End diastolic counts} - \text{Background counts}} \times 100$$

The rates of ventricular ejection (systolic indices) and filling (diastolic indices) are determined from the ventricular volume curve. The rate of ejection and filling can be determined by taking the first derivative of the ventricular time-activity curve. The first derivative curve represents the instantaneous rate of change of y (slope of the line). Because the rate of change during ventricular ejection is negative, the first derivative curve is transformed by taking the absolute value of y (Figure 15.9). The rates are normalized to the end diastolic counts and expressed as changes in end diastolic volume per second (EDV/sec).

$$\text{EDV/sec} = \text{Rate (counts/sec)} \div \text{End diastolic counts (net)}$$

The maximum emptying and filling rates are clearly identified as the peaks of the first derivative curve. The time to peak ejection is defined as the time interval from the beginning of the curve to the first peak of the first derivative curve (Figure 15.10). The time to peak filling is defined as the time interval from the end systole to the second peak of the first derivative curve (Figure 15.10). The average emptying and filling rates are determined by taking the average rate

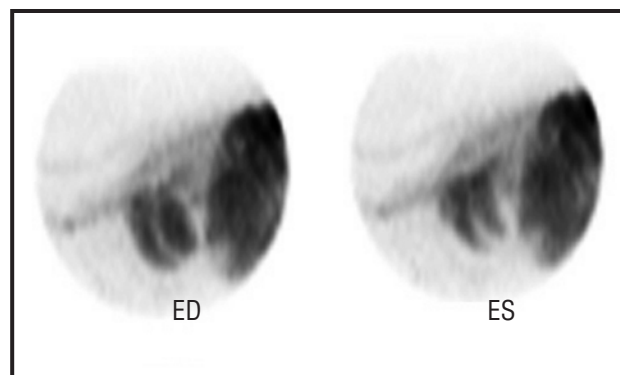


Figure 15.8: End-diastolic (ED) and end-systolic (ES) images from a gated radionuclide ventriculogram

Note the difference in left ventricular activity between the end diastolic (left) and end systolic (right) frames.

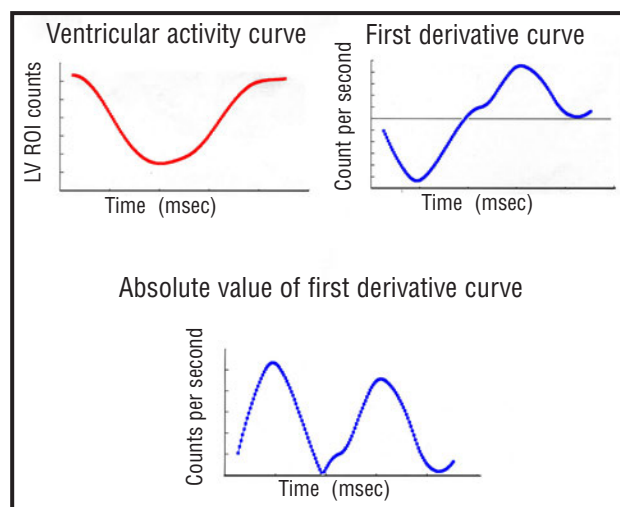


Figure 15.9: Rate and time of maximum ventricular ejection and filling derived by the first derivative of the ventricular volume curve

The first derivative curve represents the instantaneous slope of the ventricular volume curve. During systole, the ventricular activity is decreasing. Therefore, the first derivative curve is negative. During diastole, the ventricular activity is increasing so the first derivative curve is positive. By taking the absolute value of the first derivative curves, both peaks become positive. The peaks represent the time and rate of maximum ejection (systole) and filling (diastole) of the left ventricle.

Table 15.1: Indications for Gated Radionuclide Ventriculography

Evaluation of global ventricular function such as ejection fraction.
Determination of the severity of mitral regurgitation
Determination of systolic function parameters, including rate of ventricular ejection and time to peak ejection.
Determination of diastolic function parameters, including rate of ventricular filling and time to peak filling.

Table 15.2: Imaging Parameters for Gated Radionuclide Ventriculography

Radionuclide	Dose		
	Species	mCi	MBq
	Dog	10-20	370-740
	Cat	2-5	74-185
	Horse	50-70	1,850-2,590

Radionuclide

^{99m}Tc-Labeled Autologous Red Blood Cells (in vivo or in vitro labeling).

Acquisition Parameters

Animal preparation	Allow the animal to get acclimated to ECG leads and lateral recumbency. If using an autologous red blood cell label, the red blood cells must be prepared using the standard kit (UltraTag, Mallinckrodt) or injection of a pyrophosphate kit followed by sodium ^{99m} Tc-pertechnetate.
Acquisition parameters	Gated frame mode acquisition with an R-to-R interval based on the animals resting heart rate. Set an acceptance window at the 15% to 20% range of the average R-to-R interval time. At least 16 frames are needed to temporally resolve the volume curve. If available, one can also choose a 32-bin format. For evaluation of filling or ejection rates, 32 frames are suggested. Images are acquired to a count density of at least 150 counts per pixel within the region of the heart, with 240 counts per pixel preferred. This usually takes between 5-10 minutes to acquire.
Acquisition	If using a list mode acquisition, the images should be framed so that one uses 2/3 forward and 1/3 backward reconstruction.
Matrix	64 × 64 × 16 or 128 × 128 × 16.
Collimator	Low-energy, all-purpose.
Time of imaging	20 minutes following injection of final red blood cell label to allow for equilibration and steady state of the ^{99m} Tc-pertechnetate tag within the red blood cells.
Positioning	Position gamma camera under the imaging table.
Views	Left lateral.

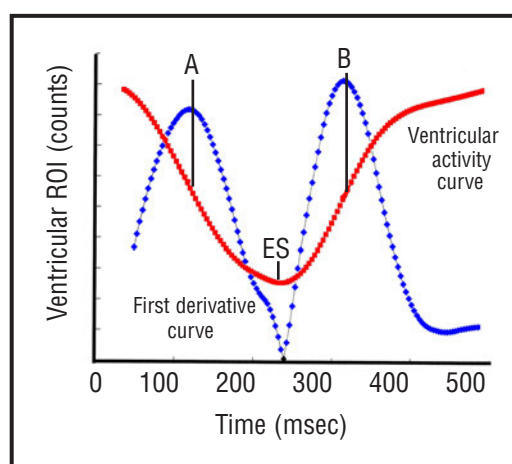


Figure 15.10: Superimposing absolute value of first derivative curve over ventricular volume curve easily identifies point of maximum ventricular ejection (A) and maximum ventricular filling (B).

Note that at end systole (ES), there is no change in ventricular activity so the first derivative curve is 0.

of change over the first and second peaks of the first derivative curve (Figure 15.10).

The indications for radionuclide ventriculography are summarized in Table 15.1. The acquisition parameters are summarized in Table 15.2. Acquisition of the study uses ECG gating. Sinus arrhythmia should be controlled with atropine or glycopyrrolate. Imaging is terminated based on a counts-per-pixel determination with the blood pool of the ventricles. A count density of 240 counts per pixel is preferred, which will usually take 5 to 10 minutes to acquire.

Principles of Interpretation

It is well-known that functional changes of the myocardium often precede morphologic changes in cardiac size and shape or the development of congestive heart failure. The RNV studies have been shown to be more sensitive than thoracic radiographs or echocardiography for staging the progression of cardiac disease, monitoring response to therapy, or providing potential future outcomes and prognostic information.^{7,17} In addition, RNV studies are noninvasive and can be repeated several times after acute pharmacologic interventions within hours of each other,

following a single injection of the ^{99m}Tc-labeled red blood cells. Therefore, the RNV study can also be used to evaluate the heart in a resting state and after challenges with exercise or pharmacologic intervention.^{7,17} The ability of the heart to respond to such challenges may provide a more sensitive index of cardiac dysfunction.

Ejection fraction has been shown to be an important predictor of patient mortality in humans and dogs. Although ejection fraction is the most widely reported index of ventricular systolic function in humans, it should be noted that this index is influenced by acute changes in preload and afterload.^{1,18,20} A more sensitive indicator of left ventricular dysfunction is the acute response of the ventricle to the demands of exercise. It has been shown that a decrease in contractile reserve often precedes a decrease in resting function (ejection fraction at rest).^{7,11} Dobutamine has been used as a pharmaceutical agent to mimic the stress on the myocardium as would be seen with exercise.

Mitral regurgitation produces varying degrees of retrograde blood flow across the mitral valve and the heart compensates for this regurgitate flow by increasing ejection fraction.¹⁹ RNV studies from dogs with compensated mitral valvular insufficiency show an enlarged left atrium with a hyperkinetic left ventricle and increased ejection fraction (Figure 15.11). After months or years of volume overload, the ventricle dilates (eccentric hypertrophy) and is hyperkinetic resulting in increased end diastolic and end systolic volumes. As the disease progresses, left ventricular contractility decreases, reducing the ejection fraction.

Animals with dilated cardiomyopathy have left ventricular dilation with diffuse wall motion abnormalities resulting in decreased ejection fraction. Cardiac toxicity due to adriamycin also decreases ejection fraction, with the severity of cardiotoxicity proportional to the reduction in ejection fraction.¹⁷ In either case, the ventricular volume curve will appear shallow.

The rate of ejection of blood from the ventricles reflects the ability of the myocardium to generate force. In human studies, the ejection rate appears to be more sensitive than ejection fraction for detecting changes in the inotropic or contractile state of the heart.^{7,10,11,15,16,23,24} In a recent study of experi-

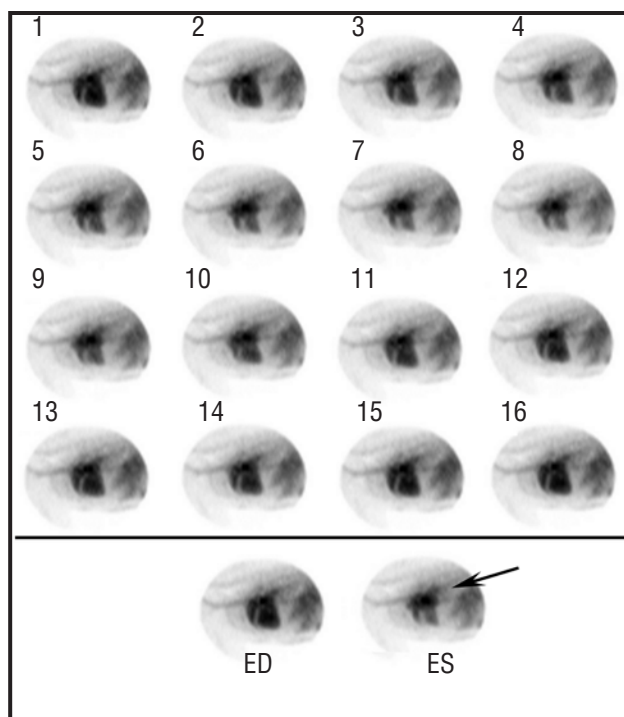


Figure 15.11: Gated radionuclide ventriculography and left ventricular volume curve in a dog with mitral insufficiency

On the top image, there is an increase in left ventricular volume at end-diastole (ED). At end systole (ES) the left ventricular volume is drastically reduced indicating a high ejection fraction. Also note at end systole there is marked left atrial enlargement due to retrograde flow of blood across the mitral valve (arrow). The left ventricular time-activity curve for a cardiac cycle. The ventricular radioactivity changes proportional to ventricular volume. Note the rapid decrease in ventricular activity and the difference from end diastole to end systole. This is indicative of a hyperkinetic left ventricle that has compensated for the retrograde flow caused by mitral valve endocardiosis with resultant mitral insufficiency.

mentally induced heart failure, the maximum and average ejection rates showed a greater magnitude of change than other ventricular systolic functional indices.²

Diastolic filling is altered in many cardiac diseases, especially those characterized by myocardial compliance failure, such as restrictive myocardial diseases, pericardial effusion, myocardial ischemia, or hypertrophic cardiomyopathy.^{2,4,6,7,25} An increase in the time to peak filling or a decrease in the maximum filling rate are both indicators of diastolic dysfunction. In many circumstances, alteration in diastolic function precedes ventricular systolic dysfunction and resultant congestive heart failure.

Sinus arrhythmia, common in dogs, has an adverse effect on the determination of diastolic function by

RNV study. With sinus arrhythmia, the time from the T wave to the P wave varies, producing misalignment of image frames at the end of the cardiac cycle. This results in spuriously low counts at the end of the volume curve. Because diastolic indices are obtained during the second half of the volume curve, these measurements are affected by sinus arrhythmia. However, a window can be selected to reject those R to R intervals from single cardiac cycles outside a predefined R to R interval thereby reducing (but not completely eliminating) the effect of sinus arrhythmia. Some computers that are capable of acquiring RNV studies in list mode acquisition store each scintillation count separately in a serial manner as opposed to the traditional frame mode acquisition in which data from each interval of the cardiac cycle are added to data previously

Ventricular Indices Measured using RNV	Left Ventricle Mean $\pm$ SD	Right Ventricle Mean $\pm$ SD
Ejection Fraction (%)	59.6 $\pm$ 10.9%	34.0 $\pm$ 11%
Peak Ejection Rate (EDV/sec)	5.32 $\pm$ 1.57	2.72 $\pm$ 0.9
Peak Filling Rate (EDV/sec)	4.52 $\pm$ 0.58	2.28 $\pm$ 0.67

Table 15.3: Normal left and right ventricular radionuclide ventriculography indices from normal dogs obtained using a left lateral view

acquired then stored to the computer disc. List mode acquisitions can, therefore, be used to reconfigure the images using forward and backward gating, thus aligning the frames at the beginning and end of the cardiac cycle. The list mode studies can also be reconfigured to include only specific R-to-R intervals. These list mode methods would then remove count drop-off of the ventricular volume curve seen as a result of sinus arrhythmia.

Regional wall motion may be evaluated from the RNV study by displaying the radionuclide ventriculogram on the computer monitor in rapid sequence. Ventricular dyskinesia is characterized by asymmetrical contractions. Focal hypokinesis of a region of the left ventricle may be seen as a result of myocardial tumors or ischemia/infarction. Although myocardial infarction is a rare event in dogs, RNV can provide volumetric data about regional and global left ventricular function in this clinical setting. Ventricular aneurysms are characterized as focal regions of the ventricle with paradoxical wall motion.

Because of the geometry of the right ventricle, it is difficult to measure right ventricular function from equilibrium blood pool studies.¹⁹ The right ventricle overlaps the left ventricle, and it is not possible to image the right ventricle without overlap from other cardiac chambers. Despite this limitation, a recent study has shown good correlation between right ventricular systolic function and several hemodynamic measurements. Right ventricular ejection fraction and average right ventricular ejection rate correlated

inversely with the pulmonary arterial pressures and pulmonary capillary wedge pressure suggesting that right ventricular ejection fraction and right ventricular ejection rate are related to afterload and may be used as noninvasive means of predicting changes in pulmonary artery pressure. Normal right and left ventricular indices derived from RNV studies are summarized in Table 15.3.

Radionuclide ventriculography (RNV) can also be used to quantify the severity of mitral valvular insufficiency and calculate the regurgitant fraction from an average cardiac cycle. The stroke volume ratio, derived from the RNV, is used to quantify the severity of mitral regurgitation.¹⁹ The difference in

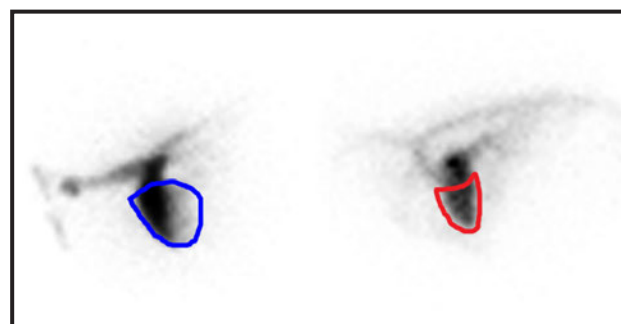


Figure 15.12: Dextrophase and levophase images from a first pass radionuclide ventriculography

ROIs are hand drawn over the left and right ventricle.

ventricular activity between end diastole and end systole represents the stroke volume. Normally, the right and left ventricular stroke volumes should be the same. In the case of mitral insufficiency, the left ventricular stroke volume must increase to maintain adequate forward output. Previous studies conducted in humans using nuclear scintigraphy have shown that the left over right stroke volume ratio increases as the severity of mitral regurgitation increases.

The right and left ventricular stroke volumes measured from the RNV are never equal because of the inherent factors of planar imaging, such as overlapping cardiac chambers, differential attenuations of the ventricles, and unequal ventricular to collimator distances. As a result, the measured right ventricular stroke volume counts are considerably less than the left ventricular stroke volume counts. By combining data from the FPRA and the RNV, partial correction of these factors is possible.

The amount of overlap of the right and left ventricles can be determined from a first pass radionuclide angiogram study. Because the right and left ventricles are temporally separated in the FPRA, ROIs are drawn around the left and right ventricle and the radioactivity within each chamber measured (Figure 15.12). The peaks of the ventricular time-activity curves represent the passage of the radioactive bolus through the right or left ventricles. The integrated area under the peak of the right ventricular time-activity curve (RVTAC) is proportional to the blood volume in the right ventricle. The amount of right ventricular overlap with the left ventricle is determined by the area under the small peak seen on the left ventricular time-activity curve (LVTAC) during the dextrophase (Figure 15.13). The percentage of the right ventricle superimposed over the left ventricle ($\%RV_{\text{overlap}}$) can be determined by dividing the area under the peak of the LVTAC by the area under the RVTAC during the dextrophase of the FPRA.

$$\%RV_{\text{overlap}} = \frac{\text{Area under 1st LV peak}}{\text{Area under 1st RV peak}}$$

The radioactivity seen in the left ventricle ROI during the dextrophase of the FPRA represents activity in the portion of the right ventricle that is superimposed over the LV where as the radioactivity in right ventricle ROI represents the total right ventricular activity. Stroke volume images are created from the RNV study by subtracting the end-systolic frame

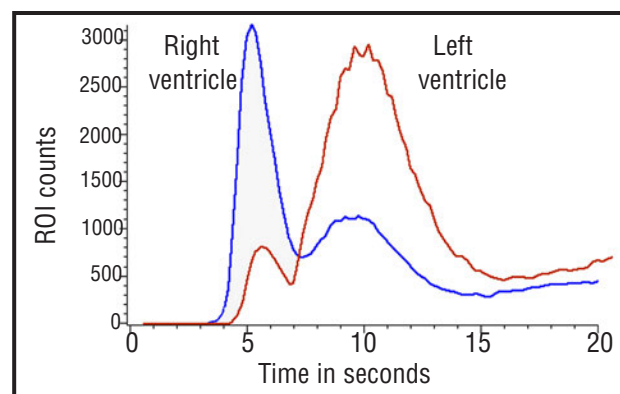


Figure 15.13: Time-activity curves generated from the ROIs in Figure 15.12

The integrated area under the peak of the right ventricular time-activity curve is proportional to the blood volume in the right ventricle. The right ventricular volume superimposed over the left ventricle is determined by the area under the small peak seen on the left ventricular time-activity curve during the dextrophase. From this the percentage of overlap of the two ventricles and the count contribution of each ventricle can more accurately be determined.

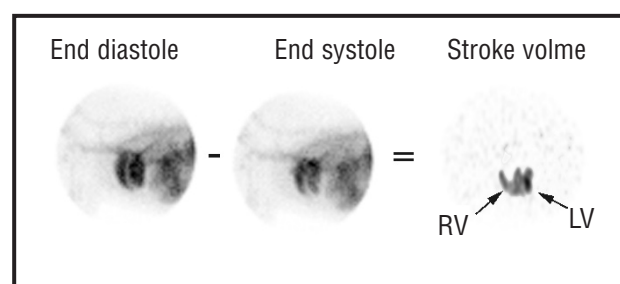


Figure 15.14: A stroke volume image is created by subtracting the end-systolic image from the end-diastolic image. RV = right ventricle; LV = left ventricle

from the end-diastolic frame (Figure 15.14).

Hand-drawn ROIs are placed around the right ventricle (RV) and left ventricle (LV). The LV ROI encloses the entire LV and the overlapping portion of the RV, whereas the RV ROI encloses only the portion of the RV that was visually separated from the LV. The counts in the right and left ventricular ROIs represent the uncorrected stroke volume. Because the right ventricle overlaps the left ventricle, the counts from the ventricular ROIs underestimate

the RV stroke volume and overestimate the LV stroke volume. The typical % RV_{overlap} is between 25% to 30%. The measured RV radioactivity (RV ROI counts) represents the portion of the total RV stroke volume that does not overlap the LV (1 - % RV_{overlap}). The corrected right ventricular stroke volume counts (RVSV_{corr}) are determined using the following formula:

$$\text{RVSV}_{\text{corr}} = \frac{\text{RVSV counts}}{(1 - \% \text{RV}_{\text{overlap}})}$$

The measured LV radioactivity represents the actual LV stroke volume counts plus the counts from the portion of the RV that overlaps the LV. The corrected left ventricular stroke volume counts (LVSVC_{corr}) is determined from the following formula:

$$\text{LVSVC}_{\text{corr}} = \text{LV ROI}_{\text{counts}} - [\text{RVSV}_{\text{corr}} \times \% \text{RV}_{\text{overlap}}]$$

The stroke volume ratio (SVR) is then determined from the ratio of the calculated left and right stroke volumes from the previous equations.

$$\text{Stroke volume ratio} = \frac{\text{LVSVC}_{\text{corr}}}{\text{RVSV}_{\text{corr}}} \times 100$$

The normal stroke volume ratio in dogs has been reported to be 1.17 ± 0.2 .¹⁹

Summary

Radionuclide ventriculography has been the mainstay in humans for evaluating global and regional myocardial function. Indices of systolic and diastolic function can be derived from these studies. Important prognostic information can be obtained to assess overall cardiac response to medication. Although somewhat involved, the stroke volume ratio can be calculated for dogs with mitral valve endocardiosis and regurgitation. The use of RNV in veterinary medicine has not been explored due to the ease of performing echocardiographic examinations. However, in humans RNV is a more consistent indicator of global, volumetric ventricular function and documents global dysfunctional changes in left ventricular performance earlier than echocardiography can.

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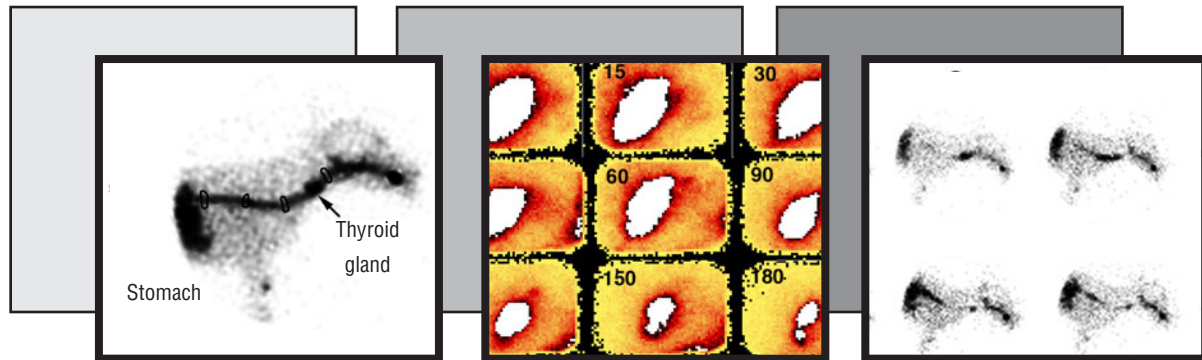
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Gastrointestinal Nuclear Medicine

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Introduction

A number of physiologic parameters of the gastrointestinal tract can be assessed by scintigraphy with esophageal transit and gastric emptying (solid or liquid phase) being the most commonly measured. Radiolabeled meals, food components, or radiolabeled fluids can be used for these evaluations. Scintigraphy can also be used to localize sites of gastrointestinal blood loss and excessive gastrointestinal protein loss. Because these procedures are non-invasive, they can be repeated to evaluate response to therapy. This chapter focuses on esophageal transit using scintigraphy.

Esophageal Scintigraphy

Evaluation of the esophagus using scintigraphy provides a quantitative assessment of esophageal motility. Normally, the cricopharyngeus muscle relaxes as the food or liquid bolus is moved from the oropharynx into the esophagus in a coordinated series of neuromuscular events. This then initiates a primary esophageal peristaltic wave that moves the bolus in an aboral direction into the stomach. Secondary peristaltic waves are waves of esophageal contraction that originate within the esophagus (unrelated to the act of swallowing) secondary to volumetric distention of the esophageal lumen. Secondary peristaltic waves are normal, if food material and liquid remain within the cervical esophagus. Once initiated, a secondary peristaltic wave moves the food or liquid bolus in an aboral direction into the stomach. The indications for scintigraphic evaluation of esophageal motility are summarized in Table 16.1.

A dynamic frame mode acquisition or a list mode acquisition can be utilized for imaging. The dynamic data set or the reformatted list mode data set should

include a minimum of two frames per second with a matrix size of $128 \times 128 \times 16$. The animal should stand next to the gamma camera either on the floor or on a table to obtain a left lateral view. The data acquisition begins simultaneous with the ingestion of the food bolus (Figures 16.1 and 16.2). Multiple dynamic acquisitions can be obtained with the administration of subsequent food boluses. The acquisition parameters and dosages are summarized in Table 16.2

To evaluate gastroesophageal reflux, 30 to 60 second static images should be obtained every 5 minutes for 30 minutes after termination of feeding. Dorsal images may also be helpful in evaluating reflux (Note: gastric emptying can be calculated by obtaining additional images). It is often helpful to withhold food for 12 hours prior to the study to promote the likelihood of the animal eating well.

Principles of Interpretation - Esophageal Scintigraphy

The operator forms a composite image of all of the frames that encompass entrance of the food bolus into the esophagus and then exit into the stomach. Small regions of interest (typically regions are 2 to 3 pixels wide and tall as the esophageal activity in each section of the esophagus) are drawn at the midcervical, thoracic inlet, heart base, and distal thoracic esophagus. The regions of interest are applied to the dynamic study, and the change of counts in each region are plotted over time. The area of each region of interest (ROI) should appear as a narrow spike on the time-activity curve (Figure 16.3). Normal transit of the radioactive bolus from a single peristaltic contraction will be seen as the ROI peaks occur in sequential fashion. Widening of any of the peaks suggests a delay in transit secondary to lack of motility or a motility dysfunction. Overall, esophageal transit can also be calculated by determining the number of frames needed for the bolus to transit the esophagus and then multiplying by the acquisition rate (time of acquisition per frame). The total transit time in normal dogs (<30 kg) is less than 5 seconds. Delays in transit can result from anatomic obstructions or neuromuscular dysfunction. Correlation with radiographs and/or an esophagram may be necessary to determine a specific etiology. Follow-up scintigraphic examinations would then provide a quantitative assessment of response to therapy.

Table 16.1: Indications for Esophageal Scintigraphy

Quantify esophageal motility and transit time.
Use esophageal transit times as indicators of response to therapy.
Evaluate the presence and amount of gastroesophageal reflux.

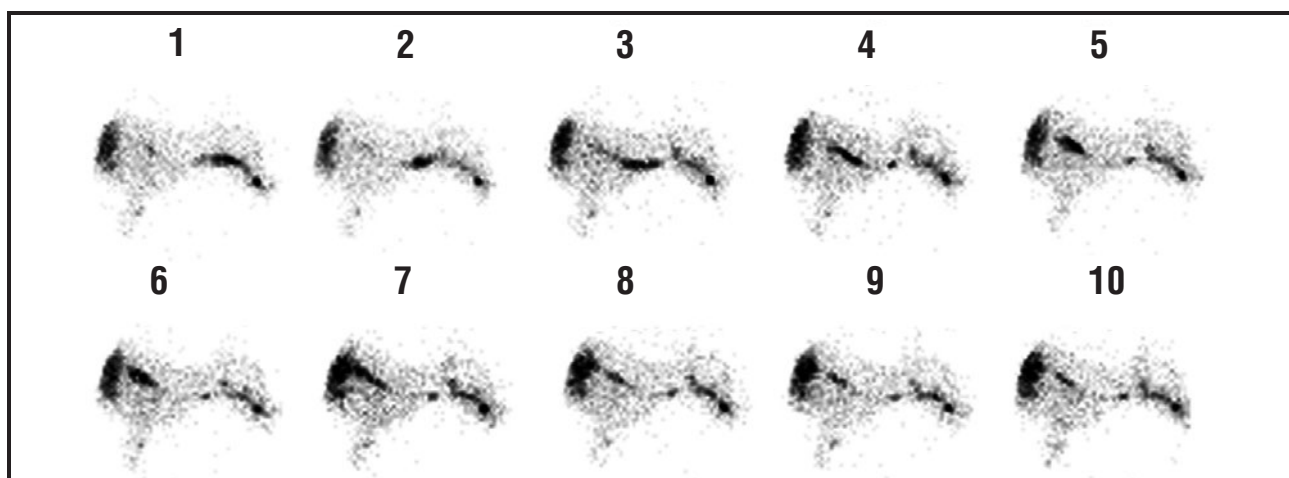


Figure 16.1: Esophageal scintigraphy in a normal dog

The images have been reformatted to one frame per second. The dog was given 37 MBq (1 mCi) of ^{99m}Tc -pertechnetate 20 minutes prior to the images. The pertechnetate provides background activity to identify anatomic regions of the body relative to the radioactive food bolus. The stomach and parotid salivary glands provide landmarks for the proximal and distal aspect of the esophagus. A bolus of dog food labeled with ^{99m}Tc -mebrofenin was administered orally. The food bolus can be seen transverse the esophagus from frame 1 to 7.

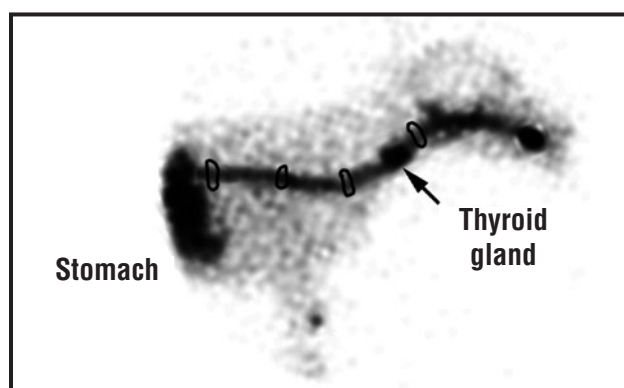


Figure 16.2: Esophageal scintigraphy in a normal dog

This is a summed image from a dynamic acquisition of an esophageal swallow using a bolus of dog food labeled with ^{99m}Tc -mebrofenin. The dog had been given 37 MBq (1 mCi) of sodium ^{99m}Tc -pertechnetate 20 minutes prior to image acquisition. The esophagus is readily identified on the summed image. In this example, ROIs were drawn over the esophagus at the proximal end, thoracic inlet, heart base, and distal end.

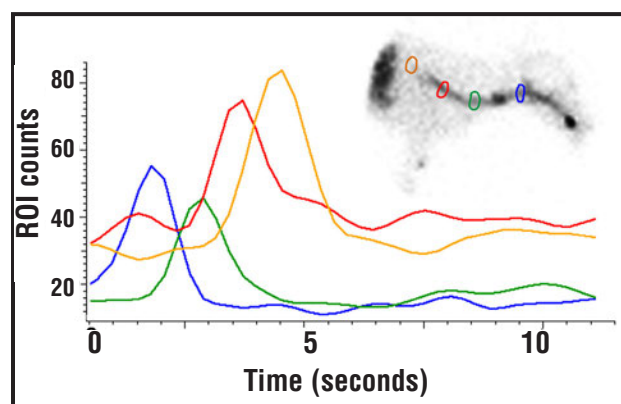


Figure 16.3: Esophageal scintigraphy in a normal dog

This is a time-activity curve created by applying the esophageal ROIs to the dynamic acquisition. Esophageal transit times can be measured from the peaks created from each esophageal ROI. The esophageal transit rate can be determined if the distance between ROIs is measured on the summed image.

Gastric-Emptying Scintigraphy

Gastric-emptying scintigraphy is considered the gold standard for noninvasive evaluation of gastric emptying (GE) in humans and animals.¹⁻³ GE scintigraphy measures the transit of a standardized test meal

Table 16.2: Imaging Parameters for Use With Esophageal Scintigraphy

Animal Preparation

Stand the animal next to the gamma camera either on the floor or on a table. Inject the animal with 37 MBq (1 mCi) of sodium ^{99m}Tc -pertechnetate 20 minutes prior to allowing the animal to eat. The patient should have been fasted for at least 12 hours. Previous thoracic radiographs are beneficial to rule out esophageal obstructions secondary to radiopaque foreign bodies and to check for the presence of aspiration pneumonia. Feed the animal upright simultaneous with the start of the dynamic acquisition.

Radionuclide

Any ^{99m}Tc -radiopharmaceutical can be used for liquid-phase. For solid-phase imaging, ^{99m}Tc -sulfur colloid or ^{99m}Tc -DISIDA derivatives are mixed with food.

Dose

Inject the patient with 37 MBq (1 mCi) of sodium pertechnetate to act as an in vivo marker of the proximal and distal extent of the esophagus (salivary uptake of ^{99m}Tc -pertechnetate marks the proximal extent, and gastric uptake marks the distal extent). Mix 37-74 MBq (1-2 mCi) of ^{99m}Tc -mebrofenin with canned food for solid-phase emptying evaluation. Baby food mixed with water can also be used for evaluation of liquid-phase emptying.

Acquisition Parameters

Mode	Dynamic frame mode acquisition of 0.5 second per frame for 2 minutes (total of 240 frames). Repeated dynamic acquisition attempts may be necessary to catch an entire peristaltic sequence.
Matrix	128 × 128 × 16 or 256 × 256 × 16.
Collimator	Low-energy, all-purpose.
Time to image	Start acquisition simultaneous with feeding of the patient.
Positioning	Left side of the patient against the camera with the animal in a standing position.
View	Left lateral.

through the stomach. By varying the labeled meal component, the emptying of liquids and solids can be studied either independently or simultaneously. GE scintigraphy has the benefits of using a meal that is typical and physiologically appropriate for the patient. In addition, the technique is simple, easily quantified, and repeatable.

Emptying of the stomach occurs via peristaltic waves that push food towards the pylorus. These peristaltic waves should be coordinated with opening of the pylorus to allow the ingesta to exit the stomach. The fundus/body acts as a reservoir for ingesta. Gastric emptying is a multifactorial process, which can be influenced by meal composition, meal volume, pH

of the meal, and gastric contents and various disease states that will either delay or increase the emptying rate of the stomach. The indications for GE are summarized in Table 16.3

Radiopharmaceutical and Dosage

1. Solid-Phase Emptying Study

^{99m}Tc -disofenin or ^{99m}Tc -mebrofenin have good (>90%) in vitro solid-phase retention and excellent in vivo stability. These can be used to label dry and canned dog and cat diets.^{2,4-7} Good label retention and in-vivo stability have also been demonstrated in concentrate rations for horses.⁸

Table 16.3: Indications for Gastric-Emptying (GE) Scintigraphy

Quantify and characterize patterns of GE.
Document gastric outflow obstruction.
Determine and monitor effect of medical or surgical treatment on GE.

While these labels have been shown to be stable with a wide variety of feeds, in vitro and in vivo stability should be assessed for each diet and species. Because of the recycling of pertechnetate by the gastric mucosa, prepared disofenin or mebrofenin kits should be tested following manufacturer's recommendations to document the presence of any radiochemical impurities prior to the study. If labeling efficiency is considered acceptable, one can proceed with the GE study.

The animal should be fasted for 12 to 18 hours to encourage consumption. For best results, the diet selected for the test meal should be one that the animal is accustomed to eating. Meal size will vary with the individual patient. In general, a medium-sized dog will consume a 400 g can of dog food in less than 10 minutes. Cats should be offered 40 g of dry kibble or 60 g of canned food. Place the food within a disposable dish. Mix 37 to 111 MBq (1 to 3 mCi) of ^{99m}Tc -mebrofenin with canned food or kibble (10 to 20 mCi [370 to 740 MBq] for horses). After the radiolabel has been applied to the surface of dry extruded kibble diets, should be then mixed with 2 g of beef baby food. If a canned diet is used, the radiolabel should be thoroughly blended with it. The radioactive meal to incubate at room temperature for 10 minutes. One can also mix 37 to 111 MBq (1 to 3 mCi) of ^{99m}Tc -sulfur colloid with a raw egg and cook in a microwave for 30 seconds, chop up the egg, and mix it with the test meal.

The test meal is weighed and the weight recorded prior to offering it. Next the animal is allowed to eat for 10 to 15 minutes or until the food is consumed, and then the remaining food is weighed. It is not recommended to force feed the animal or pass an oral-gastric tube because the induced stress may alter the GE results. In those animals with a gastrostomy tube, meals may be blended with water and fed via

the tube.¹¹ Water should be offered ad libitum during the study, and water intake recorded. After the test meal has been fed to the animal, imaging can begin using static frame mode acquisitions. The operator records imaging times when the study is started and when each lateral is obtained.

2. Liquid-Phase Emptying

^{99m}Tc -DTPA or ^{111}In -DTPA can be added to liquids (usually water) for evaluation of liquid-phase gastric emptying.^{10,11} Simultaneous liquid-phase and solid-phase emptying can be assessed with a dual radionuclide method (^{99m}Tc -mebrofenin labeled solids and ^{111}In -DTPA in water) if the gamma camera has the capability of a dual peaking function.

The operator mixes the 37 to 111 MBq (1 to 3 mCi) of ^{99m}Tc -DTPA with an appropriate volume of water or other liquid, passes a stomach tube, and delivers the liquid into the stomach. A total dose of 370 to 740 MBq (10 to 20 mCi) can be used for imaging the liquid phase of GE in horses. If a simultaneous solid- and liquid-emptying study is desired, simply pour over the labeled solid-phase meal. Dual phase (solid and liquid phase imaging) would include the use of 0.5 mCi (17.5 MBq) of ^{111}In -DTPA in combination with the solid test meal (^{99m}Tc -mebrofenin). ^{111}In decays by electron capture, and has a physical half-life of 2.82 days. ^{111}In has two gamma emissions consisting of 172 and 247 keV. These can be separated from the 140 keV emission of ^{99m}Tc if the gamma camera has a dual peaking function. A medium-energy collimator should be used for the ^{111}In .

Imaging Protocol

For clinical solid-phase studies, left and right lateral static images of the abdomen should be acquired immediately after removing the test meal. Repeat examinations should be made at 30-minute intervals for 4 to 6 hours. For research animals, images may be made more frequently (every 10 to 15 minutes) during the first hour to characterize the onset of GE. For liquid- or dual-phase studies, images should be acquired every 5 minutes for the first 90 minutes and then at 30-minute intervals until 4 to 6 hours. After the last gastric image is made, obtain a lateral of the cervical region to evaluate for the presence of thyroid uptake.

Using a matrix of $128 \times 128 \times 16$ and a 15% window, each static image for 30 seconds (approximately 100,000 to 250,000 counts). A 30-second left lateral image is needed only for horses. Short acquisition times are preferable to minimize patient motion or the need for excessive restraint that may influence emptying. For ^{111}In -DTPA labeled liquid studies, use a 20% window centered at the 174 keV and 247 keV photopeaks. Imaging times of 2 minutes may be required to obtain images with $> 100,000$ counts. Right and left lateral images should be acquired every 15 minutes until count density in the stomach drops to 10% of original counts. Acquisition protocols for solid-food and liquid-phase emptying are summarized in Table 16.4 (A and B).

Principles of Interpretation

Scintigraphic GE studies are not commonly used in veterinary medicine as clinical diagnostic tests. The broad range of normal values and the differing protocols reported in the literature limit the usefulness of gastrointestinal scintigraphy as a clinical diagnostic method. In light of the relative insensitivity of these techniques and the radiation safety considerations,

other diagnostic methods may be preferable in clinical patients. GE scintigraphy may have better clinical application if serial studies are done so that disease progression or response to treatment can be documented.

The three phases of GE include an initial lag phase for trituration (mixing without emptying), a linear phase of initial emptying and then a delayed phase that defines fiber GE. ROIs should be drawn around the stomach on each view and the total counts recorded (Figure 16.4). The counts are then decay corrected to time 0 (time at which the first image was obtained).

Geometric Mean

For dogs and cats, the geometric mean of the activity within the right and left lateral ROIs is calculated. The geometric mean is used to account for attenuation and projection differences from either lateral view and is calculated by the following equation:

$$\text{Geometric mean} = \sqrt{\text{Right lateral total counts} \times \text{Left lateral total counts}}$$

Table 16.4A: Solid-Phase Gastric-Emptying

Radiopharmaceutical

$^{99\text{m}}\text{Tc}$ -disofenin or $^{99\text{m}}\text{Tc}$ -mebrofenin

Acquisition Parameters

Dose

Species	mCi	MBq
Dog	3-6	111-222
Cat	3	111
Horse	30	1,110

Animal preparation	Fast animal for 12-18 hours.
Static frame acquisition:	20- or 30- second static frame mode acquisition should yield between 100,000 to 250,000 counts per image.
Matrix	$256 \times 256 \times 16$ or $128 \times 128 \times 16$.
Collimator	Low-energy, all-purpose or high-resolution.
Time to image	After ingestion of the radioactive meal, the dog or cat will be imaged every 5 minutes through 60 minutes and then every 30 minutes through 5 hours.
Positioning	Small animal is placed in lateral recumbency over the gamma camera; the horse is stood next to the camera for the study.
Views	Left lateral and right lateral.

Percentage of Retained Gastric Activity (PRGA)

The gastric geometric mean data is normalized. Gastric activity is expressed as the percentage of retained gastric activity (PRGA) at a given time. It is calculated using the initial value of 100% for gastric activity at time 0, (Figure 16.5).

$$\text{PRGA} = \frac{\text{Decay corrected geometric mean at given time}}{\text{Decay corrected geometric mean at time 0}} \times 100$$

If using both the ^{111}In and $^{99\text{m}}\text{Tc}$ dual-imaging protocols, then each radionuclide will have to undergo the same decay correction and normalization prior to plotting the time-activity curve.

Models for Quantifying Gastric Emptying

1. T_{50} Calculation/Estimation

There are two methods of interpretation commonly used for evaluation of solid-phase GE scintigraphy. The simplest method involves calculating the PRGA at hourly intervals until it reaches a value of less than 50% of the original value of 100%. This is called the time to half emptying, or T_{50} . The advantages of this method are its ease and quantitative result. The method is limited by the inability to characterize the pattern of GE, and the relatively broad range of normal values, making it unlikely to detect GE changes unless the alterations are severe.

Table 16.4B Liquid-Phase Gastric-Emptying

Radiopharmaceutical

$^{99\text{m}}\text{Tc}$ -DTPA or ^{111}In -DTPA.

Dose

Species	mCi	MBq
Dog/Cat ^{111}In -DTPA	0.5-1.0	17.5-37
Dog/Cat $^{99\text{m}}\text{Tc}$ -DTPA	3.0-6.0	111-222

Acquisition Parameters

Animal preparation	Fast animal for 12-18 hours.
Static frame acquisition	20- or 30- second acquisition should yield 100,000 to 250,000 counts for $^{99\text{m}}\text{Tc}$. 2-minute acquisition should yield 50,000 to 100,000 counts for ^{111}In .
Matrix	256 × 256 × 16 or 128 × 128 × 16.
Collimator	Low-energy, all-purpose collimator for $^{99\text{m}}\text{Tc}$; medium-energy collimator for ^{111}In .
Time to image	Immediate and then every 5 minutes for 90 minutes, then every 30 minutes for 4-6 hours.
Positioning	Animal in lateral recumbency over the camera or next to the standing horse.
Views	Left lateral and right lateral.
Window setting	15% window centered at 140 keV for $^{99\text{m}}\text{Tc}$ and 20% windows centered at 174 and 247 keV photon energies for ^{111}In .

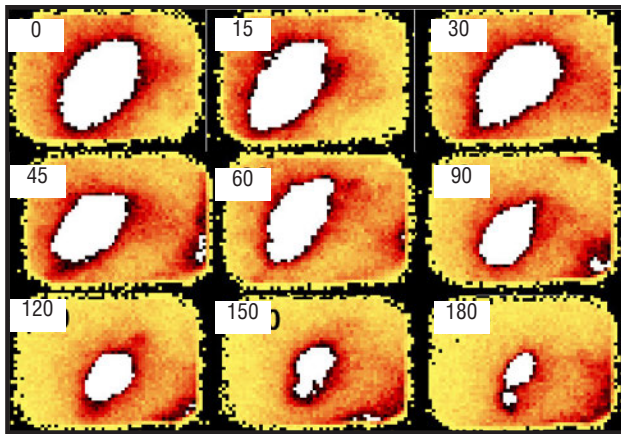


Figure 16.4: Solid-phase gastric-emptying study

Shown are left lateral images of a normal dog given a radioactive meal. Note the decrease in gastric activity over time. The time (in minutes) to each image is shown in the upper left-hand corner of each.

The T_{50} can be more accurately defined if reference values are developed for a similar meal type, meal size (kcal/kg body weight), and water intake. The need to establish normal ranges for various food types, meal sizes, and water intakes is imperative in research applications.

Power Exponential

The second method for interpretation of GE data involves development of a statistical model (or predictive curve) from the observed data. In research applications, a more in-depth characterization of the pattern of GE is of interest; however, these values may have greater clinical implications. Values characterizing different aspects of the GE curve can be extrapolated from the modeled data. Typically, the onset of gastric emptying is described by T_{90} or T_{95} , or the time to 90% or 95% PRGA (10% or 5% emptying), respectively. The time to 50% PRGA (or 50% emptying) is called T_{50} and reflects the overall rate of GE. The time required to reach 20% PRGA is called T_{20} and describes the emptying of the majority of the digestible portion of the meal. Ideally, then, a statistical model should allow for analysis of the whole GE curve, rather than a single point or part of the curve, and the resultant curve should fit the observed data from individuals fed a wide variety of diets. The parameters of the model should have biologic meaning. A variety of models of solid phase

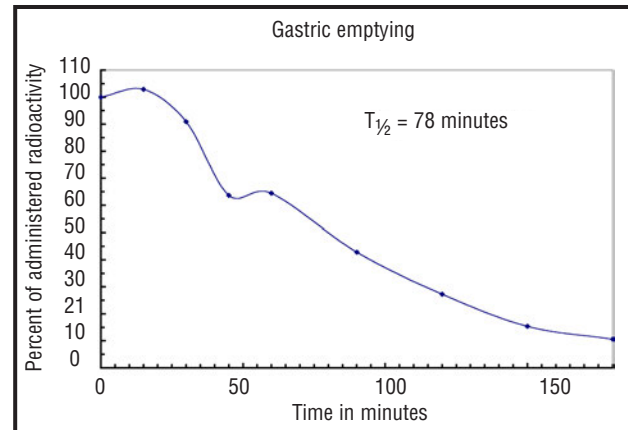


Figure 16.5: Solid-phase gastric-emptying study

This is a gastric time-activity curve created by ROI analysis of the gastric activity in the dog in Figure 16.4. The gastric activity has been decay corrected and expressed as a percentage of the activity measured in the first image. Regression analysis of the time-activity curve gives a $T_{1/2}$ emptying rate of 78 minutes.

emptying have been described. The power exponential model most appropriately represents the physiologic characteristics of GE in animals. The power exponential equation can be expressed as:

$$Y = [-\alpha(t)]^{\beta}$$

Where α and β are the shaping parameters of the curve, t is time, and Y is percent retained gastric activity (PRGA).

Alpha (α) is the parameter that is used to describe the shape of the shoulder of the gastric emptying curve also called the lag phase. This corresponds to trituration of the meal or the delay to onset of GE. Beta (β) provides the “general” shape of the GE curve. The toe region of the curve represents the last phase of GE.

While providing the best fit for solid-phase emptying, the power exponential model tends to be less accurate at the end of GE due to noise and the tendency of the curve to go up if the study period becomes too long.

Normal Scintigraphic Findings

There is no universal set of normal scintigraphic

Table 16.5: Reference Ranges for the T_{50} for Gastric Emptying Previously Reported in Veterinary Medicine²⁻¹⁴

Species	Test Meal	Reported T_{50} Range
Feline	75 g scrambled egg	210-769 minutes
Feline	80 g canned food	146-176 minutes
Feline	50 g dry food	218-246 minutes
Feline	18 mL water	60-96 minutes
Feline	36 mL water	101-170 minutes
Canine	2 oz beef baby food 1 cup kibble	176-412 minutes
Equine	150 g crimped oats 100 g bran 200 mL water 2 scrambled egg yolks	34-251 minutes
Equine	200 mL water	10-74 minutes

ic parameters established in veterinary medicine because many of the studies that have been done have used different food formulations, meal volumes, caloric intake, and various radiopharmaceuticals. The results from studies involving different animal species are summarized in Table 16.5. In general, the reported T_{50} for dogs is < 5 hours when water intake is adequate. The T_{50} for cats is < 4 hours. Several other generalizations from some of the studies where a set feeding protocol was used include the following. In one study of cats, GE was delayed after intravenous diazepam. In a separate study in cats, GE was increased in the presence of a gastric PEG tube. Indwelling nasogastric tubes have also been found to increase liquid-phase GE in horses. The impact of other pharmacologic agents or surgical procedures on gastric emptying has not been documented. Therefore, more work in this area needs to be done to better understand the impact that various drugs and/or procedures might have on GE.

Abnormal Scintigraphic Findings

Gastric emptying in dogs with chronic outflow obstruction (eg, pyloric hypertrophy) has increased T_{50} values (> 5 hours). Delays in GE have also been

identified in animals that are stressed by excessive handling. This latter factor must be considered in animals unaccustomed to restraint and handling.

Gastrointestinal Blood Loss Imaging

One can identify gastrointestinal (GI) blood loss by observing the accumulation of ^{99m}Tc -labeled red blood cells (RBC) or ^{99m}Tc -sulfur colloid within the gastrointestinal tract over time. Precise localization may not be possible due to background radioactiv-

Table 16.6: Indications for GI Blood Loss Imaging

Document the presence or absence of gastrointestinal bleeding.
Semi-quantify degree of blood loss and determine the severity of bleeding.
Determine the location if active bleeding is present.

Table 16.7: Imaging Parameters for Gastro-intestinal Blood Loss Imaging

Animal preparation	No specific preparation required.
Static frame acquisition	1-minute acquisition times.
Matrix	256 × 256 × 16.
Collimator	Low-energy, all-purpose or high-resolution, low energy.
Time to image	5, 15, 30, 60, 120, 180, and 240 minutes postintravenous administration if using red blood cell labeling techniques. Images should be obtained 24 hours after intravenous administration of the labeled red blood cells. If using ^{99m}Tc -sulfur colloid, then images are obtained 15 minutes after intravenous administration.
Views	Right laterl, left lateral and ventral.
Window setting	^{99m}Tc ; 140 keV with 20% window.

Table 16.8: Imaging Parameters for Protein-Losing Enteropathy Scintigraphy

Animal preparation	No specific preparation required.
Static frame acquisition	Acquire 150,000-200,000 counts for the lateral or dorsal images. Using ^{111}In , this will take between 2 and 4 minutes, depending on the injected radioactivity.
Matrix	256 × 256 × 16.
Collimator	Medium-energy, all-purpose.
Time to image	45 minutes, 2, 4, and 24 hours postintravenous injection of the ^{111}In dium chloride or ^{111}In dium-labeled transferrin.
Views	Right lateral, left lateral and ventral.
Window setting	Dual-energy photon imaging for ^{111}In with a 20% window set on the 174 and 247 keV photopeaks.

ity and the need for follow-up imaging at 24 hours postinjection when using labeled red cells. For either study to be valid, active bleeding must take place during the scintigraphic examination. Because of the rapid uptake of the ^{99m}Tc -sulfur colloid within the macrophages of the liver, and spleen (and lungs in the cat), bleeding must be active at the time of injection.

The advantages of using ^{99m}Tc -sulfur colloid include the absence of substantial background radioactivity, sensitivity rates of at least 0.1 mL of blood loss

per minute and immediate imaging capabilities. The disadvantages include the fact that the bleeding must be present at the time of injection, re-imaging at a later time is not applicable unless a second injection is made and the cranial gastrointestinal tract will be obscured by the radioactivity of the liver and spleen. The advantages of using ^{99m}Tc -RBC include, similar sensitivities as with sulfur colloid imaging, although a total of 3 mL per min of blood must accumulate to be visualized due to the high amount of background

radioactivity (decreased signal to noise ratio). This technique is better for imaging intermittent bleeding versus the necessity for bleeding to be present at the time of injection. In human studies, labeled red blood cells have been shown to be more sensitive than sulfur colloid studies for detecting GI bleeding. Delayed imaging is strongly recommended, with the last image being obtained the next day. The disadvantages of ^{99m}Tc -RBC include the possibility of false-positive findings due to normal vascular structures. Additionally, the labeling of the red blood cells is time intensive and, as red blood cells can become denatured due to the rough handling of the cells, splenic uptake can occur. If the labeling of the red blood cells was poor, sodium pertechnetate uptake within the stomach can result in false-positives if interpreted as being abnormal. The indications are summarized in Table 16.6.

Principles of Interpretation

Each image should be evaluated for accumulation of radioactivity in the stomach, small intestine, or colon for confirmation of

. Images are read in a reverse order, ie, viewing starts with the last image of the study. If there is a GI bleed, there should be radioactivity seen within the colon. Colonic radioactivity is conspicuous because the radiolabeled red blood cells will be concentrated in the colon secondary to water removal. On imaging, the colon will have a characteristic appearance as expected for a lower GI study. If the study is positive, there will be colonic radioactivity, particularly on the 24-hour image. The images are then inspected in reverse order to determine the time and relative location where the first intestinal radioactivity is seen. Intestinal radioactivity should appear linear after time, but can will be seen first as just a focal accumulation of the radiolabeled blood (Figure 16.6). The acquisition parameters are summarized in Table 16.7.

^{111}In -Transferrin for Protein-Losing Enteropathy

^{111}In is a ferric iron analog and readily binds to iron receptors within the body. ^{111}In -transferrin scintigraphy is used to determine the presence of protein

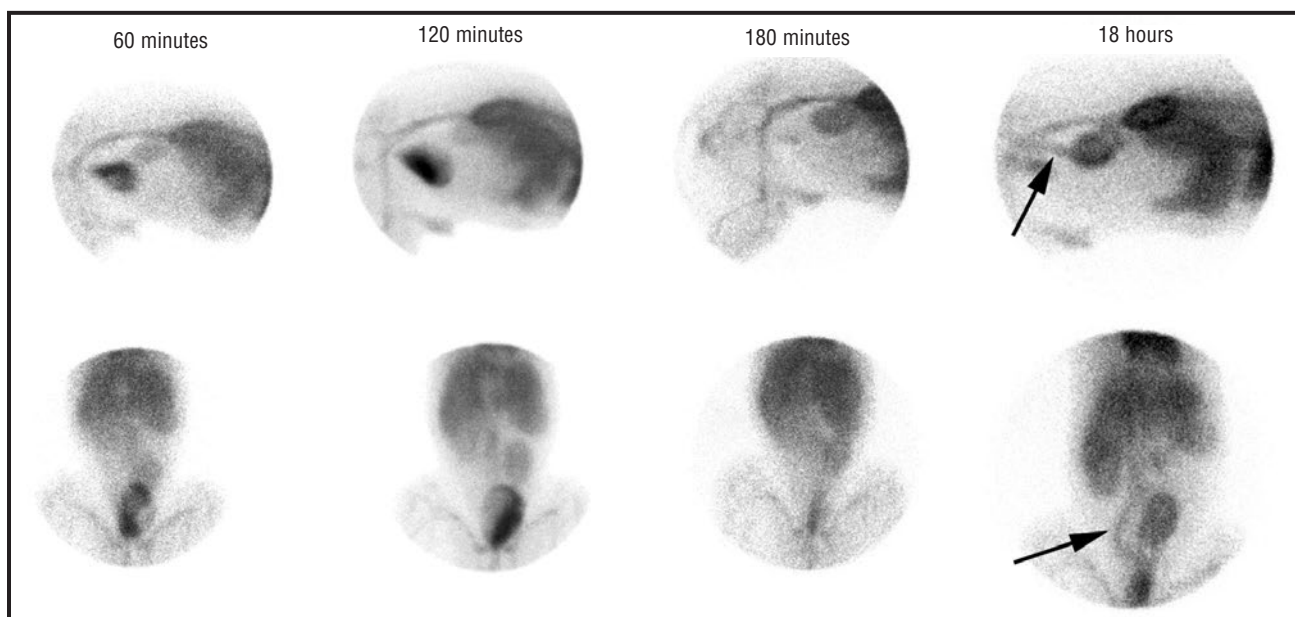


Figure 16.6: Gastrointestinal bleeding study in a dog with a distal GI bleed

Right lateral and ventral images from a dog obtained at 1, 2, 3, and 18 hours following injection of ^{99m}Tc -RBCs. On the last image set, there is linear activity seen on the dorsal caudal abdomen (arrows) corresponding to the area of the descending colon. The location of the bleed appears to be in the area of the distal ileum or proximal colon. Radioactivity in the urinary bladder is secondary to ^{99m}Tc dissociation from the labeled red blood cells.

losing enteropathies in dogs. The kinetics of normal ^{111}In -labeled transferrin has been reviewed in dogs.¹⁹ The ^{111}In -transferrin localized in the liver and bone marrow by 48 hours in normal dogs with some urinary excretion noted on early images (24 hours). Plasma clearance of the ^{111}In -transferrin was noted to be biphasic, with an initial clearance half-time of 6 hours and a delayed clearance-half time of 40 hours.¹⁹ The ^{111}In -transferrin was also evaluated in a series of four dogs with clinical signs and histology intestinal changes consistent with protein-losing enteropathy.²⁰ Rapid accumulation of the ^{111}In -transferrin within the intestinal tract was noted on 4- and 24-hour images. In one dog after a course of treatment and resolution of clinical signs, there was no evidence of ^{111}In -transferrin accumulation in the intestinal tract. Restricted access to ^{111}In and the long physical half-life (equating to prolonged holding times for the patients) has resulted in limited use of this technique. The acquisition parameters are summarized in Table 16.8. ^{111}In -transferrin has yet to be investigated in cats or in protein-losing enteropathies.

Summary

Gastro-intestinal scintigraphy has a variety of applications that are unique to nuclear medicine and are sensitive techniques for evaluating gastric emptying for liquids or solids. Due to individual and population variations within a species, gastric emptying studies may be best suited for follow-up evaluations after treatment.

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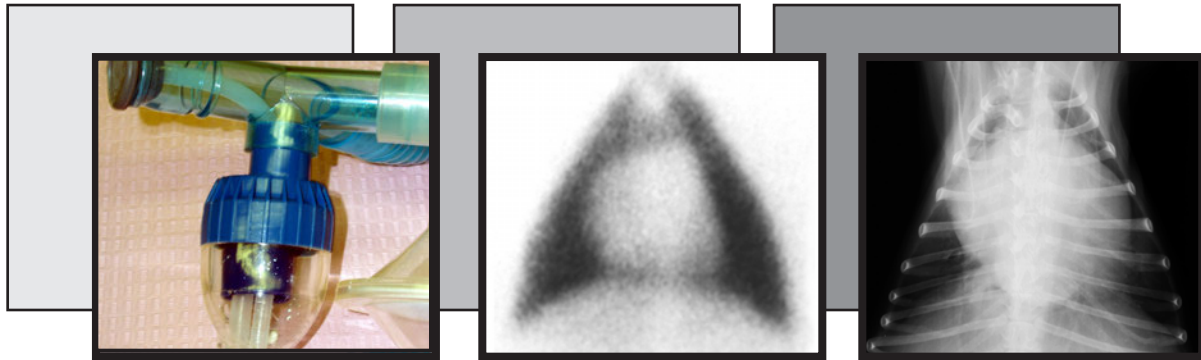
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Pulmonary and Mucociliary Scintigraphy

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Introduction

Pulmonary perfusion imaging has been used in veterinary medicine primarily for assessing small animal patients suspected of having pulmonary thromboembolism and horses with chronic obstructive pulmonary disease or exercise-induced pulmonary hemorrhage.¹⁻⁷ The advent of spiral CT and CT angiography will limit the use of pulmonary perfusion scans in the future.^{8,9} Ventilation studies have been predominantly limited to research applications due to the requirement of patient cooperation or general anesthesia. Morbidity, mortality, and probabilistic studies have not been done in veterinary medicine to estimate the prevalence and significance of pulmonary thromboembolism. Quantitative perfusion or ventilation washout studies may be shown to provide information regarding the pathophysiology of various pulmonary disorders in future investigations.^{6,10-18} A current set of orthogonal radiographs of the thorax is necessary when interpreting perfusion scans for detecting thromboemboli, even when utilizing the combination of ventilation and perfusion scintigraphy.

Pulmonary Physiology

An understanding of pulmonary blood flow and ventilation physiology is necessary to understand the utility of these imaging modalities. The basic function of the lungs is to exchange gas (oxygen and carbon dioxide) between the circulation and the outside environment.¹⁹ The lungs have a tremendous surface area (alveoli) for gaseous exchange, and the pulmonary circulation receives the total cardiac output. Ideally, the pulmonary ventilation will match lung perfusion so maximum gaseous exchange between alveoli and pulmonary capillaries can take place. Under steady-state conditions, the partial pressure of any gas in the alveolar space is determined by the ratio of ventilation to perfusion (V-Q). Even in the normal lung, ventilation (V) and perfusion (Q) are not perfectly matched. In disease states, the degree of V-Q inequality may become quite high. Gravity-dependent blood flow and ventilation gradients are normally seen in the human lung.²⁰ The dependent portion of the lung receives a greater amount of the blood flow and a slightly greater amount of air when compared with the nondependent portion of the lungs. Similar ventilation gravity-dependent

gradients exist in the standing conscious dog and horse.^{10,11} In humans and animals, an autoregulatory mechanism exists so blood flow is shunted away from nonventilated or hypoxic areas of the lung and redirected toward areas of better ventilation.

When abnormalities occur that alter the normal V/Q ratio of 1:1, a mismatch results. Increased V/Q ratio occurs when there is normal ventilation and decreased pulmonary blood flow to a region of lung. This pattern is seen with pulmonary thromboembolism and, to some degree, with emphysema due to the destruction of pulmonary alveolar walls and capillaries. A decreased V/Q ratio can be seen in animals where there is increased or normal perfusion but decreased or absent ventilation. Inadequate ventilation may be due to abnormal airway resistance, such as is seen with chronic obstructive pulmonary disease or asthma. Inadequate ventilation may also be due to abnormal alveolar compliance as seen with lobar pneumonia, pulmonary edema or recumbent atelectasis. The indications for ventilation/perfusion scintigraphy include evaluation of pulmonary perfusion or in patients with chronic obstructive lung disease.

Ventilation/Perfusion Scintigraphy

Radiopharmaceuticals

A wide variety of radionuclides and radiopharmaceuticals are used for lung scintigraphy in humans, and many subsequently find their way into the veterinary field. For practical reasons, ^{99m}Tc is the radionuclide of choice for most procedures and is used in conjunction with a functional, dependent pharmaceutical, (eg, macroaggregated albumin [MAA] or diethylene-triamine-pentetic acid [DTPA]). Except for perfusion imaging and occasional ventilator studies, however, there are few published reports of clinical studies in animals.

Pulmonary Perfusion Scintigraphy

Pulmonary perfusion imaging is based on physical blockade of the pulmonary capillary bed by particles of ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA). Ninety percent of these particles measure 10 to 40 μ m in diameter and, when injected intravenously, will lodge in the first capillary bed encountered, in

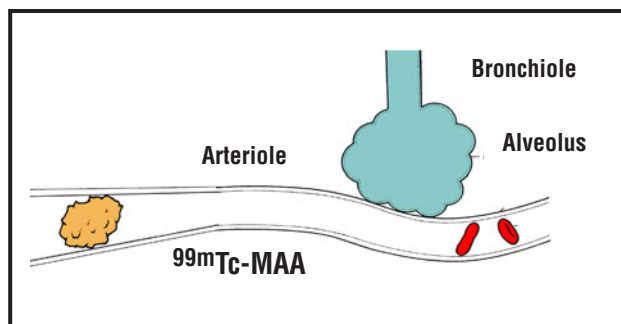


Figure 17.1: Diagram of a terminal bronchiole and alveolus showing the mechanism of localization of ^{99m}Tc -MAA

this case, the pulmonary capillaries (Figure 17.1).²¹ If the particles are evenly mixed in the venous blood, their distribution in the lungs is proportional to pulmonary blood flow. The number of particles injected is an important consideration. A commercial MAA kit contains 4.0 to 12.0 million particles.²² The typical number of particles injected in a human patient is between 400,000 and 1,200,000 particles or one tenth of the kit.²² In a 70 kg person, it is estimated that this number of particles would occlude 0.1% of the pulmonary capillary beds.²³ The occlusion of the capillary beds is temporary with a biologic half-life of 4 to 6 hours before the particles are removed by pulmonary macrophages.²²⁻²⁴ As the label dissociates, the majority of the oxidized $^{99m}\text{TcO}_4^-$ is excreted by the kidneys.

The radiopharmaceutical can be injected away from the gamma camera as the particles remain in position in the lungs for several hours. At the same time, there is no need to delay imaging as the ^{99m}Tc -MAA particles will lodge immediately after intravenous injection. If ^{99m}Tc -DTPA ventilation imaging precedes perfusion, 5 to 10 times the radioactivity of the ^{99m}Tc -DTPA administered during the ventilation study is given during the perfusion study. Acquisition is similar to that for the ventilation studies. Images should be acquired for 300,000 to 500,000 counts per image in small animals and 500,000 to 600,000 counts per image for large animals. Images should include right and left lateral, dorsal right and left oblique, and dorsal and ventral images for small animals. The operator should obtain left and right lateral views in horses, where the number of images required to cover the entire lung field will be depen-

dent upon the size of the gamma camera crystal and the horse.

^{99m}Tc -MAA is prepared from lyophilized kits 15 minutes prior to intravenous injection. In dogs, one must inject between 300,000 to 500,000 particles per patient which represents one tenth to one twentieth of the volume within the vial. The use of ^{99m}Tc -MAA is contraindicated in patients with severe pulmonary hypertension. Although rare, in the authors' experience, right-sided heart failure and even death have been seen in dogs following injection of ^{99m}Tc -MAA. Pulmonary perfusion scintigraphy is considered safe, but the number of particles injected should be considered before determining the injected dose. The indications and acquisition parameters for ventilation/perfusion scintigraphy are summarized in Tables 17.1 and 17.2.

Ventilation Scintigraphy

Ventilation scintigraphy evaluates the flow of air to the lungs. The delivery of the radionuclide/pharmaceutical depends on the patient and the alveolar exchange unit. There are two classes of radionuclides used in ventilation scintigraphy.

These are: radioactive gases ($^{133}\text{Xenon}$, $^{127}\text{Xenon}$, $^{81m}\text{Krypton}$, and "technegas") and radioaerosols (^{99m}Tc -DTPA).^{3,4,12,13,15,21,25-27} These radioactive gases are summarized in Table 17.3.

Radioactive Gases

$^{81m}\text{Krypton}$ is a radioactive noble gas with a 13.6 second physical half-life, and a 190 keV gamma photon. ^{81m}Kr is delivered by an exhaust-vented breathing circuit from a $^{81}\text{Rubidium}$ generator (parent $T_{1/2} = 4.7$ hours).²¹ Research studies in horses using ^{81m}Kr have been reported.^{11,25} These studies are usually acquired in a dynamic frame mode format and the images summed to form a composite image with a greater number of counts. ^{81m}Kr excretion is primarily by in situ decay due to the short physical half-life. The remainder of the ^{81m}Kr will rapidly decay in the exhaust system after being exhaled from the lungs. An investigational method for using ^{81m}Kr eluate that is delivered in physiologic saline has been reported for the evaluation of pulmonary perfusion

Table 17.1: Indications for Ventilation/Perfusion Scintigraphy

Evaluate pulmonary perfusion. - Pulmonary thromboembolism (^{99m}Tc-MAA). - Chronic obstructive pulmonary disease. - Help to lateralize a pulmonary lesion in the horse (right versus left lung lobe). - Determine the severity of lung disease, (eg, canine or feline heartworm disease).
Evaluate global and regional pulmonary ventilation. - Ventilatory flow: washin technique for identifying nonventilated lung (^{131}Xe, ^{99m}Tc-DTPA, and ^{81m}Kr). - Single breath-hold techniques are not applicable in veterinary medicine; but evaluating the radionuclide as it comes into the lungs can be done using a dynamic study format. - Equilibrium imaging (^{131}Xe, ^{99m}Tc-DTPA, and ^{81m}Kr). - Washout technique for identifying air trapping (^{133}Xe).
Calculate ventilation/perfusion ratios on a regional or global basis using parametric imaging.
Measure solute absorption from the trachea, airways, or pulmonary alveoli (^{99m}Tc-DTPA pulmonary clearance studies).

in horses. The route of excretion for this inert, non-soluble gas is 100% diffusion into the alveoli on first pass through the lungs.

^{131}Xe is a radioactive noble gas with a 5.3-day physical half-life and an 81 keV gamma photon.²¹ A mixture of ^{131}Xe and oxygen is inhaled as either a single deep breath or as a continuous rebreathing circuit for 3 to 5 minutes. A closed rebreathing system is necessary to trap the exhaled gas. ^{131}Xe washin and washout techniques can be used in small animals. They are not applicable for horses because of the low photon energy and marked attenuation. ^{131}Xe is lipid soluble, and uptake in a fatty infiltrated liver is possible. Elimination of the ^{131}Xe is by exhaling the radioactive gas from the lungs. The radioactive gases are then trapped in a lead-shielded container to allow for decay.

Radioaerosols

Radioaerosols can be used as an alternative to radioactive gases for ventilation studies. A solution of ^{99m}Tc -diethylene-triamino-penta-acetic acid (^{99m}Tc -DTPA) is nebulized into small particles. Radioaerosol particles less than 2 μm can reach the alveoli.²⁸ The radioaerosols are generated from an ultrasound or positive-pressure nebulizer. Small disposable nebulizers are now commercially available (Figure 17.2).¹⁷

The radioaerosol is administered to the patient using a closed ventilation circuit.¹⁴ A closed rebreathing system with a filter is necessary to trap the radioaerosol in the exhaled gas. For best results, the aerosol droplets should average 0.5 to 1.0 μm mean aerodynamic diameter.^{3,13,15,21,27} Typically 740 to 2,220 MBq (20 to 60 mCi) of ^{99m}Tc -DTPA is placed into the jet nebulizer. The typical delivered dose is much lower so that the animal breathes the radioaerosol mixture until there is adequate lung activity seen on the persistence scope prior to starting the acquisition. The actual delivered dose to the lungs of the dog is 9.25 MBq (0.25 mCi), the cat is 3.7 MBq (0.1 mCi), and the horse is 111 to 185 MBq (3 to 5 mCi). The oxygen flow rate for most nebulizer units is in the 10 to 12 L per minute range.

^{99m}Tc -DTPA is a small soluble molecule that is absorbed across the alveolar membrane into the blood stream. Subsequent excretion is almost exclusively by the kidneys.

For small animals, static images are acquired using a matrix size of $256 \times 256 \times 16$ immediately following radioaerosol administration. A dynamic acquisition mode may be required for ^{81m}Kr where a single summed image is created from the dynamic image set after motion correction.

Table 17.2: Acquisition Parameters for Evaluating Large and Small Animals Using Perfusion Scintigraphy**Radiopharmaceutical**^{99m}Tc-Macroaggregated albumin (MAA).**Dose**

Species	mCi	MBq
Dog	0.5 - 2	17.5 - 74
Cat	0.5	17.5
Horse	15 - 20	555 - 740

For small animals, the total number of ^{99m}Tc-MAA particles should not exceed one tenth of the total number of particles in a vial.

Acquisition Parameters

Horses	
Matrix size	256 × 256 × 16.
Time to imaging	1 to 5 minutes after intravenous injection of ^{99m} Tc-MAA. The particles should localize in the lungs within 30 seconds.
Collimator	Low-energy, all-purpose.
Views	Right and left lateral images with as many views as it takes to cover the entire lung field on both sides. One can use an external ⁵⁷ Co marker if images are to be merged as a single image. Dorsal and dorsolateral oblique images can be obtained if the camera system will allow for placing the elevation of the camera to the appropriate height.

Dogs and Cats	
Matrix size	256 × 256 × 16.
Time to imaging	1 to 5 minutes after intravenous injection of ^{99m} Tc-MAA. Make the injection with the dog or cat in sternal recumbency to ensure even distribution of the ^{99m} Tc-MAA. Images should contain 250,000 to 500,000 counts.
Collimator	Low-energy, all-purpose.
Views	Dorsal, ventral, right and left lateral, and the two dorsolateral obliques.

For large animals, a dynamic acquisition that can be motion corrected should be obtained. The acquisition parameters for the dynamic study include 24 frames of 2.5 seconds each (128 × 128 × 16), with an external reference marker (⁵⁷Co) so the frames can be reviewed, motion corrected, and summed to form a final composite image. Two nebulizers are placed

in the circuit, each containing 1 to 2 ml (1,110 MBq per mL or 30 mCi per mL) of ^{99m}Tc-DTPA. Horses should breathe through the closed circuit prior to turning on the nebulizers. Compressed air (15 L per minute) is used to aerosolize the ^{99m}Tc-DTPA within each nebulizer unit.^{4,13}

Table 17.3A: Comparison of the Physical Properties of Radioactive Gases and Radioaerosols Used for Ventilation Scintigraphy

Radionuclide/ Pharmaceutical	Radioactive Form	Physical Half-Life	KeV Principle Gamma	Decay	Ventilation Techniques Employed
^{81}Kr	Gas	13 seconds`	191 (65%)	Isomeric transition	Washin
^{127}Xe	Gas	36.4 days	203 (65%)	Electron capture	First breath (washin), equilibrium, and washout
^{133}Xe	Gas	5.7 days	81 (39%)	Beta minus	First breath (washin), equilibrium, and washout
$^{99\text{m}}\text{Tc}$ “technegas” labeled carbon particles measuring 0.02 to 0.2 μm in diameter	Gas	6 hours	140 (86%)	Isomeric transition	Equilibrium studies
$^{99\text{m}}\text{Tc}$ -DTPA	Aerosol	6 hours	140 (86%)	Isomeric transition	Equilibrium and clearance studies

Table 17.3B: Advantages of Each of the Gases and Radioaerosols Used for Ventilation Scintigraphy

Radioactive Form	Advantages	Disadvantages
^{81}Kr	Short $T_{1/2}$ and decays in lungs. Photon energy and mode of decay.	Expensive. ^{81}Rb generator that must be replaced daily. Limited availability. Single view. Never equilibrates in poorly ventilated regions of the lung. Demonstrates an initial distribution of the gas (flow study) and lacks washout information so the obstructive changes or air trapping cannot be demonstrated.
^{127}Xe	Better gamma photon energy and ^{133}Xe . Washin, equilibrium, and washout techniques possible.	Moderate expense. Longer physical half-life. Medium energy collimators needed.
^{133}Xe	Washin, equilibrium, and washout techniques possible. Can detect areas of air trapping.	Longer physical half-life. Not useful in horses due to low photon energy and poor photon flux. Beta minus decay results in radiation safety considerations.
$^{99\text{m}}\text{Tc}$ “technegas”	SPE[C]T capabilities (20-minute equilibrium phase). More homogeneous distribution than radioaerosol.	Not commercially available in the United States.
$^{99\text{m}}\text{Tc}$ -DTPA	Photon energy and physical half-life ideal. SPE[C]T capabilities. Inexpensive, readily available. Can record aerosol images in multiple views.	6% of studies in humans are not interpretable. Central deposition of the radioaerosol in patients with chronic obstructive lung disease (may also be seen in tachypneic patients). Will not demonstrate areas of air trapping.

Ventilation/Perfusion (V/Q) Scintigraphy

^{99m}Tc -DTPA aerosol ventilation and ^{99m}Tc -MAA perfusion scans using the previously mentioned techniques are completed to calculate a V/Q ratio.³ If both ventilation and perfusion studies are to be done on the same day, the ^{99m}Tc -DTPA aerosol

study should be performed first. The perfusion study follows at a higher dose (5 to 10 times the inhaled ventilation dose). In this manner, the quantity of ^{99m}Tc -MAA for the perfusion study overrides the residual ^{99m}Tc -DTPA from the ventilation study. One aligns the ventilation and perfusion images using external reference markers for creating, calculating, and displaying the combined V/Q images.

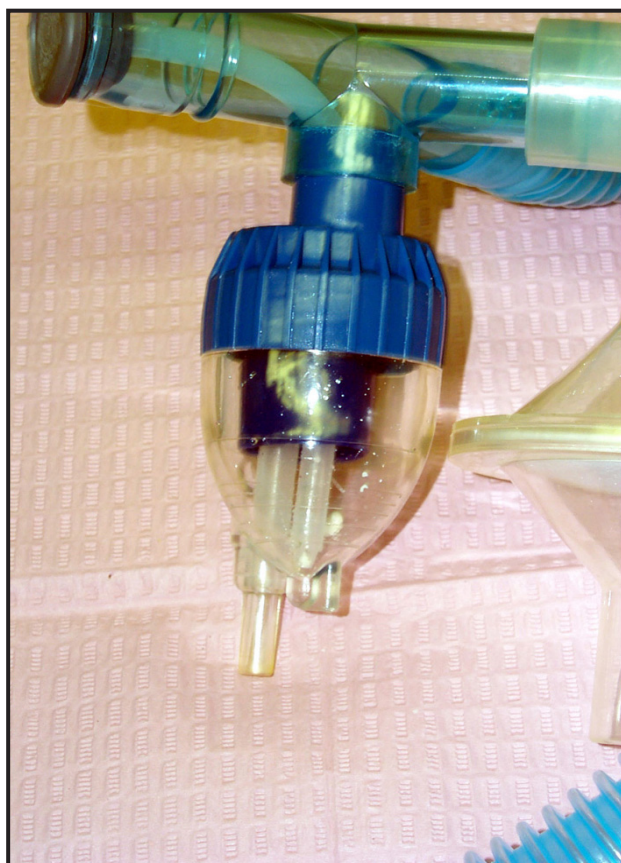


Figure 17.2: Jet nebulizer used to aerosolize ^{99m}Tc -DTPA

Evaluation of Pulmonary Capillary Membrane Permeability

^{99m}Tc -DTPA impacts the bronchial and alveolar walls and will gradually be absorbed. The rate of absorption is a measure of capillary membrane permeability.²⁹ Increased capillary membrane permeability is seen in patients with chronic interstitial lung disease, acute pulmonary injury, radiation pneumonitis, and active interstitial lung disease.²⁹ To measure pulmonary clearance of ^{99m}Tc -DTPA aerosol, a series of 8 to 20 dorsal static images of the lungs in a $128 \times 128 \times 16$ format are obtained at 5- to 8-minute intervals or until the mean number of counts are less than 50% of the original image. Clearance half-times can be calculated from decay-corrected, time-activity curves for each lung or from the total counts from both lungs. The curves are fitted using a least squares, mono-exponential fit. The pulmonary clearance half-time is determined from the rate constant derived from the mono-exponential fit. The expected pulmonary clearance half-time is 55 minutes for horses and 48 minutes for dogs (Table 17.4).

Table 17.4: Representative Washout (Clearance) Values for ^{99m}Tc -DTPA Radioaerosol Studies in Different Species.

Species	Clearance Half-Time (minutes)	Reference
Horse	55.6 ± 14.2 (Std Dev)	O'Callaghan (1987)
Dog	66 ± 11 (Std Dev)	Oberdorster (1984)
Dog	43 ± 12 (Std Dev)	Harnagle (1989)
Sheep	293 ± 74 (Std Dev)	Hornof (1988)
Humans	59 ± 5 (Std Error)	Jones (1980)

Mechanisms of Localization and Image Acquisition

1. Ventilation Imaging with Radioaerosols

Radioaerosols document the flow distribution in the air exchange regions of the lungs by depositing aerosol droplets in the terminal airways and alveoli. The physical characteristics of the aerosol and the conditions of delivery are critical to avoid radioaerosol deposition in the larger airways. Suitable aerosols must fall within a narrow size range having a measured mean aerosol diameter of 0.5 to 1.0 μm . Droplets larger than 2.0 μm are deposited in the nasal cavity, trachea, and large airways.²⁸ Larger particles have high inertia and are predominantly deposited by impaction, as they are unable to follow changes in airway direction. Turbulence increases larger particles, impacting the airways by increasing the initial velocities toward the airway walls. Smaller particles are called droplets (less than 0.1 μm) and remains suspended during the respiratory cycle. These can be exhaled into the filter trap of the breathing circuit.²⁸ Droplets are deposited in the airways either by impaction or by sedimentation. Smaller particles in the diagnostic range are predominantly deposited by sedimentation as their settling velocities exceed airflow velocity. Brownian movement and minor air currents keep most of the tiny particles in suspension.

Numerous methods of producing small particle aerosols are now available. Most nebulizers are based on the Venturi effect; however, ultrasonic nebulizers that will deliver a greater volume of the radioaerosol with consistent small particle sizes are also available. The ventilation circuit design must be adapted to the size of the subject. Human systems fitted with a face-mask may be suitable for large dogs. Key features of the nebulization system should include low airway resistance, minimal dead space in the mask and tubing, a filter system that removes exhaled radioactive particles, a leakproof circuit, and appropriate radiation shielding for the nebulizer and tubing.

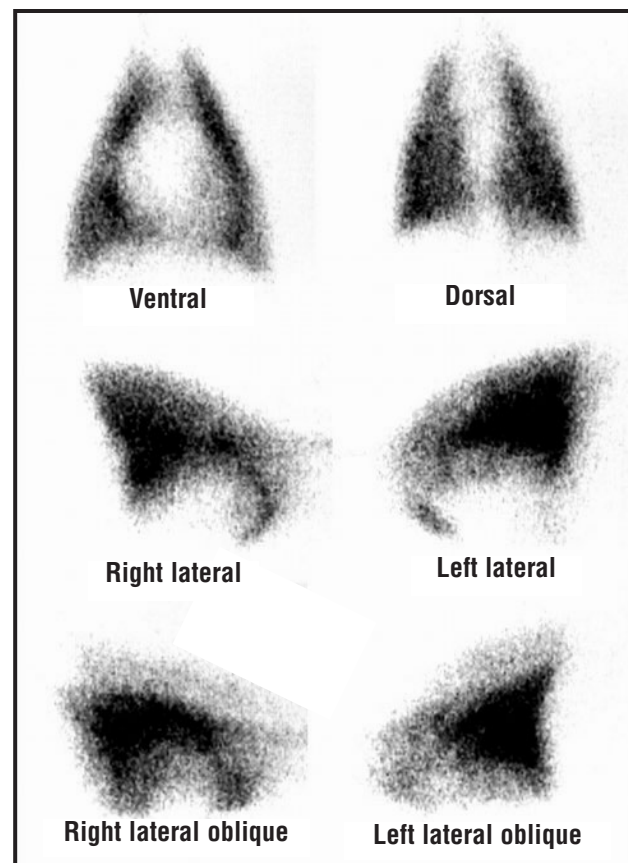
Aerosol delivery requires a tightfitting mask with minimal dead space (separate inflow and outflow tubing). The exact protocol for aerosol delivery is not critical; however, it should be completed in less than 5 minutes. Ideally, the total number of accumulated counts per field of view should be at least 50,000 to

100,000. In horses, separate cranial and caudal images are needed to view the entire lung. These images can be merged into a single lung image by using an external ^{57}Co marker for realignment. Depending on the mechanical limitations of the camera system, dorsal oblique and/or dorsal views can also be obtained. Images should be acquired with minimal delay owing to rapid absorption of the $^{99\text{m}}\text{Tc}$ -DTPA. Left and right lateral, ventral, and dorsal images are routinely acquired in small animals (Figure 17.3).

The recorded aerosol images represent the accumulated sum of multiple flow-weighted events, despite aerosol remaining in the lung for some time. Local airway disease or obstruction impairs air flow, resulting in abnormal aerosol deposits. Unlike a gas such as ^{131}Xe , equilibration through collateral flow does not occur when using $^{99\text{m}}\text{Tc}$ -DTPA radioaerosols, so potential areas of “air trapping” remain unknown.

Figure 17.3: Radioaerosol scan in a normal dog

This scan was obtained after inhalation of $^{99\text{m}}\text{Tc}$ -DTPA. Images were acquired for 100,000 counts.



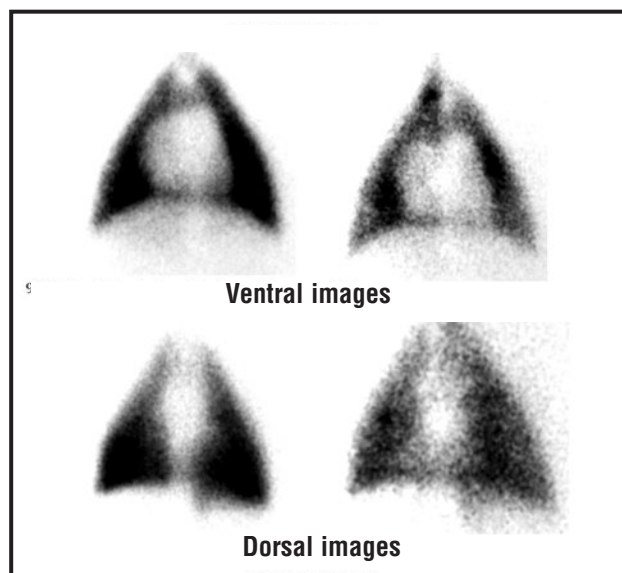


Figure 17.4: Perfusion (right) and ventilation (left) images of a normal dog

The perfusion study was done after injection of ^{99m}Tc -MAA, while the ventilation study was done after nebulization of ^{99m}Tc -DTPA. Note the matching patterns of ventilation and perfusion.

Radioaerosol deposition has been shown to be proportional to lung volume and, therefore, is considered flow weighted. ^{131}Xe and ^{127}Xe lung activity, as documented on equilibrium images, reflects lung volume; and only the washin (first breath) or washout images should be compared to the pulmonary perfusion images.

Principles of Interpretation

Normal Ventilation Scintigraphy

A homogeneous distribution of the radionuclide is expected, no matter which radioactive gas or radioaerosol is used (Figure 17.4). When using ^{99m}Tc -DTPA, ventilate the dog for 3 to 5 minutes and then initiate imaging. Due to the long clearance half-time of ^{99m}Tc -DTPA (for the dog, 48 ± 12 minutes), SPE[C]T imaging can be performed. The major advantage of using ^{133}Xe is for the evaluation of air trapping. When air trapping occurs, photopenic regions are seen on initial washin images. These photopenic areas represent regions of small airway obstruction or mucous plugging. The lung pattern

becomes homogeneous on equilibrium images as collateral flow of the radioactive gas filling in the cold areas from adjacent ventilated alveoli. The areas of air trapping retain the ^{133}Xe during the washout images and, therefore, appear hot. This flip-flop pattern is characteristic of air trapping. Normally, ^{133}Xe washes out of the lungs within 3 to 5 minutes with a clearance half-time of 2 minutes.

Using face masks, radioaerosol studies can be performed in animals. Careful attention to radiation safety is required to ensure a closed system and a tight seal at the patient-mask interface. A higher concentration of ^{99m}Tc -DTPA (740 to 1,110 MBq per mL; 20 to 30 mCi) and a high compressed air flow rate ensures rapid delivery of an adequate amount of the radioaerosol. Only 5% to 10% of the radioaerosol is delivered to the lungs.

Radioaerosol ventilation studies in normal horses show uniform distribution without evidence of central airway deposition. The portion of the lung adjacent to the diaphragm contains the most radioactivity, corresponding with the thickest area of the lung.

Normal Perfusion Studies

A homogeneous distribution of ^{99m}Tc -MAA is present throughout all lung fields (Figure 17.5). On the right lateral, and ventral views, a photopenic area for the cardiac notch is present. In horses, linear photopenic bands are seen as a result of rib attenuation (Figures 17.6 and 17.7). The radiopharmaceutical should be confined exclusively to the lung. Radioactivity outside the lung could be due either to poor labeling efficiency or a right to left shunt. The appearance of thyroid or gastric activity on initial images indicates free pertechnetate. If a right to left shunt is present, radioactivity would be expected in the cerebral cortex and the renal cortex. Pleural or diaphragmatic abnormalities, such as pleural effusion, masses, diaphragmatic hernia, and hemidiaphragmatic paralysis can result in a false positive diagnosis for a pulmonary perfusion abnormality. Cardiomegaly can also cause compression atelectasis of the adjacent lung, resulting in perfusion defects (Figure 17.8).

Ventilation/Perfusion Ratio

Parametric lung images can be made from dorsal ventilation and perfusion images in dogs and lateral images in horses. Provided there is no patient move-

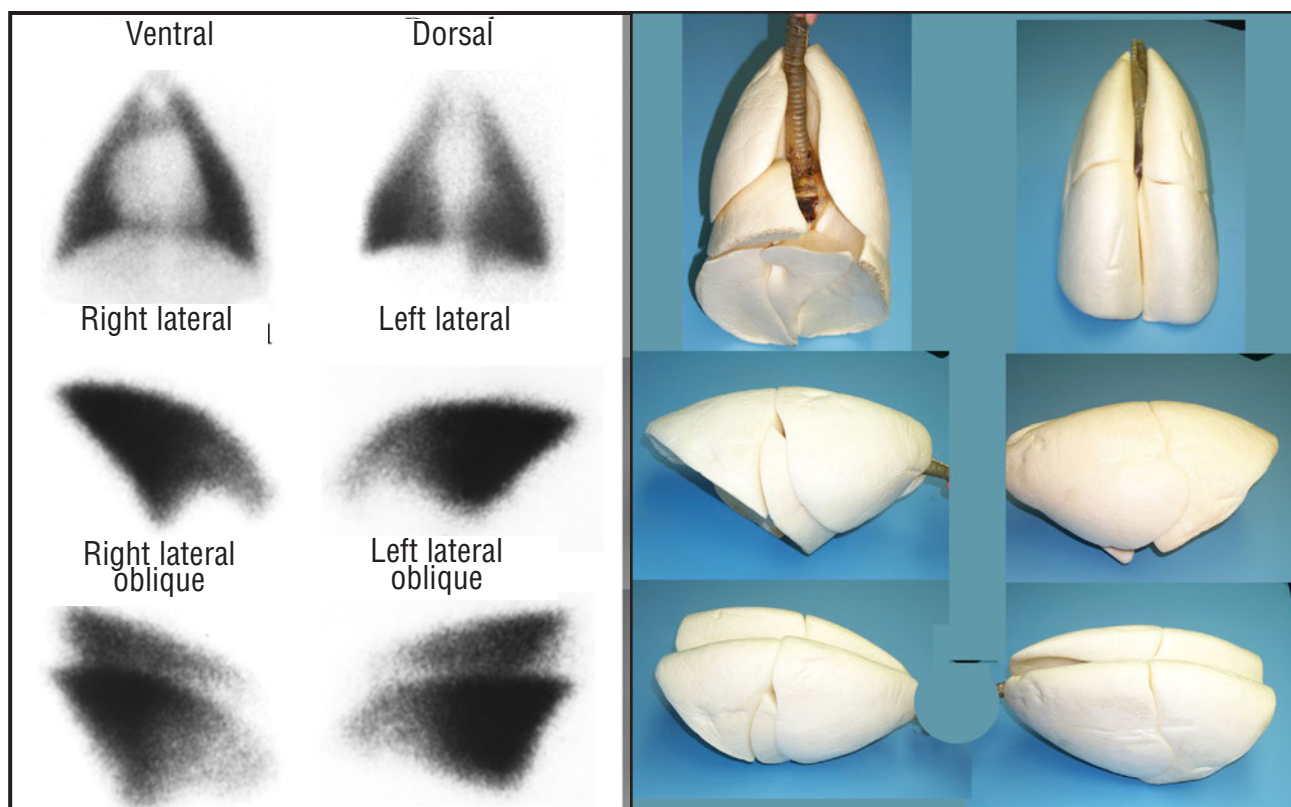


Figure 17.5: Perfusion images of a normal dog showing the routine views of the lungs

Photographs to the right show canine lungs that correspond to the perfusion-image positions.

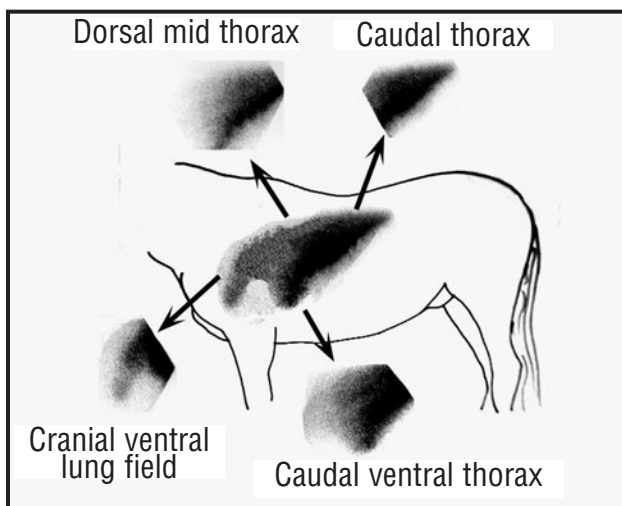


Figure 17.6: Pulmonary perfusion images in an adult horse

Because of the size of the equine lungs, multiple images of each lung are necessary to view the entire organ. With a 15-inch round camera, four images are needed. The diagram shows the position of each image relative to the horse. With a 15 x 20-inch rectangular camera, the equine lung can be imaged with two views.

ment, the parametric image is created by dividing the ventilation image by the perfusion image.⁹ Because the perfusion image has a much higher number of counts than the ventilation image, the two images must be normalized. The most common method is a point operation in which each pixel of the ventilation image is multiplied by a scaling factor needed to equalize the total number of counts of the images. The parametric image is created by an algebraic operation, which performs a pixel-by-pixel division of the ventilation image by the perfusion image. If the pixel intensity is the same on the ventilation and the perfusion images (V/Q match), the assigned pixel value in the parametric image will be 1. If the pixel intensity on the perfusion image is less than that on the ventilation image (perfusion defect), then the assigned pixel value in the parametric image will be > 1 . If the pixel intensity on the ventilation image is less than that on the perfusion image (ventilation defect), then the assigned pixel value in the parametric image will be < 1 . In this manner, small variations in V/Q patterns become conspicuous on a parametric (V/Q) image (Figure 17.9).

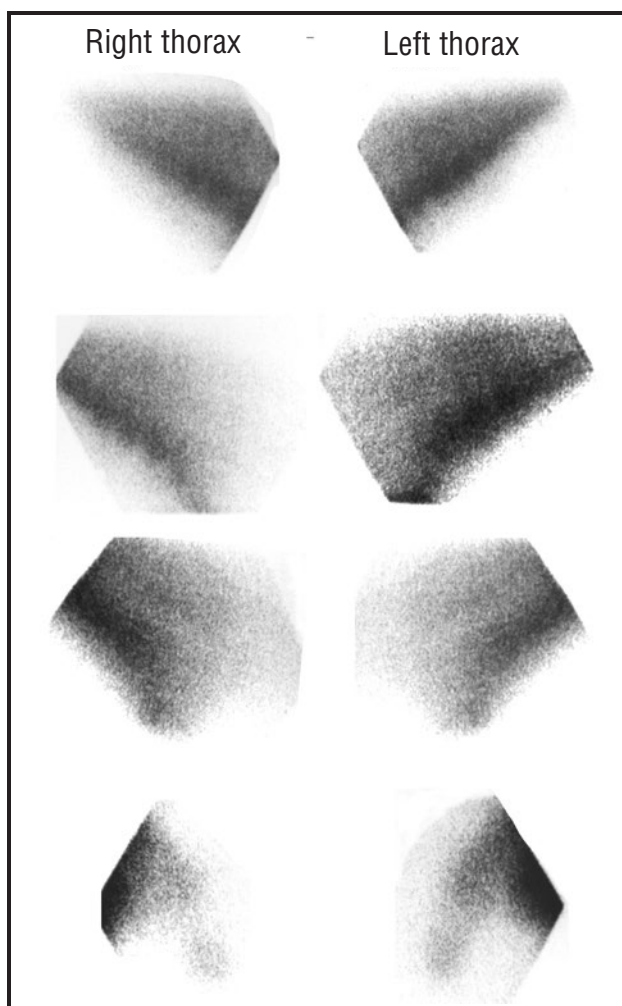


Figure 17.7: Pulmonary perfusion scan of a normal adult horse

The location of each image can be determined by referring to Figure 17.6. Note the perfusion pattern and the linear photopenic regions caused by rib attenuation.

Abnormal Ventilation Scintigraphy

Ventilation images obtained using ^{99m}Tc -DTPA radioaerosol should be homogeneous in appearance and any photopenic areas (excluding the cardiac notch) considered nonventilated areas of the lung. Correlating the ventilation image with a current set of thoracic radiographs (preferably within the last 24 hours) is done to rule out reasons for airway or bronchiole obstruction (eg, tumor or foreign body) or lobar consolidation. Experimental washout or clearance studies in dogs using intravascular occlusion of the pulmonary arteries as a model for pulmonary

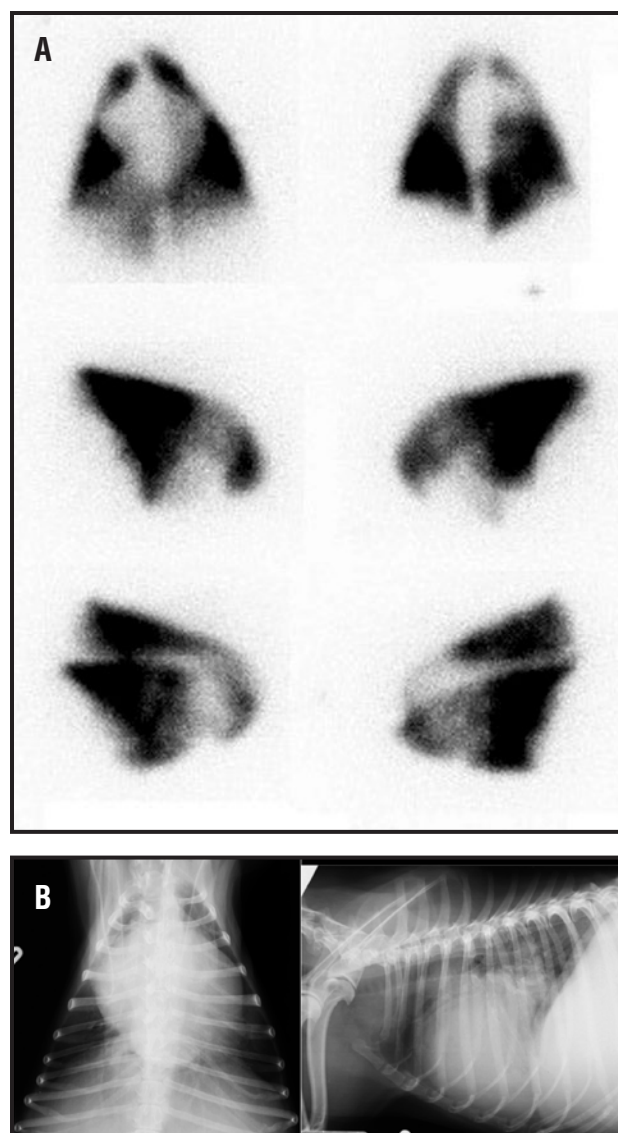


Figure 17.8: Pulmonary perfusion scan (A) and thoracic radiographs (B) in a dog with generalized cardiomegaly from chronic mitral valvular endocardiosis

A larger than expected photopenic void is seen secondary to the cardiomegaly. There is poor perfusion of the right middle lung lobe as a result of compression atelectasis from the heart.

thromboembolism show a delayed clearance ($T_{1/2} = 54 \pm 18.8$ minutes) versus the nonoccluded contralateral lung ($T_{1/2} = 43.1 \pm 12$ minutes).³⁰ Certain diseases in humans are known to accelerate the clearance half-time of pulmonary ^{99m}Tc -DTPA. These diseases include: interstitial lung disease, chronic

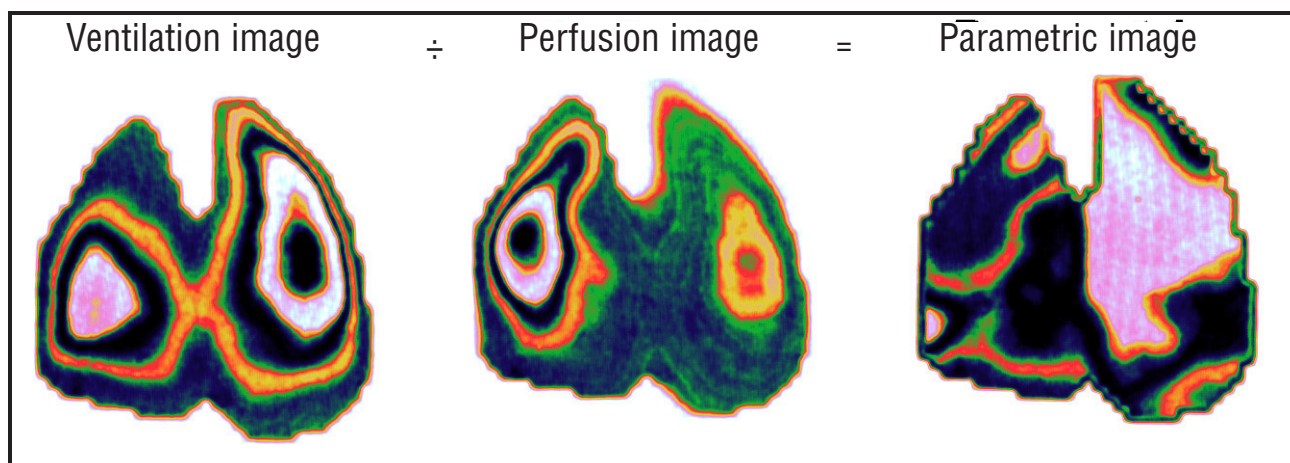


Figure 17.9: Dividing the normalized ventilation image by the perfusion image on a pixel-by-pixel basis creates parametric (V/Q) lung images

A normal parametric image should be homogenous. In this example, there is decreased perfusion in the right lung. Note that the area of decreased perfusion is more conspicuous on the parametric image.

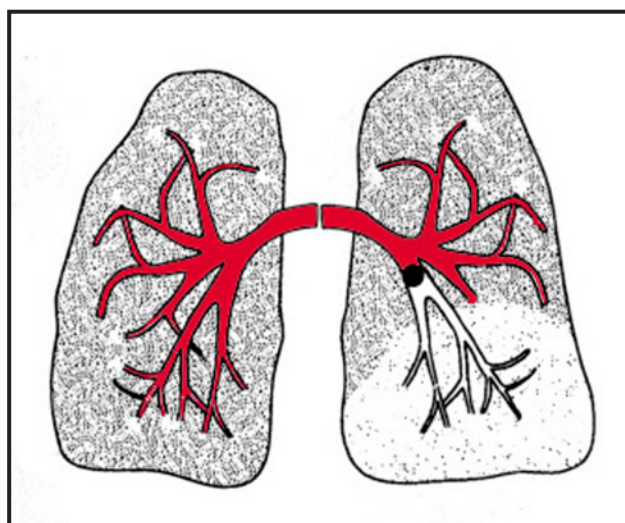


Figure 17.10: Consequence of a thromboembolus in a pulmonary artery

Note the watershed pattern of the perfusion defect distal to the occlusion in this diagram. The resultant perfusion defect will extend to the pleural surface, and it will be wedge shaped with the widest portion of the wedge seen along the pleural surface.

obstructive pulmonary disease (COPD), acute respiratory distress syndrome, and chronic pulmonary changes related to cigarette smoking.

Similar diagnostic results of ventilation studies are obtained in humans when comparing ^{131}Xe (currently the most common ventilation agent used) and $^{99\text{m}}\text{Tc}$ -DTPA. However, in patients with chronic obstructive lung disease, $^{99\text{m}}\text{Tc}$ -DTPA deposition in the peripheral lung fields is poor; and there is usually a large amount of central deposition of the radioaerosol. This uneven distribution of the radioaerosol limits the ability to detect air trapping associated with lower airway obstructive disease and, therefore, limits the total acceptance of $^{99\text{m}}\text{Tc}$ -DTPA. Some nuclear medicine physicians consider significant activity in the trachea and bronchi with a patchy distribution of the radioaerosol in the peripheral lung fields to be diagnostic for obstructive lung disease. Parenchymal lung disease of any etiology shows some reduction in the radioaerosol distribution to the abnormal area on the ventilation study.

Abnormal Perfusion Scintigraphy

Pulmonary thromboemboli result in blockage of blood flow distal to the lesion. The area of the lung distal to the occlusion will not receive the $^{99\text{m}}\text{Tc}$ -MAA particles and will be seen as an area void of radioactivity or as a high-contrast photopenic defect

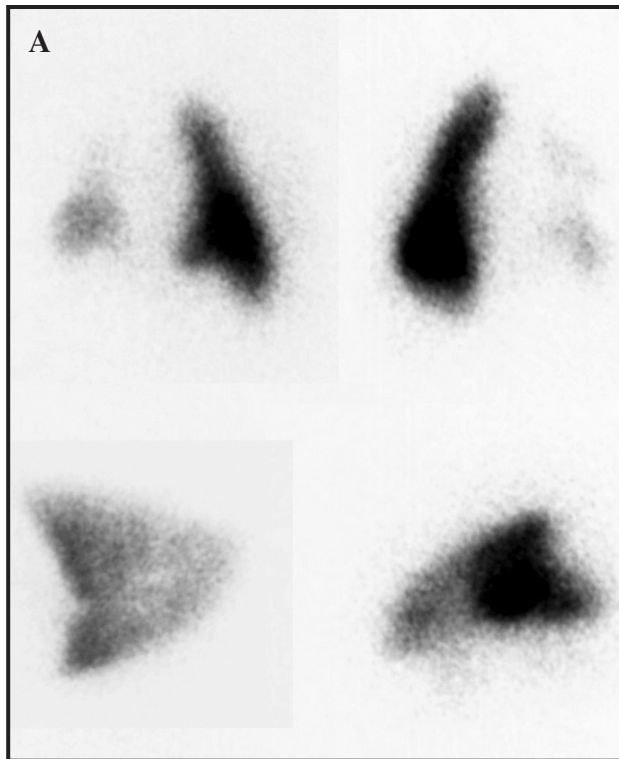
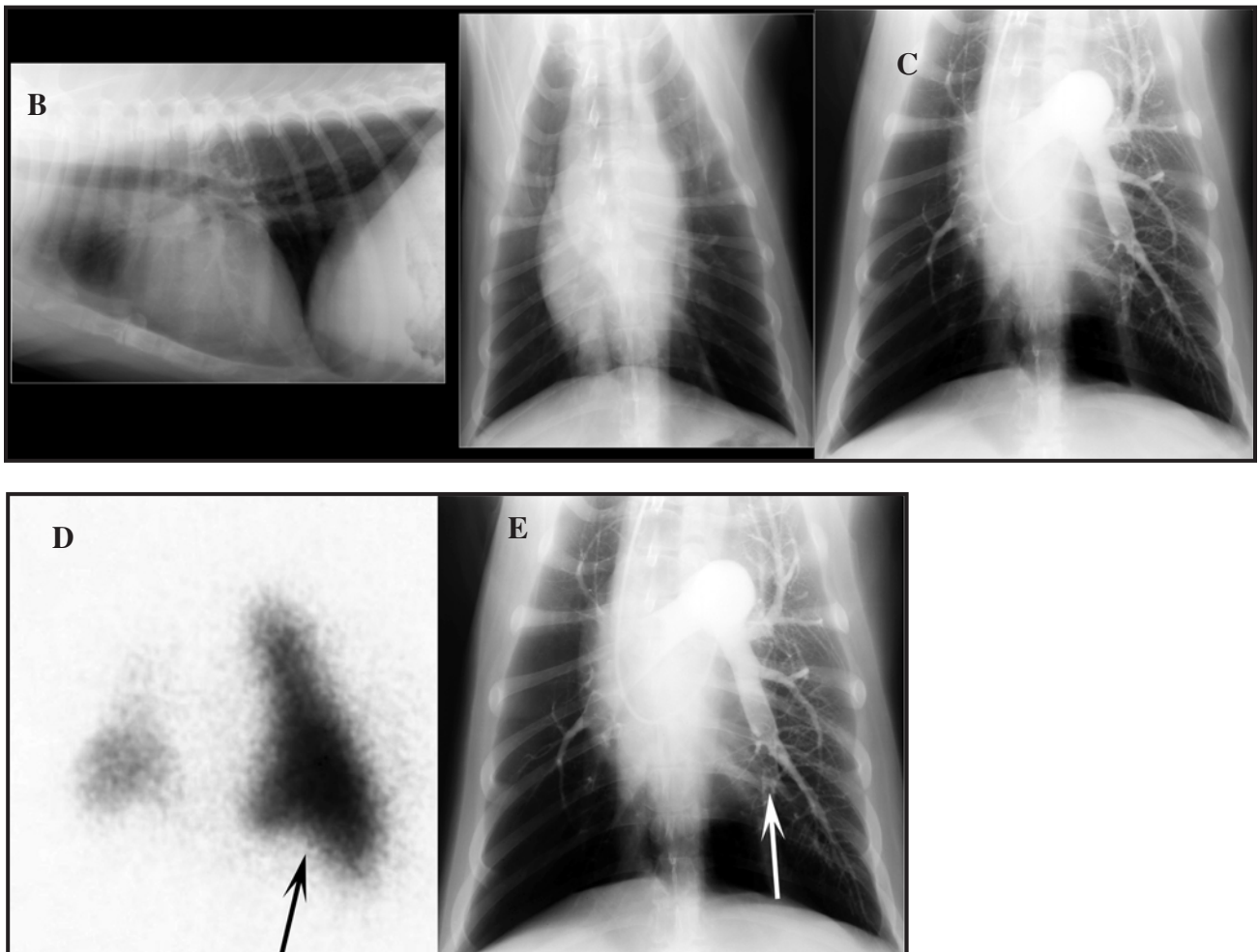


Figure 17.11: Pulmonary perfusion images from a dog with two large pulmonary thromboemboli

A, ^{99m}Tc -MAA images. There is markedly decreased perfusion to the right lung. In addition, there is a wedge-shaped, pleural-based defect in the left caudal lung lobe. **B**, Thoracic radiographs and pulmonary angiogram of the same dog. The vessels in the right lung are decreased in size and the lung appears radiolucent. The imaging abnormalities are more conspicuous on the pulmonary perfusion scan than on the thoracic radiographs. **C**, The pulmonary angiogram confirmed the decrease blood flow to the right lung. **D**, The ventral perfusion scan image is shown adjacent to the pulmonary angiogram. The large thrombus in the right main pulmonary artery is preventing blood flow to the majority of the right lung. Note the intravascular filling defect in the left caudal lobar artery. **D** and **E**, Note the small wedge-shaped perfusion defect on the lung scan (**D**) corresponds to this angiographic lesion (**E**).



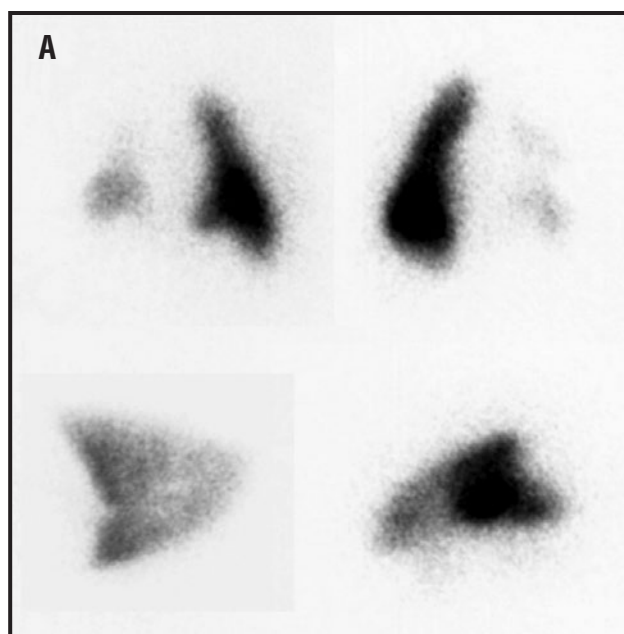
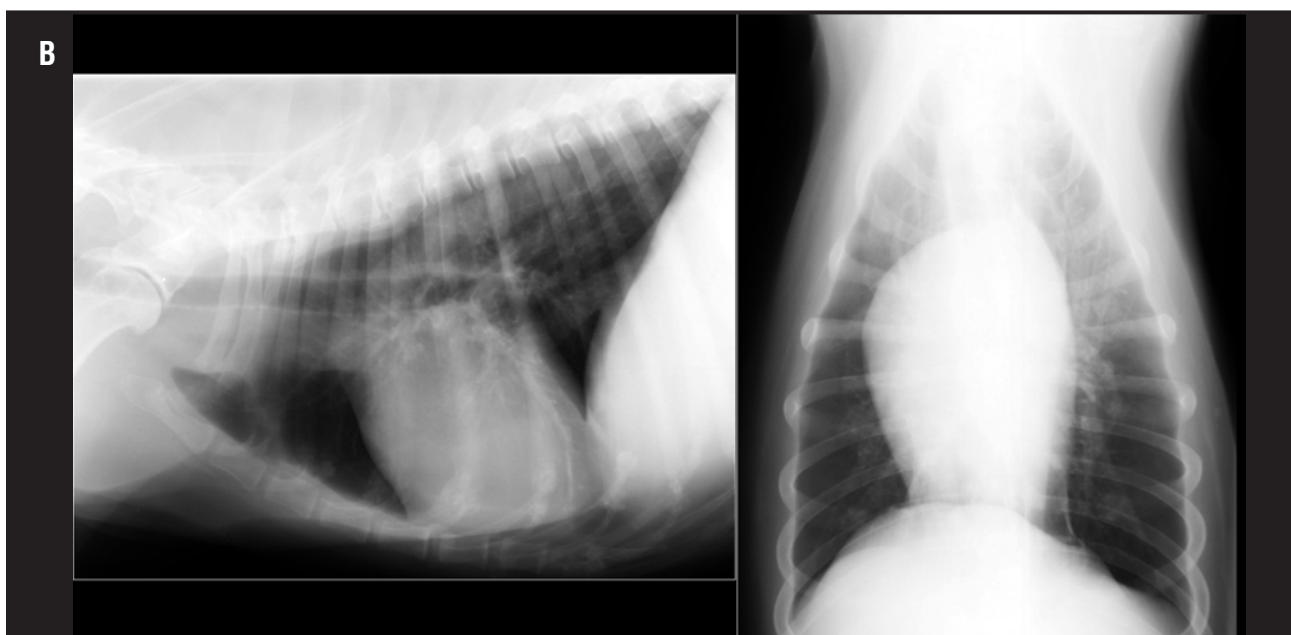


Figure 17.12: Pulmonary perfusion study from a dog with one large and multiple small pulmonary thromboemboli

A, There is complete lack of blood flow to the left cranial lobe. There are multiple wedge-shaped, pleural-based defects along the dorsal and diaphragmatic borders of the lung. **B**, Normal thoracic radiographs of the same dog made just prior to the perfusion study.



(Figure 17.10). Photopenic defects in pulmonary perfusion are readily recognized on perfusion images in dogs with pulmonary thromboemboli (Figure 17.11). The classic pattern of a pulmonary thromboemboli is a photopenic, wedge-shaped, pleural-based defect that has a pulmonary lobar or segmental distribution. The patterns seen in dogs do not always have this classic appearance. If the thrombus occludes a major lobar artery, the entire lung lobe may be involved and, thus, the lung lobe will not be seen on the perfusion scan (Figure 17.12). Multiple small emboli may result in a mottled perfusion pattern that may

be confused with COPD. Multiple small emboli are common in dogs with heartworm disease.^{1,7,20}

Other differentials for photopenic regions on ^{99m}Tc -MAA studies include pulmonary mass lesions (tumor, abscess, granuloma) and areas of alveolar opacity (low contrast photopenic area). In each case, radiographic correlation can be used to confirm the reason for the lack of perfusion to a specific area of the lung (Figure 17.13).

COPD results in a mottled perfusion pattern caused by multiple perfusion defects seen throughout all

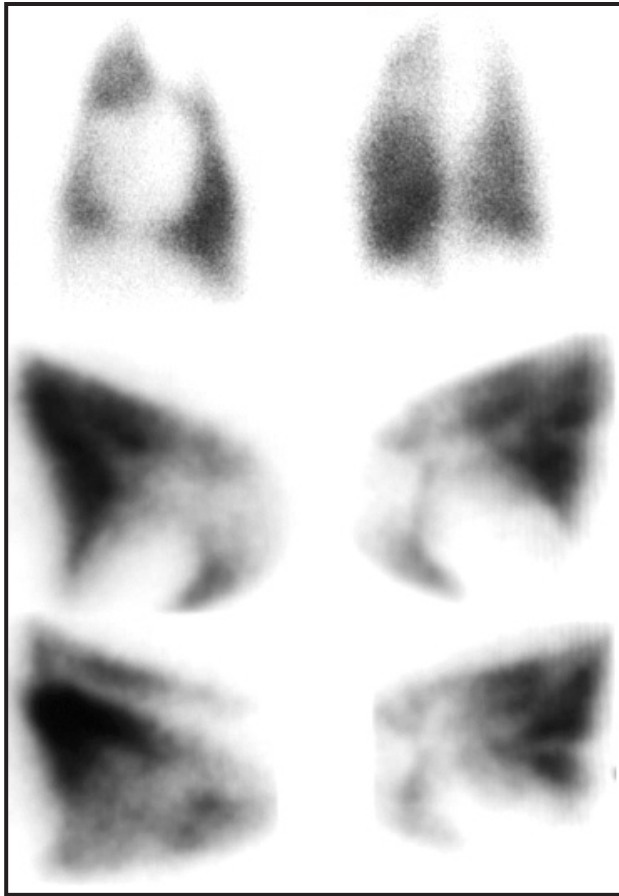


Figure 17.13: Pulmonary perfusion study in a dog with a pneumonic infiltrate in the dependent lung region (cranial and ventral)

There are low-contrast perfusion defects seen in the area of the ventral cranial and middle lung lobes. The cardiac silhouette and major pulmonary vessels are also very prominent. These changes are consistent with perfusion abnormalities secondary to ventilation hypoxic vasoconstriction in the affected pneumonic areas.

lung fields. The mottled perfusion pattern is due to hypoxic vasoconstriction of pulmonary arteries in an attempt to maintain a V/Q match in areas that are well ventilated. Regional hypoxemia occurs secondary to the bronchial constrictions or small airway mucous plugs seen in chronic bronchitis or asthmatic disease (Figure 17.14). Because of hypoxic vasoconstriction, blood flow is shunted away from the underventilated areas of the lung resulting in perfusion defects seen (Figures 17.15 and 17.16). In patients with emphysema, visible perfusion defects

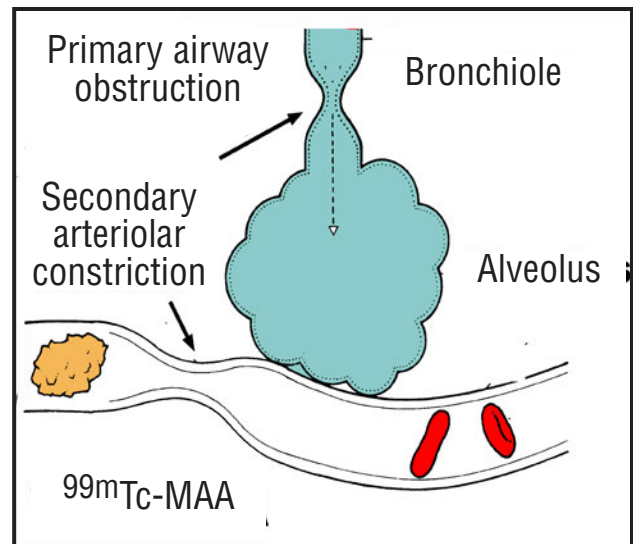


Figure 17.14: Diagram of a terminal bronchiole and alveolus

Bronchial constriction results in decreased ventilation distally. The resultant hypoxemia produces reflex arterial vasoconstriction causing a perfusion defect seen on the pulmonary perfusion scan. If both a ventilation scan and perfusion scan were performed, there would be matching ventilation defects.

area also caused by air trapping. The increased intra-alveolar pressure restricts capillary blood flow and this contributes to the mottled perfusion patterns. If a ventilation and perfusion scan were performed, the defects should match.

A focal high-intensity uptake can be seen as a radiopharmaceutical artifact. ^{99m}Tc -MAA has a tendency to form clots if it is mixed with blood in the syringe prior to injection. Clotting occurs if the operator is having difficulty hitting a vein or blood is allowed to sit in the syringe for a short period of time. If the clot is injected back into the patient, it will localize in the lung and will be seen as a focal hot spot (Figures 17.17 and 17.18). Possible other interpretive considerations include evaluation for right to left shunts. As the ^{99m}Tc -MAA particle size varies between 10 and 140 μm (90% being between 10 and 40 μm), a small percentage of smaller particles (< 5 μm) will pass through the capillary bed into the lungs and some renal, splenic, and hepatic activity may be seen. This should not exceed 5% of the injected dose by 5 minutes postinjection. If > 5% of the injected dose is seen in the systemic circulation (kidneys, brain, etc.),



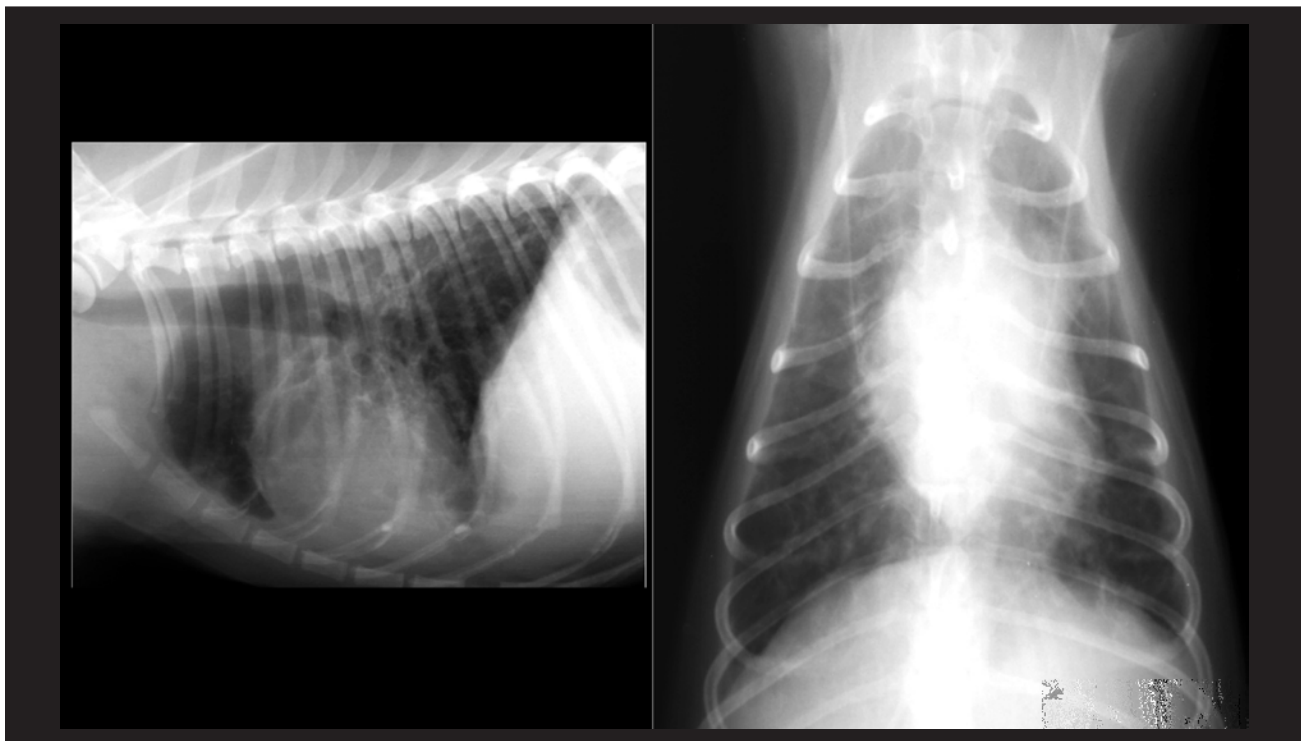
a right-to-left, intra- or extracardiac shunt should be considered.

Ventilation/Perfusion Parametric Images

The clinical utility of the V/Q scan (Figure 17.4) primarily determines the presence or absence of pulmonary thromboembolism (PTE). The hallmark scintigraphic features include a lobar or segmental perfusion defect with a corresponding area of normal ventilated lung and no pulmonary radiographic abnormality (Figure 17.19). The pulmonary perfusion images and current thoracic radiographs should be interpreted together for evaluating animals suspected to have PTE (Table 17.5). These findings are termed a V/Q mismatch and considered “high probability” for the diagnosis of a pulmonary embolus. Several caveats must be kept in mind when interpreting V/Q

Figure 17.15: Pulmonary perfusion scan in a dog with COPD and emphysema

A, There is a mottled perfusion patterns seen throughout all lung lobes. **B**, Thoracic radiographs of the same dog. Note the chronic bronchial and interstitial lung disease with peripheral focal soft tissue pulmonary opacity.



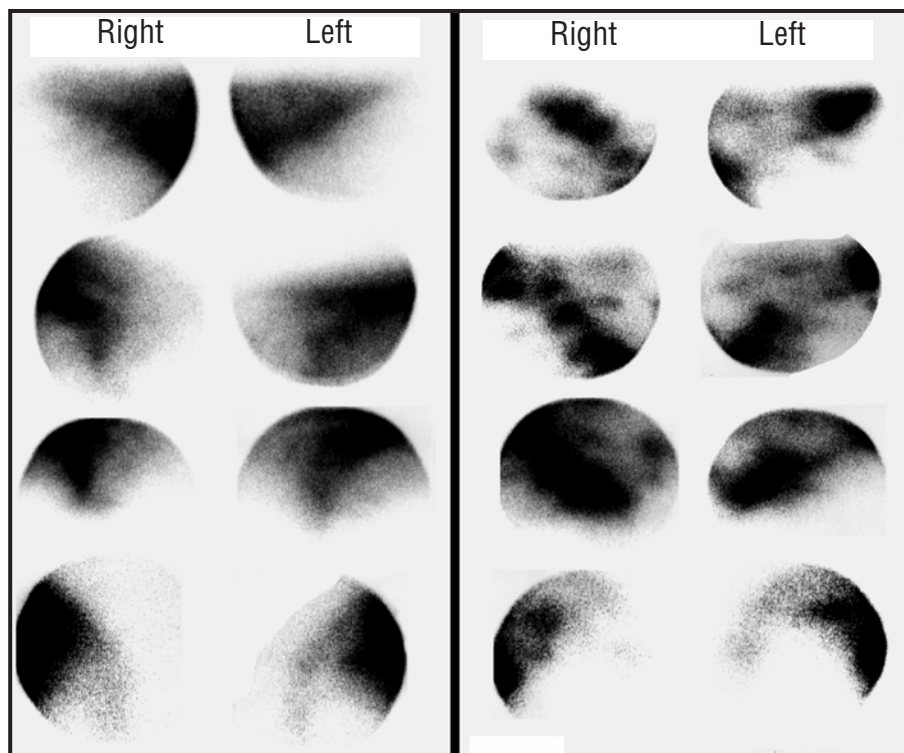


Figure 17.16: Pulmonary perfusion studies from two horses with COPD

The disease is considered mild in the horse on the left and severe in the horse on the right. Note the mottled perfusion pattern seen in both. The severity of the perfusion defects is far greater in the horse on the right.

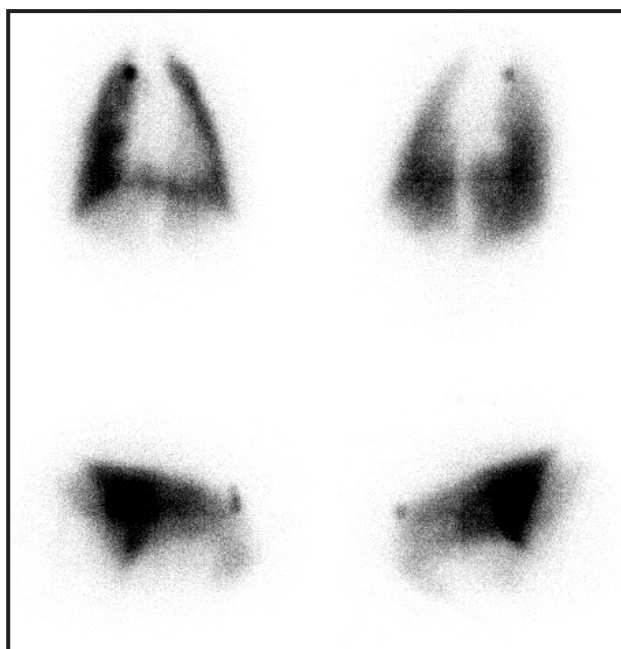


Figure 17.17: Pulmonary perfusion study in a dog

Note the round focal increased uptake (arrow) in the medial aspect of the right cranial lung lobe. This focal uptake is due to an aggregate or clot of the ^{99m}Tc -MAA.

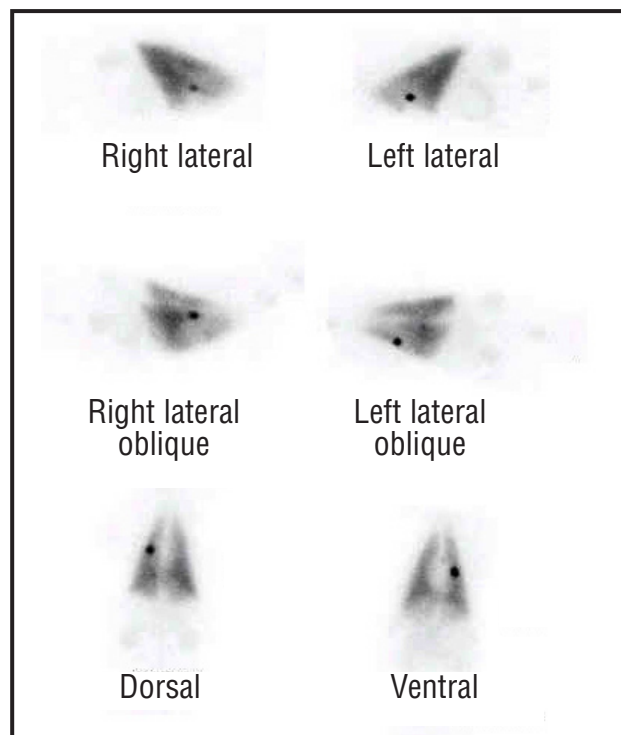


Figure 17.18: Pulmonary perfusion study in a cat

The image views are labeled. Note the round focal increase uptake (arrow) in the dorsal aspect of the left lung. This focal uptake is due to an aggregate or clot of the ^{99m}Tc -MAA.

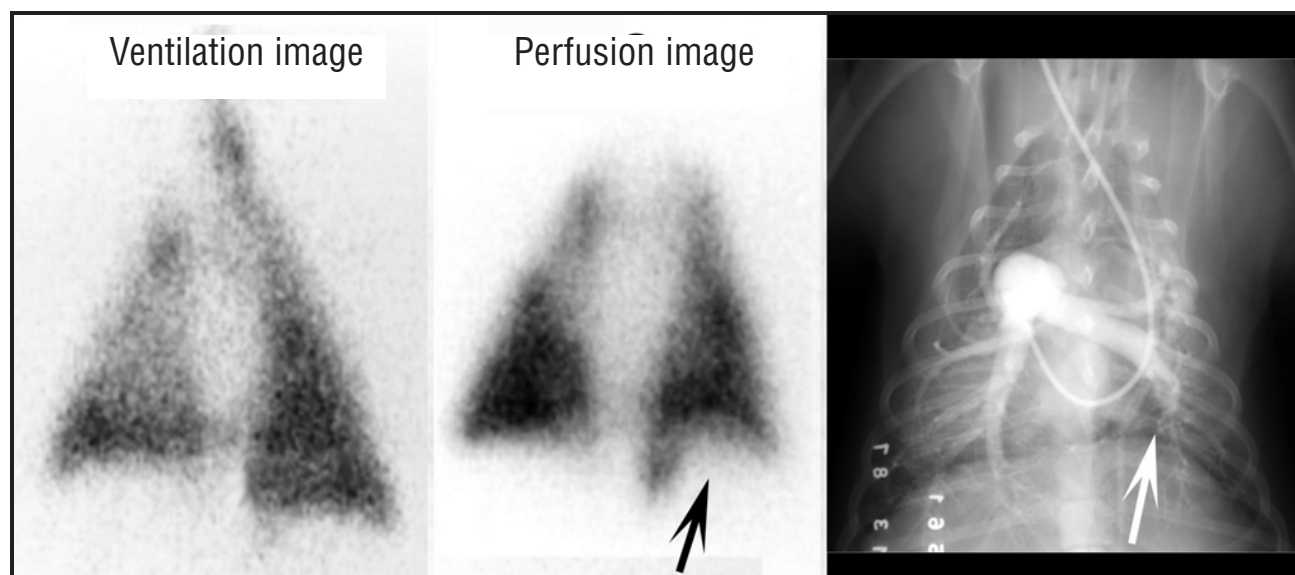


Figure 17.19: Pulmonary ventilation scan (V), perfusion scan (Q), and pulmonary angiogram in a dog with a pulmonary thromboembolism in the right caudal lung lobe

The pulmonary angiogram has been flipped horizontally to match the nuclear medicine studies (dog's right is toward the right). There is a normal ventilation pattern and a wedge shaped pleural based perfusion defect (black arrow) indicating a V/Q mismatch. This corresponds to an area of decreased blood flow (regional oligemia) noted on the pulmonary angiogram (white arrow).

studies in animals. First, the true incidence of PTE in animals is not known. The selecting of patients with clinical signs referable to cardiopulmonary distress with hypoxia to evaluate for PTE may, therefore, be skewed. Second, multiple studies in humans have resulted in specific criteria for positive (high probability), negative (normal), and indeterminate results. Using digital subtraction angiography or selective pulmonary angiography as the gold standard, the sensitivity and specificity of PTE in humans with high probability V/Q scans is 41% and 97%, respectively.^{1,31-33} Third, a negative pulmonary perfusion scan in humans virtually excludes the presence of clinically significant pulmonary emboli.

Pulmonary scintigraphy has essentially been replaced by CT angiography for the detection of pulmonary thromboembolism in humans.⁸ As the number of multislice, spiral CT scanners increases in veterinary teaching hospitals and large specialty practices, the use of pulmonary scintigraphy in veterinary medicine for the detection of pulmonary thromboemboli will likely follow suit.

In veterinary medicine, due to the lack of patient

compliance, it appears that ventilation studies are currently limited to research applications.

Mucociliary Scintigraphy

Introduction

Animals that present with chronic, recurrent, respiratory tract infections may have an underlying problem with the function of the ciliated epithelium of the respiratory tract. One of the body's major defense mechanisms in the respiratory tract is the mucociliary transport system. The function of this system is to remove particles from the lung, thus keeping the airway surface clean. The respiratory epithelium is covered by vigorously beating cilia. The surface of the epithelium is coated with a mucous or viscous layer. Particulates are trapped in this mucous layer and propelled toward the pharynx where they are cleared from the respiratory tract. The function of this system can be evaluated using mucociliary clearance scintigraphy.^{34,35}

Table 17.5: Interpretation Criteria Using Ventilation and/or Perfusion Scintigraphy and Thoracic Radiographs for the Presence or Absence of Pulmonary Thromboemboli (PTE)

Perfusion Study	Ventilation Study (if available)	Thoracic Radiographs	Diagnosis
NL	NL	NL	PTE not present
LD (1 or more)	NL	NL	PTE present*
LD (1 or more)	Matched abnormality	PC†	Cannot Determine§
Normal	LD (reverse abnormality)	PC	Atelectasis

Note: pulmonary perfusion deficit is considered to be the presence of a photopenic area that has a normal lobar distribution (wedge shaped) and a peripheral or pleural-based location.

Areas of atelectasis are typically due to recumbent atelectasis.

NL = normal; PTE = pulmonary thromboembolism; LD = lobar photopenic defect that has a wedge-shaped appearance with a broad pleural base; PC = pulmonary consolidation.

*Other differentials to be considered in the diagnosis for V/Q mismatches include pulmonary neoplasia (with pulmonary artery compression), vasculitis (e.g., heartworm disease), and congenital pulmonary artery atresia (rare). Usually these abnormalities would be identified on the thoracic radiographs.

†Any area of pulmonary consolidation or atelectasis is abnormal on a ventilation study. Thoracic radiographic changes associated with pulmonary thromboembolism in the dog are variable (eg, regional oligemia with absent pulmonary infiltrates to overt pulmonary consolidation and pleural effusion) and thoracic radiographs may be normal. In the case of pulmonary consolidation and a perfusion abnormality, an angiographic study is required to evaluate the patency of the pulmonary arteries. The differential diagnosis for a matched V/Q abnormality includes: (1) chronic obstructive lung disease, (2) bronchiectasis, (3) pulmonary bulla, (4) pulmonary edema, (5) pleural effusion, (6) asthma, (7) smoke inhalation injury, and (8) mucous plugs with airway obstruction.

§Cannot determine. Requires CT angiography, selective angiography, or digital subtraction study.

Table 17.6: Indications for Mucociliary Clearance Scintigraphy

Diagnosis of ciliary dyskinesia.
Evaluate the impact of any pulmonary disease on normal mucociliary clearance.
Evaluate the therapeutic effects of drug intervention on mucociliary clearance.

Ciliary dyskinesia is a hereditary disease characterized by immotile or dyskinetic cilia. Other terms used to describe this disease include immotile cilia syndrome and primary ciliary dyskinesia. When situs inversus, bronchiectasis, and rhinosinusitis are present in conjunction with ciliary dyskinesia, the term Kartagener's Syndrome is used.³⁶ Ultrastructural

lesions in cilia and sperm flagella (a modified cilium) have been documented in affected individuals.³⁶ Indications for mucociliary clearance scintigraphy are listed in Table 17.6.

The principle behind mucociliary clearance scintigraphy is to measure the movement of radioactive particulates that have been deposited onto the tracheal or nasal epithelium over time. Tracheal clearance is routinely used for diagnosing ciliary dyskinesia. The two radioactive particulates that can be used include ^{99m}Tc-MAA or ^{99m}Tc-sulfur colloid (^{99m}Tc-SC), with a preference for ^{99m}Tc-MAA. A small droplet of the ^{99m}Tc-MAA is placed at the distal aspect of the trachea and a series of static images is obtained to document the movement of the ^{99m}Tc-MAA proximally.

General anesthesia is required for this study. A heat

and moisture exchanger is used to prevent drying of the tracheal mucosa. A short endotracheal tube should be used to intubate the animal. It is important that the endotracheal tube does not extend caudal to the cervical trachea so as not to interfere with the movement of the ^{99m}Tc -MAA. A right-angle connector (90° bend) with port is used to connect the endotracheal tube to the anesthesia tubing. The patient is placed in sternal recumbency under a large field of view gamma camera. The two external radioactive markers (^{57}Co or ^{99m}Tc) are placed adjacent to the lateral thorax of the dog at the level of the trachea. The caudalmost marker should be adjacent to the carina which is as estimated to be at the level of the caudal border of the scapula or the fifth intercostal space (Figure 17.20). A lateral thoracic radiograph of the patient taken prior to anesthesia is helpful in approximating this position. The second marker is placed 20 cm cranial to the caudal marker. A sleeved polystyrene catheter is used to deposit the ^{99m}Tc -MAA droplet. A 10 French male urinary catheter with the tip removed works well for the outer sleeve. A 5 French catheter is used as the inner catheter. A small quantity of ^{99m}Tc -MAA (<1 mCi in 30 μL volume) is aspirated into the tip of the inner catheter. The tip of the inner catheter is withdrawn into the outer catheter to prevent contamination of the trachea during catheter positioning. It is helpful to mark the proximal aspect of the catheters to know how far the inner catheter has to be advanced to extend beyond the tip of the outer catheter. The catheters are inserted through the port on the right angle connector of the anesthesia tubing. Alternatively, the anesthetic machine may be momentarily disconnected to advance the catheter combination into the trachea. The persistence scope is used to judge the position of the catheter, based on the visualization of the external markers. The catheter is advanced until the tip of the catheter (containing the ^{99m}Tc -MAA) is at the level of the caudal external marker (level of the carina). The inner catheter is advanced 1 cm beyond the outer sleeve. A small volume of air is injected into the inner catheter, thereby depositing the radiopharmaceutical droplet into the trachea. A forceful bolus of air will disperse the droplet and coat the carina as opposed to producing a single droplet of radioactivity. The inner catheter is retracted into the outer sleeve, and both catheters are removed as a unit from the trachea. A series of 60-second static frame images is started immediately after withdrawal of the catheters. Dorsal images of the thorax are acquired

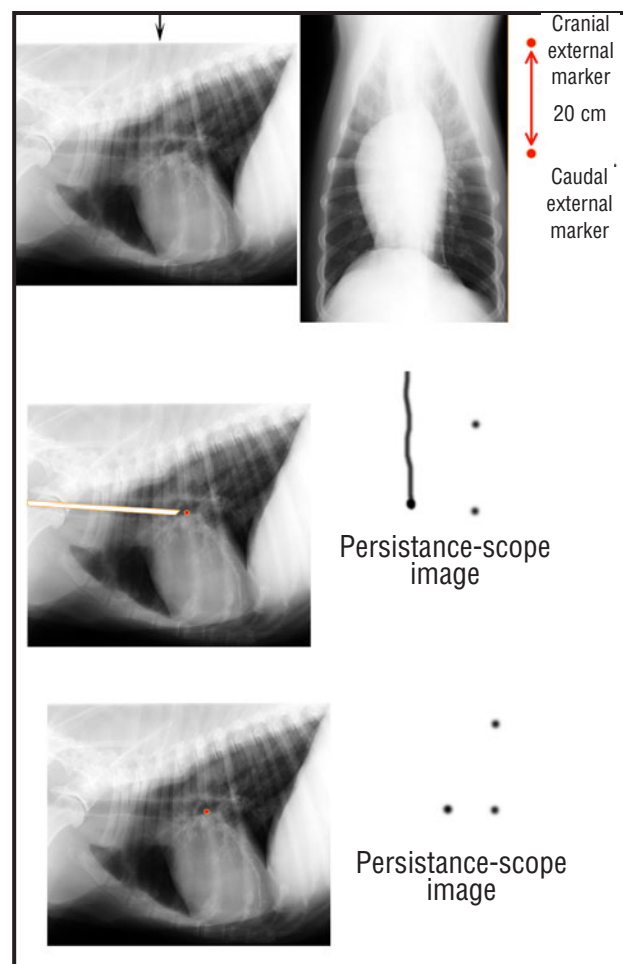


Figure 17.20: Radiographic and scintigraphic imaging showing procedure for depositing a ^{99m}Tc -MAA droplet at the distal trachea

The red dots to the right of the thorax in the top row of images show the position of the radioactive external markers. The caudalmost marker has been placed beside the dog at the level of the carina. The caudal border of the scapula is a useful anatomic landmark, to help determine the level of the carina. The two external markers will be seen on the persistence scope. The ^{99m}Tc -MAA in the tip of the internal catheter will show up on the persistence scope as it advances down the trachea. The catheter is advanced until the ^{99m}Tc -MAA is at the level of the caudal external marker. The droplet is deposited onto the tracheal epithelium and the catheter withdrawn. At this time, the only objects seen on the scan are the two external markers and the deposited ^{99m}Tc -MAA droplet.

at 5-minute intervals for a total of 40 minutes. The movement of the ^{99m}Tc -MAA is measured by com-

Table 17.7: Acquisition Parameters for Mucociliary Clearance Scintigraphy**Radiopharmaceutical**

^{99m}Tc -MAA (macroaggregated albumin).

Dose

The goal of dosage is 18.5 to 37 MBq (0.5 and 1.0 mCi) in 20–40 μL volume. To achieve this concentration, between 25–50 mCi per mL would need to be added to a MAA vial. The 20 μL volume given to the patient is estimated. The authors typically place a drop of the ^{99m}Tc -MAA in the cap of the 6 mL syringe casing. The tip of the 5 French catheter is placed into the drop and a small volume is aspirated into the catheter. The desired volume will occupy a length of 3–5 mm of the lumen of the catheter.

Acquisition Parameters

Frame mode	A series of dorsal static frame mode images.
Matrix size	256 $\times$ 256 $\times$ 16.
Time of imaging	Images are acquired for 30–60 seconds each at 0, 5, 10, 15, 20, 25, 30, and 40 minutes after radiotracer deposition in the trachea.
Collimator	Low-energy, all-purpose.
Views	Dorsal or lateral. External markers are placed so that quantification of the clearance rate can be done.

puting the distance traveled relative to the external markers divided by the elapsed time. The acquisition parameters for mucociliary clearance scintigraphy are summarized in Table 17.7.

The small quantity of radioactivity used in this procedure does not necessitate special handling of the patient. The endotracheal tube should be considered contaminated and held to allow for decay of the radionuclide. The intratracheal ^{99m}Tc -MAA is presumably cleared and swallowed if the mucociliary apparatus is functional.

Principles of Interpretation**Normal**

The ^{99m}Tc -MAA droplet is cleared by the mucociliary blanket and usually moves as a discrete spot. Droplet movement usually starts within 1 to 2 minutes of deposition (Figure 17.21). Often there is a residual low-intensity area at the original site of deposited radioactivity. Sometimes two spots may form, but both droplets usually move with the same velocity toward the larynx.

Abnormal

Congenital ciliary dyskinesia results in an absence of ^{99m}Tc -MAA movement throughout the scintigraphic study (Figure 17.22). Confirmation of this diagnosis requires biopsy of respiratory epithelium for in vitro electron microscopic cilia analysis. Often, clinical diagnosis is based on the nuclear medicine test. False positives (no droplet movement) can occur if the droplet is deposited in the secondary bronchi because of fewer ciliated epithelial cells. If the ^{99m}Tc -MAA is deposited in an ulcerated area of the trachea, then no movement may be observed. It is important that the endotracheal tube does not extend into the thorax because if the droplet contacts the end of the tube, movement will stop.

Occasionally, droplets may move normally and then either slow down or stop. If this occurs in the trachea, some possible causes include: the endotracheal tube stops droplet movement or the droplet encounters an area of dried mucus or exudate within the trachea. If normal droplet movement is documented before it slows or stops, then it is unlikely that congenital ciliary dyskinesia is present.

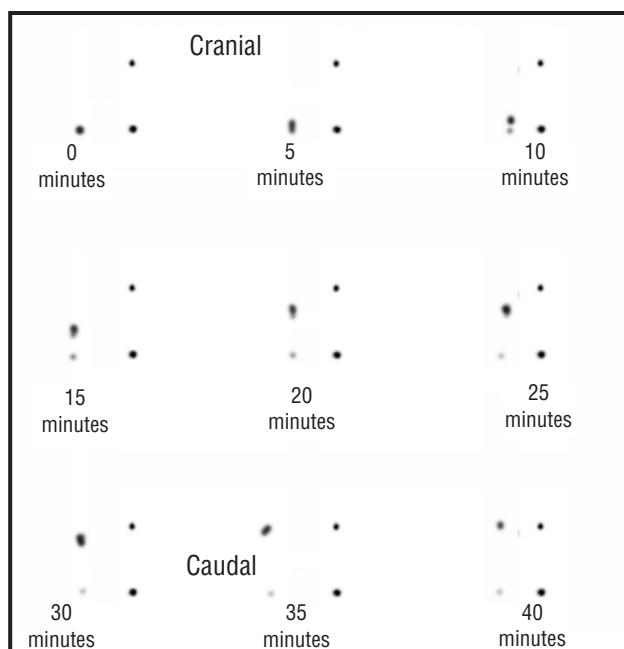


Figure 17.21: Dorsal images from a dog with a normal mucociliary scan

Shown are dorsal images. The two dots to the right of each image are the external markers positioned at the caudal border of the scapula and 20 cm cranially. The images were taken in the following order from top left to lower right: 0, 5, 10, 15, 20, 25, 30, 35, and 40 minutes. Note the ^{99m}Tc -MAA droplet is at the level of the caudal external marker on the 0 minute image. Over time, this droplet moves cranially indicating normal mucociliary clearance.

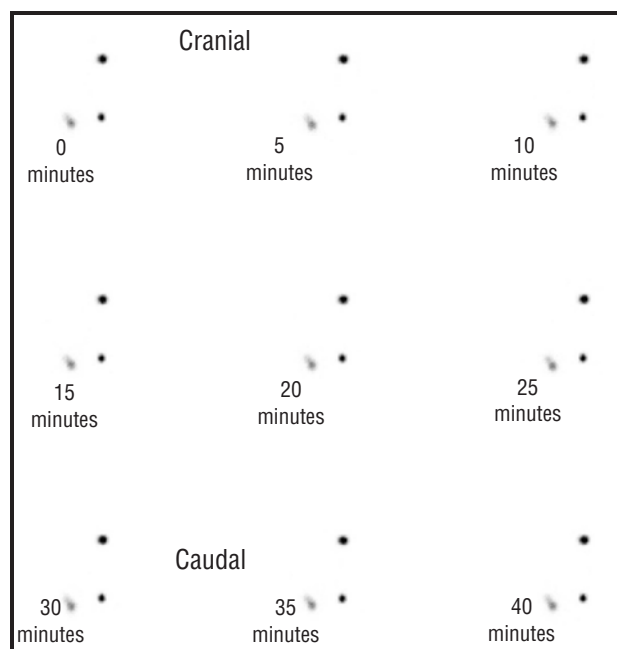


Figure 17.22: Dorsal images from a mucociliary scan in a dog with ciliary dyskinesia

The two areas of radioactivity noted to the right of each image are external markers that have been positioned at the caudal border of the scapula and 20 cm cranially. The images were taken in the following order from top left to lower right: 0, 5, 10, 15, 20, 25, 30, 35, and 40 minutes. Note the ^{99m}Tc -MAA droplet does not move from its original position, indicating absent mucociliary function.

The mucociliary clearance mechanism can be evaluated in pulmonary diseases other than congenital ciliary dyskinesia. In these instances, one is measuring absolute velocity and comparing the results to published normal values. In different diseases, however, the significance of slightly impaired but not absent mucociliary clearance is difficult to interpret. This is because a wide range of normal exists, even among healthy animals in similar age groups. In addition, different test protocols (eg, awake versus anesthetized) may yield different velocities in the same animal. The potential effect of drugs on mucous transport velocities (increased or decreased) can be evaluated using this technique. Results are more meaningful however, if comparison measurements are done using the animal as its own control. An absolute decrease in droplet velocity results from

various pulmonary diseases (particularly those that result in a thinning of the mucous blanket or a change in the viscoelastic properties of the mucus), drugs (atropine, which acts to dry secretions), irritants such as smoke, and dry inhaled air (versus humid air).³⁵ Rates of mucociliary transport increase with increased temperature, certain drugs or drug combinations (ethylenediamine dihydroiodide, clenbuterol, and atropine used in conjunction with pentobarbital). In addition, velocities are faster in young adult (9.7 mm per min) and middle aged dogs (6.9 mm per minute) compared to immature (3.6 mm per minute) and aged dogs (2.9 mm per minute).³⁷

Summary

Pulmonary perfusion and ventilation scintigraphy

provides important information regarding basic lung physiology in the clinically dyspneic patient. Additionally, the use of mucociliary clearance studies are useful for documenting ciliary dyskinesia, although the clinical influence of various drugs on mucociliary clearance has not been established in veterinary medicine.

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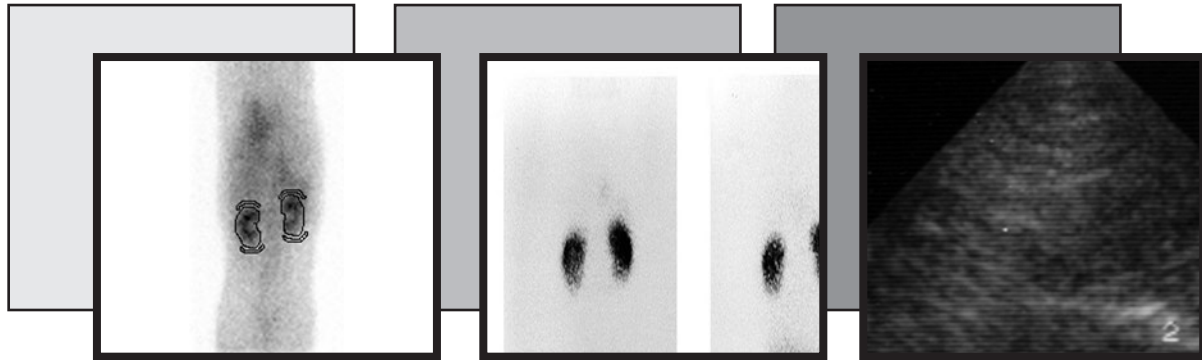
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Renal Scintigraphy

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Introduction

Quantitative renal imaging can provide both functional and morphologic information about the urinary tract. There are a variety of radiopharmaceuticals used for renal imaging. They differ in the mechanism of localization and, therefore, provide different information about renal function and morphology. The quantitative data derived from renal scintigraphy is unique and can be critical to patient management. Serial glomerular filtration rate and effective renal plasma flow studies can be used for early detection of renal disease or the evaluation of response to therapy and/or progression of renal disease. Renal morphologic scintigraphy can provide information about relative renal function and anatomic size, shape, and location.

Normal Anatomy and Physiology

The kidneys are paired organs located in the retroperitoneal space. The functional unit of the kidney is the nephron which is composed of a glomerular capsule that leads into the proximal tubule. The glomerular capsule is invaginated by a spherical rete of blood capillaries, called the glomerulus (Figure 18.1). The kidney receives 25% of cardiac output. The average renal plasma flow is 15 mL/min/kg. Twenty percent of the plasma is filtered through the glomerulus, but the percentage can change as a result of autoregulatory mechanisms. Autoregulatory mechanisms can maintain glomerular filtration rate (GFR) in the face of decreased renal blood flow (RBF) or decreases in systemic blood pressure (Figure 18.2). Blood pressure within the glomerulus determines GFR. Pressure within the glomerulus is controlled by vasoconstriction of the afferent or efferent arteriole. In times of decreased blood pressure or decreased renal blood flow, the efferent arteriole will constrict, thus increasing pressure within the glomerulus resulting in an increase in GFR.

Glomerular Filtration Rate (GFR)

The most common radiopharmaceutical used for measuring glomerular filtration rate is ^{99m}Tc -DiethyleneTriaminePentaacetic Acid (^{99m}Tc -DTPA) also known as ^{99m}Tc -pentetate. There are many commercially available kits that use stannous reduction

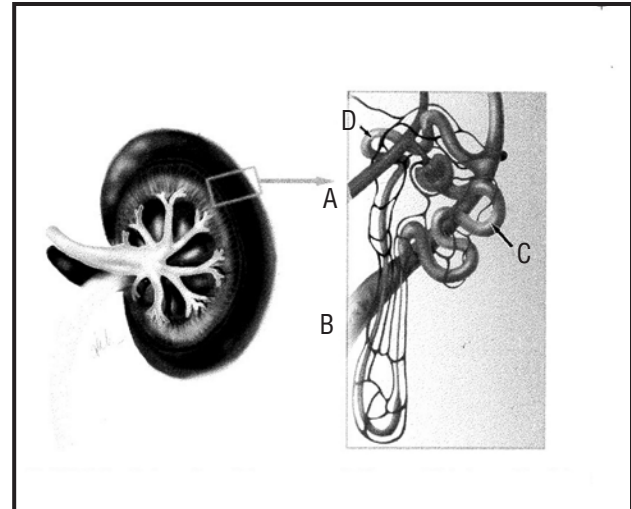


Figure 18.1: A kidney (left) and isolated nephron (right)

The afferent arteriole (A) delivers blood to the glomerulus. The ultrafiltrate passes through the glomerular membrane into the proximal convoluted tubule (C) to the distal tubule (D) that eventually empties into the collecting duct (B) (Daniel GB, Mitchell S, *Vet Radiol Ultrasound*, 1999; 40:572-587, Reprinted with permission).

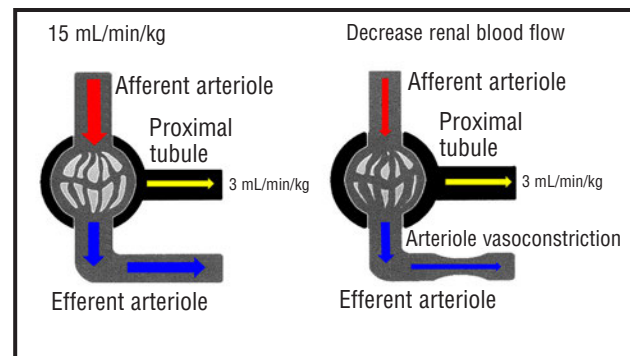


Figure 18.2: Autoregulation of GFR

Pressure within the glomerulus is controlled by vasoconstriction of the afferent or efferent arteriole. In times of decreased blood pressure or decreased renal blood flow, the efferent arteriole will constrict, thus increasing pressure within the glomerulus. This will result in an increase in GFR (Daniel GB, Mitchell S, *Vet Radiol Ultrasound*, 1999; 40:572-587, Reprinted with permission).

of ^{99m}Tc resulting in the chelation with the DTPA molecule.

^{99m}Tc -DTPA is a vascular agent that quickly equilibrates with the extracellular fluid space. It accumulates in the kidney by glomerular filtration with no tubular absorption or secretion. The uptake of ^{99m}Tc -DTPA within the kidney or the clearance from the plasma is directly related to GFR. The amount of protein binding of the radiopharmaceutical is an important factor because the portion of ^{99m}Tc -DTPA that is protein bound is not available for glomerular filtration and will falsely decrease the measured GFR. In the dog there is a minimal amount (< 5%) of protein binding of the ^{99m}Tc -DTPA, which does not significantly influence the measured GFR value. Protein binding is a significant problem in other species, such as the iguana, making DTPA an unsuitable agent. The first-pass extraction of ^{99m}Tc -DTPA is approximately 20%, resulting in a rapid blood clearance. The biologic half-life in humans is 2.5 hours, with 95% of the ^{99m}Tc -DTPA passing into the urine by 24 hours. Indications for renal scintigraphy using DTPA are listed in Table 18.1.

Gates developed a noninvasive, quantitative renal scintigraphic technique for humans that has been adapted for dogs and cats (Tables 18.2 and 18.3).¹⁻³ The regression correlation value (r) between inulin clearances and percent injected dose uptake (performed within 24 hours of each other) has been shown to

be 0.94 and 0.84 in dogs and cats, respectively.^{1,2} A small (5%) portion of the ^{99m}Tc -DTPA is bound to plasma protein(s), and these studies have shown that correction for plasma binding does not improve the correlation coefficient in either species.

Correction for kidney depth improves the correlation between percent injected dose and inulin clearance in the dog¹ but not in the cat.² Measurement for kidney depth can be made off the monitor or printed images. Various field-of-view (FOV) sizes can be used depending on the size of the animal as long as all measurements (predose, image sequences and postdose counts) are made with the same FOV size. Background regions of interest (ROIs) are set differently for the dog and the cat as described in Table 18.3 (see also Figure 18.3).

Principles of Interpretation

In the normally functioning kidney, there is an arterial renal blush of uptake seen during the first passage of ^{99m}Tc -DTPA through the kidney (Figure 18.4). The radioactivity of the kidney then decreases slightly as not all the renal plasma flow passes through the glomerular membrane. The kidney radioactivity will then increase with subsequent circulatory passes as the kidney continues to accumulate the radiopharmaceutical. Peak renal radioactivity usually occurs between 2.5 and 3.5 minutes following injection. One study evaluating eight normal dogs showed a range of 119 to 336 seconds.⁴ Time to peak renal radioactivity may be longer in poorly functioning kidneys or shorter if the animal is undergoing diuresis. Renal radioactivity then decreases as the ^{99m}Tc -DTPA passes from the collecting system into the lower urinary tract. The rate of clearance from the kidney into the lower urinary tract can be used to assess outflow obstruction. Longer acquisition times (up to 20 minutes) may be necessary to evaluate the function and patency of the renal collection system.

Global GFR values above 3 mL/min/kg are considered normal in the dog and global GFR values above 2.5 mL/min/kg are considered normal in the cat. Animals with sub clinical renal insufficiency have global values between 1.2 and 2.5 mL/min/kg (Figures 18.5, 18.6 and 18.7). Animals with global GFR values below 1.0 to 1.2 mL/min/kg often have elevations of BUN and creatinine. Quantitative renal scintigraphy with ^{99m}Tc -DTPA may be difficult to perform accurately in those animals with very severe renal insufficiency. Global GFR values below 0.25

Table 18.1: Indications for Renal Scintigraphy Using ^{99m}Tc -DTPA

Determine global and individual kidney GFRs.
Early diagnosis of impaired renal function.
Evaluate the patient's response to treatment.
Evaluate function of contralateral kidney prior to nephrectomy.
Identify and determine the severity of subclinical renal disease in an animal receiving nephrotoxic agents (eg, chemotherapeutic drugs or aminoglycoside antibiotics).
Evaluate for obstructive uropathies.
Evaluate renal morphology.

Table 18.2: Imaging Parameters for Renal Scintigraphy Using ^{99m}Tc -DTPA**Radiopharmaceutical** ^{99m}Tc -DTPA (Diethylene-triamine-penta-acetic acid)**Dose**

Species	mCi	MBq
Dog	1-4	37-148
Cat	1-3	37-111

Acquisition Parameters

Animal preparation	Normal state of hydration.
Dynamic frame acquisition	6 seconds per frame for 6 minutes (a total of 60 frames).
Static frame acquisition	60 seconds image (lateral view for measurement of renal depths).
Matrix	128 (64) $\times$ 128 (64) $\times$ 16 (Dynamic) and 256 $\times$ 256 $\times$ 16 (Static).
Collimator	Low-energy, all-purpose.
Time to image	Immediate for dynamic acquisition; total imaging time 6-8 minutes, then acquire lateral static image following the dynamic study.
Positioning	Dog or cat in left lateral recumbency with camera centered dorsal to the kidneys (dynamic). Keep dog or cat in same lateral recumbency and position the camera lateral to the kidneys.
Views	Dorsal view (dynamic) and lateral view (static).

Table 18.3: Modified Gates Procedures for Calculating Glomerular Filtration Rates in Dogs and Cats*

Imaging Procedures	
1.	Precount the unshielded dose syringe at a distance of 30 cm over the center of the gamma camera for a preset time (10 - 30 seconds) using a matrix size of 128 (64) $\times$ 128 (64) $\times$ 16. Convert the predose counts to counts per minute (cpm).
2.	Position the patient in left lateral recumbency on the imaging table with the camera positioned for a dorsal view of the cranial abdomen.
3.	Inject the ^{99m}Tc -DTPA dose as a bolus and start the dynamic acquisition simultaneously using the imaging parameters previously described.
4.	For dogs, keep the subject in the same position and rotate the camera 90° to obtain a 60-second static image of the right lateral abdomen (to be used to measure kidney depths for depth attenuation correction). A matrix size of 256 $\times$ 256 $\times$ 16 is used. Depth attenuation correction is not necessary in the cat.
5.	Rotate the gamma camera to its original position and position the dose syringe, tubing and animal's leg where the ^{99m}Tc -DTPA was injected (catheter) 30 cm from the camera. Shield the rest of the animal's body to obtain a postinjection image. Convert the total counts to counts per minute (cpm).

Table 18.3: Modified Gates Procedures for Calculating Glomerular Filtration Rates in Dogs and Cats (continued)

GFR Calculation	
6.	Check the dynamic images for subject motion and realign any images that show significant motion between 60- to 180-seconds.
7.	Reformat the dynamic study to obtain a new summed image for the 60- to 180-second acquisition interval.
8.	Draw individual ROIs over the right and left kidneys using the summed image. For the dog, draw a background ROI one pixel away from the cranial and caudal ends of the kidney ROI; draw separate background ROIs for each kidney (Figure 18.1A). For the cat, the background ROI should be drawn along the caudal and lateral margin of each kidney ROI (Figure 18.1B).
9.	For the dog, determine the kidney depths (cm) from the right lateral static view by measuring from the dorsal edge of the body to the center of each kidney on the image. The right kidney is usually located more cranial to the left, although, particularly in small animals, the kidneys may be superimposed at the same level. Calculate the actual kidney depth using the following equation: Kidney Depth = Image Depth × [(Camera Field of View Diameter)/(Image Diameter)]. Depth correction is not necessary for the cat. The image diameter is the overall size of the image on the computer display from which the kidney depth was measured. The kidney depth should be measured from the dorsal skin of the patient to the middle of the kidney. The camera FOV for a 15-inch circular system is 38.1 cm. Be sure all measurements are in the same units (cm in this example).
10.	Determine the net kidney counts for each kidney using the summed image (60-180 seconds) for each kidney. Net kidney Counts = (kidney ROI counts) - [(# kidney ROI pixels) × {(Bkgd ROI counts)/(# bkgd ROI pixels)}]
11.	Determine the percent injected dose in each kidney. If the entire procedure (including pre- and post-dose counts) takes place within 15-20 minutes, decay corrections are not necessary. $\%ID = \left[\frac{\text{Net Kidney Counts}}{\text{Predose (CPM)} - \text{Postdose (CPM)}} \right]$
12.	For the dog, determine the depth corrected percent injected dose (%ID) for each kidney: Depth corrected % ID = Noncorrected % ID × e^(0.153 × kidney depth [cm]) Where e is the base of the natural logarithm and 0.153 is the attenuation coefficient for ^{99m} Tc in soft tissues.
13.	For the dog: Global GFR (mL/min/kg) = 0.194 × (depth corrected % ID RK + depth corrected % ID LK) - 0.37
14.	For the cat: Global GFR (mL/min/kg) = 0.284 × (nondepth corrected % ID RK + nondepth corrected % ID LK) - 0.164
15.	Individual Kidney GFR: $\text{Individual kidney GFR} = \left[\frac{(\% \text{ ID for individual kidney})}{\% \text{ ID RK} + \% \text{ ID LK}} \right] \times \text{global GFR}$

Note: In kidneys with very low glomerular filtration, the removal of background activity may result in a % ID less than zero. If so, set such a value to zero before calculating the GFR for the other kidney. Using the above equations to calculate global GFR (steps 8 and 9) depends upon close adherence to the described procedures. Other methods of measuring kidney depth (eg, radiographic or ultrasonographic methods), setting background ROIs, patient positioning, etc, may alter the % ID values that are obtained and, hence, invalidate the regression equation relating % ID to inulin clearance GFR estimations.

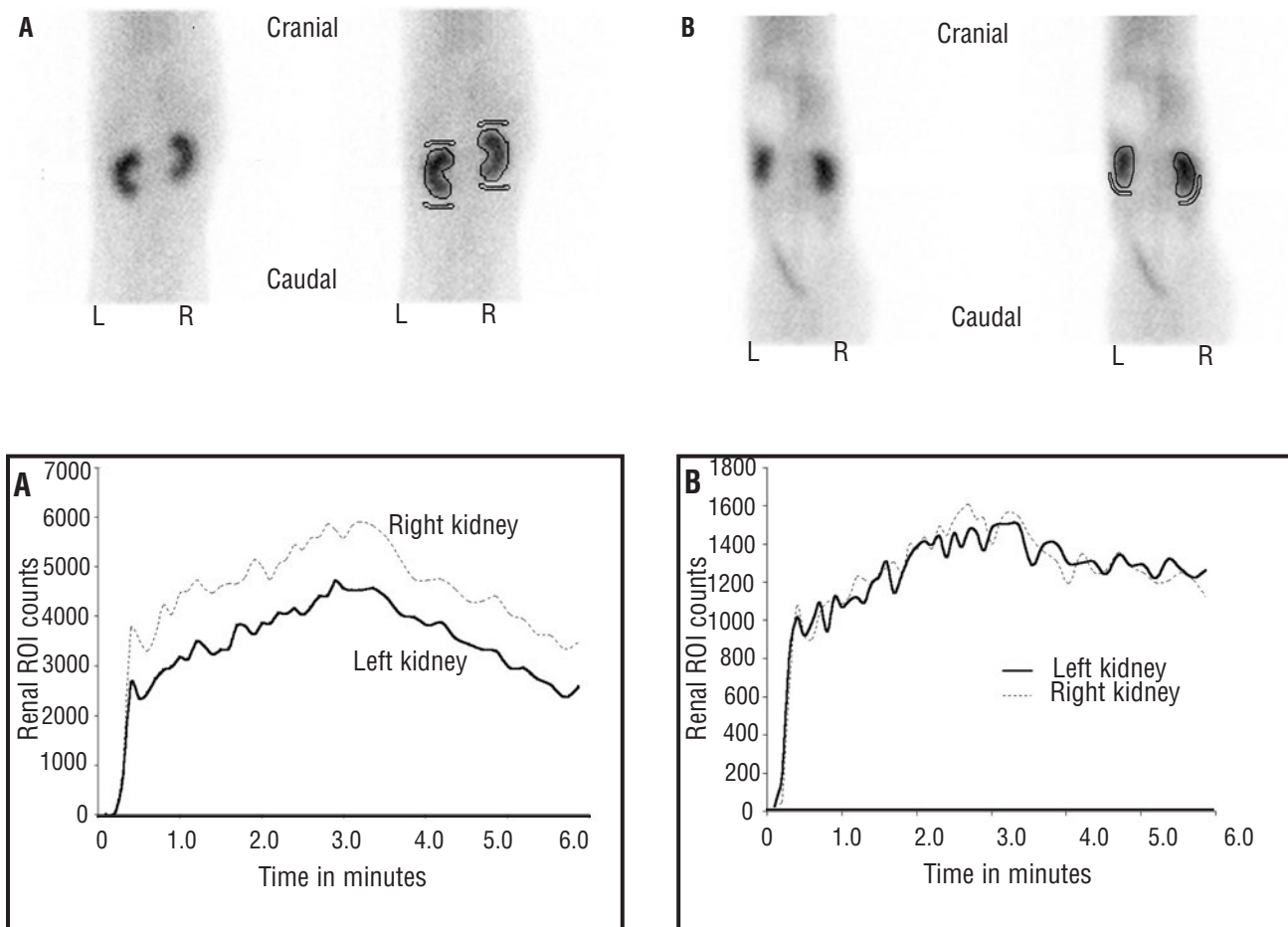


Figure 18.4: Renogram time-activity curves

A, This is the renal time-activity curve for a 1-year-old mixed breed dog that is clinically normal and has a BUN and creatinine within the normal ranges; 111 MBq (3 mCi) of ^{99m}Tc -DTPA was injected intravenously as a bolus and a dynamic frame acquisition was obtained for 6 minutes. The time-activity curve shows normal uptake and clearance of both kidneys. The total GFR was 3.25 mL/min/kg of which 56 % is contributed by the right kidney. These findings are consistent with normal renal function. **B**, This is a renal scan of a 3-year-old domestic shorthair cat that is clinically normal and has a BUN and creatinine within the normal range; 54 MBq (1.5 mCi) of ^{99m}Tc -DTPA was injected intravenously as a bolus, and a dynamic frame acquisition was obtained for 6 minutes. The time-activity curve shows normal uptake and clearance of both kidneys. The total GFR was > 2.5 mL/min/kg with a 50 % contribution from each kidney. These findings are consistent with normal renal function.

mL/min/kg are influenced by variations in the placement of the kidney and background ROIs. Often the kidneys in these animals cannot be visualized adequately for ROI placement. Nevertheless, such low uptakes give clear evidence of extremely low function. If accurate measurement in patients with such severe renal compromise is desired, ^{99m}Tc -

mercaptoacetylglycylglycylglycine (^{99m}Tc -MAG3) or ^{123}I -orthoiodohippuran can be used to measure effective renal plasma flow. Their high first-pass clearances provide much improved visualization of poorly functioning kidneys.

Animals with normal GFRs or mild subclinical renal insufficiencies have the ability to adjust their GFR

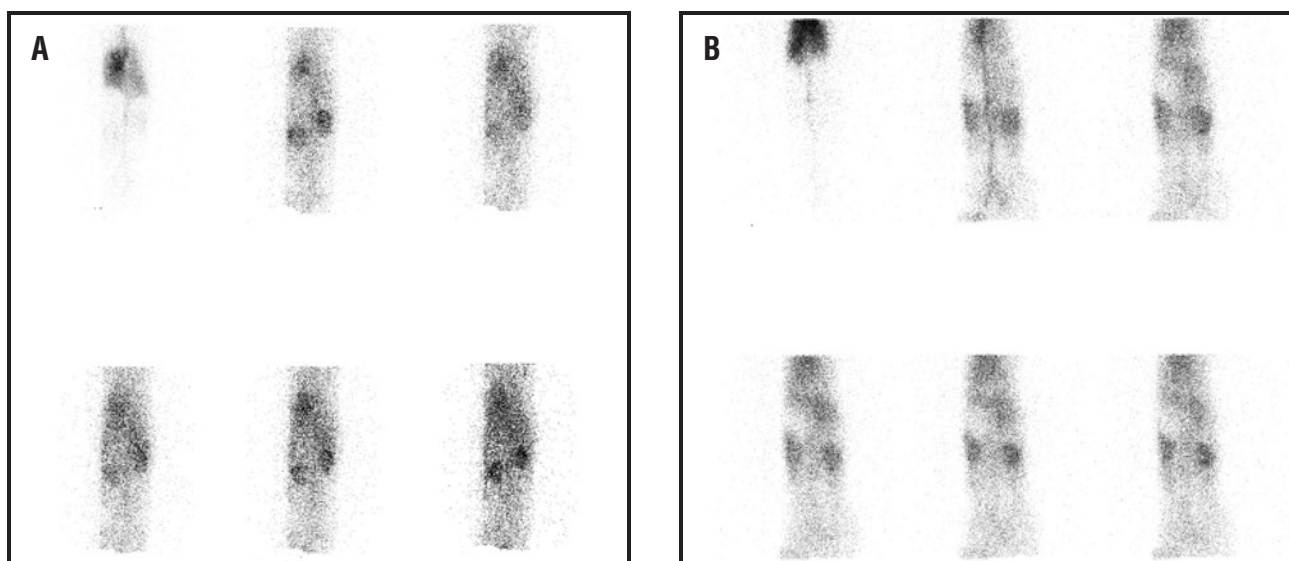


Figure 18.5: Initial Dynamic Images from a Normal Dog and Cat

A, Normal dog: Dorsal images from the first 36 seconds of the dynamic acquisition following bolus injection of ^{99m}Tc -DTPA. Note the rapid uptake of the radiopharmaceutical by the kidneys. **B**, Normal cat: Dorsal images from the first 36 seconds of the dynamic acquisition following bolus injection of ^{99m}Tc -DTPA. Note the rapid uptake of the radiopharmaceutical by the kidneys.

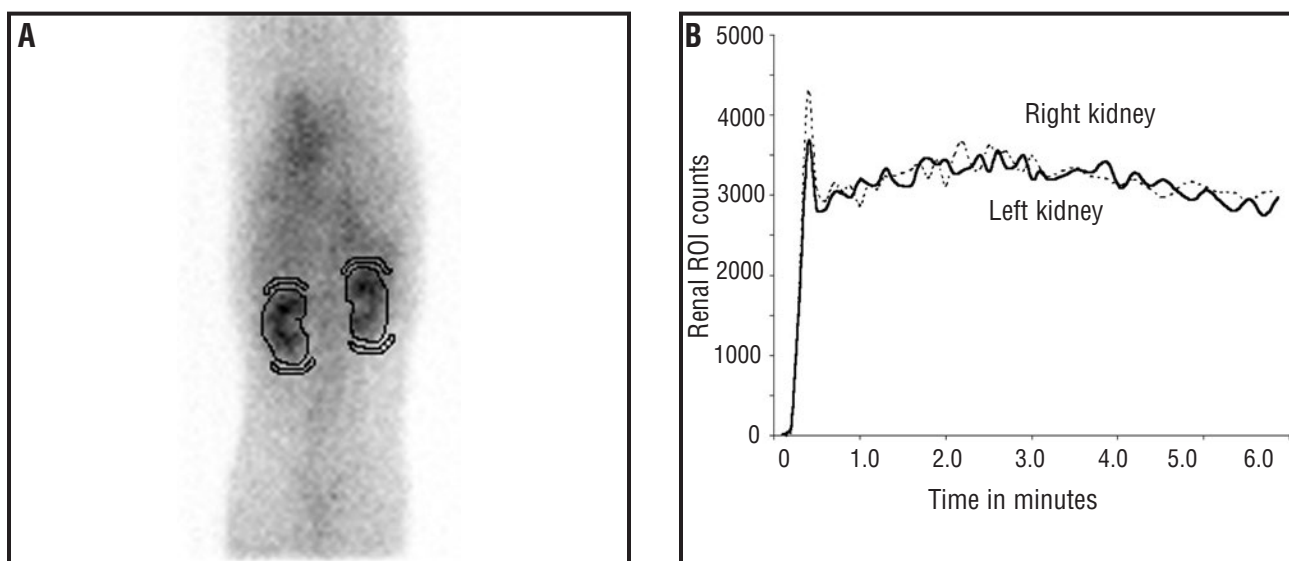


Figure 18.6: Renal scan of a 10-month-old mixed breed male dog with hereditary nephritis

A, In this dog, 111 MBq (3 mCi) of ^{99m}Tc -DTPA was injected intravenously as a bolus, and a dynamic frame acquisition was obtained for 6 minutes. Images from 1 to 3 minutes were summed to create the dorsal image. ROIs are shown for both kidneys. Note the increased blood pool activity within the thorax relative to the kidneys due to poor renal clearance. **B**, The time-activity curves are essentially flat after the arterial peak, which is accentuated. The GFR was 1.4 mL/min/kg with 48% contribution by the left kidney and 52% contribution by the right kidney. These findings are consistent with moderate renal insufficiency.

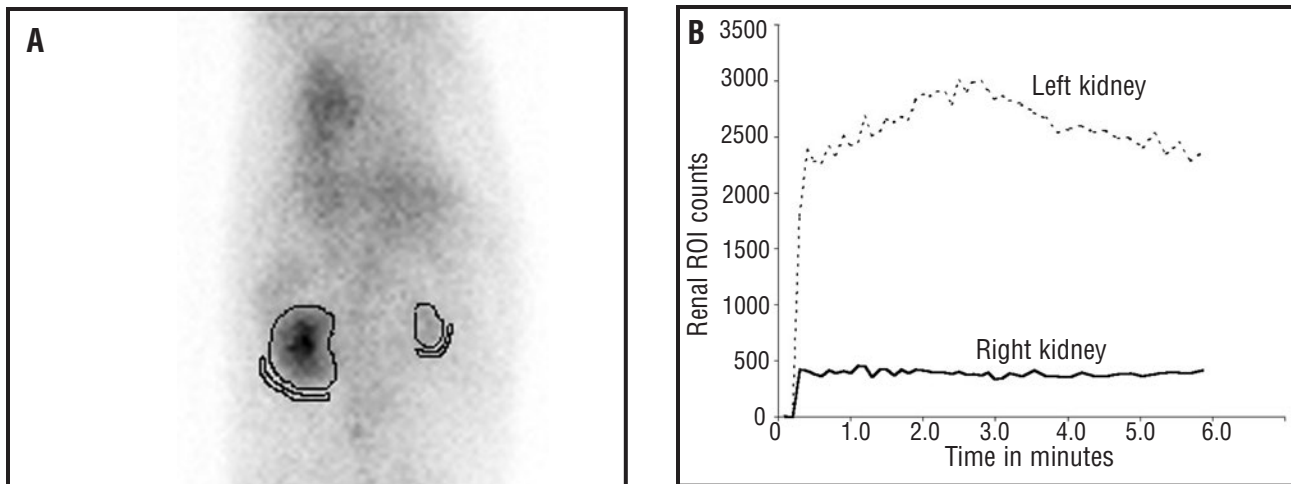


Figure 18.7: Renal scan of a 15-year-old female-neutered domestic shorthair cat with a history of a right ureteral calculus and recurrent urinary tract infection

A. In this cat, 111 MBq (3 mCi) of ^{99m}Tc -DTPA was injected intravenously as a bolus and a dynamic frame acquisition was obtained for 6 minutes. Images from 1 to 3 minutes were summed to create the image. ROIs are shown for both kidneys. Note the increased blood pool activity within the thorax. **B.** The time-activity curves show obviously differential uptake between the kidneys. The right kidney is evidently very small. The total GFR was 0.8 mL/min/kg with 92% of the function contributed by the left kidney. This finding is consistent with severe renal insufficiency, with almost no function arising from the right kidney.

to maintain homeostasis; therefore, GFR values will vary on repeat scans. Animals with moderate or severe renal insufficiency have lost their reserve capability, and the kidneys are functioning at their maximum GFR. The GFR values in these animals are more repeatable than in other animals and reflect the animal's true functional renal mass.

If possible, GFR studies should be performed on unsedated, unanesthetized animals. Most clinical patients will lie quietly in lateral recumbency for the required 3 minutes of dynamic acquisition and can be imaged without sedation. If sedation is needed, an acepromazine and butorphanol combination has been shown to have no effect on GFR in clinically normal dogs, in spite of greatly reduced blood pressure (0.05 mg/kg Acepromazine; wait 15 minutes; 0.02 mg/kg Butorphanol).⁵ Effects of sedation on animals with renal insufficiencies are not known. Isoflurane anesthesia in cats decreased percent dose uptake of ^{99m}Tc -MAG₃ approximately 20% and increased time-to-peak activity approximately 37%.⁶ The patient's hydration state must be adequate; severe dehydration has been shown to decrease GFR in dogs by 24%.⁷

Gookin et al evaluated the role of scintigraphy in decisions that clinicians made regarding treatment of renal calculi, renal masses, chronic pyelonephritis, perirenal mass, severe hydronephrosis, and hydro-ureter, and renal hypoplasia with ureteral ectopia.⁸ They concluded that a low percent uptake apparently influenced the decision to perform a nephrectomy rather than a nephrotomy.

Effective Renal Plasma Flow (ERPF)

Paraaminohippuric acid (PAH) is the gold standard for measurement of renal plasma flow. The procedure using PAH is similar to inulin clearance studies, which makes it inappropriate for routine clinical use. Ortho-iodo-hippuric acid (OIH) is chemically similar to paraaminohippuric acid and is the radiopharmaceutical of choice for evaluation of renal plasma flow. Ortho-iodo-hippuric acid has a high first-pass extraction rate (95%) due to its tubular and glomerular mechanisms of extraction, but it is not 100%, thus the term effective renal plasma flow is used. Tubular secretion accounts for 80% of OIH extraction from

the blood with glomerular filtration accounting for the remaining percentage. OIH will equilibrate with the extracellular fluid space within 4 to 5 minutes following intravenous injection. Disappearance from the plasma is biexponential with the first portion representing the distribution within the extracellular space (first compartment) and the second phase representing the intravascular (second compartment) clearance of OIH by the kidney. Ortho-iodohippuric acid is commercially available labeled with either I-123 or I-131. The I-131 form of OIH has the advantages of a long half-life (8.04 days) and being inexpensive; but it has the disadvantage of a 364 keV gamma ray, which results in poor image quality and beta emissions causing more radiation exposure of the patient and personnel. The I-123 form of OIH has superior image quality due to its 159 keV gamma ray emission, but it is more expensive and has a shorter half-life (13.2 hours). The activity of ^{123}I -OIH administered is less than technetium agents resulting in a lower photon flux from the patient. Images are of low count density, which results in a noisy image and poor counting statistics.

MAG₃ is a technetium based radiopharmaceutical with biologic properties similar to OIH, and may be used as a replacement for OIH. $^{99\text{m}}\text{Tc}$ -MAG₃ is not a true OIH analogue since it is primarily a tubular agent (90%) with little glomerular filtration (10%). $^{99\text{m}}\text{Tc}$ -MAG₃ is rapidly cleared from the blood as it is secreted by the organic anion transport system of the proximal convoluted renal tubules and to a lesser extent by glomerular filtration. Although it is highly protein bound (80-90%), the bound portion of MAG₃ is reversible so that $^{99\text{m}}\text{Tc}$ -MAG₃ blood clearance and renal uptake can be correlated to ^{131}I -OIH and PAH clearances, hence to renal blood flow. The net result is a plasma clearance that is only 70% of OIH. $^{99\text{m}}\text{Tc}$ -MAG₃ is frequently used for measurement of ERPF because of its desirable imaging characteristics. Since MAG₃ is a Tc-99m pharmaceutical, it has optimal imaging properties. The 140 keV gamma ray photon, 6.02 hour half-life and lack of particulate emission allow for higher counting efficiencies, lower radiation exposures, and better spatial resolution than OIH. Because a larger photon flux is possible, first pass (flow) images of the kidney can be performed. Mercaptoacetyl triglycine is available in a kit formation from Mallinckrodt under the name TechneScan MAG₃. A unique feature of the labeling process is that the reaction is heat depen-

dent (requires boiling) and that a small amount of air is added to the reaction vial, following the addition of pertechnetate, to consume the excess stannous ion for increased stability. $^{99\text{m}}\text{Tc}$ -MAG₃ is extracted primarily by the proximal convoluted tubule cells using the same active transport sites as OIH and PAH. The $^{99\text{m}}\text{Tc}$ -MAG₃ is then passed into the lumen of the nephron for urinary clearance. In cases of severe renal insufficiency, $^{99\text{m}}\text{Tc}$ -MAG₃ is superior to $^{99\text{m}}\text{Tc}$ -DTPA because of its high renal extraction rate, thus improving the renal to background ratios (Figure 18.8). Hepatobiliary uptake does occur and appears to be a property of the $^{99\text{m}}\text{Tc}$ -MAG₃ and not radiochemical impurities. In humans, the hepatobiliary uptake is considered an alternate route of elimination that increases with renal failure. The appearance of hepatobiliary uptake is variable in dogs but does not appear to affect renal quantification significantly.

The quantitative scintigraphic method using $^{99\text{m}}\text{Tc}$ -MAG₃ has been published for the dog and cat.⁹⁻¹¹ Percent dose uptakes have been measured for the cat,⁶ but have not been related to actual ERPF. Indications for renal scintigraphy using $^{99\text{m}}\text{Tc}$ -MAG₃ are listed in Table 18.4. Cats imaged using $^{99\text{m}}\text{Tc}$ -MAG₃ have discernable liver uptake and excretion.^{12,13} Imaging procedures are the same as described for GFR measurement, except that shorter frame acquisition times are beneficial because of more rapid radiopharmaceutical uptake and clearance; 3 seconds per frame is recommended and a 3-minute total acquisition is more than adequate (Table 18.5). $^{99\text{m}}\text{Tc}$ -MAG₃ % ID uptake correlates best with para-aminohippuran (PAH) clearance ($r = 0.82$) for the time interval 76 to 150 seconds postinjection using the following formula:⁹

$$\text{ERPF (mL/min/kg)} = 0.157 * (\% \text{ ID right kidney} + \% \text{ ID left kidney}) - 0.83$$

The current cost per vial (over \$200) is a distinct drawback to routine $^{99\text{m}}\text{Tc}$ -MAG₃ use. Thorson et al have described a method of fractionating and storing $^{99\text{m}}\text{Tc}$ -MAG₃ cold kits, which could be helpful in this regard.¹²

Blood Clearance Techniques

Both GFR and ERPF can be determined by measuring the rate of clearance of radiopharmaceuticals ($^{99\text{m}}\text{Tc}$ -DTPA for GFR and ^{131}I -OIH or $^{99\text{m}}\text{Tc}$ -MAG₃ for ERPF) from plasma. The procedure is more time-consuming than quantitative renal scin-

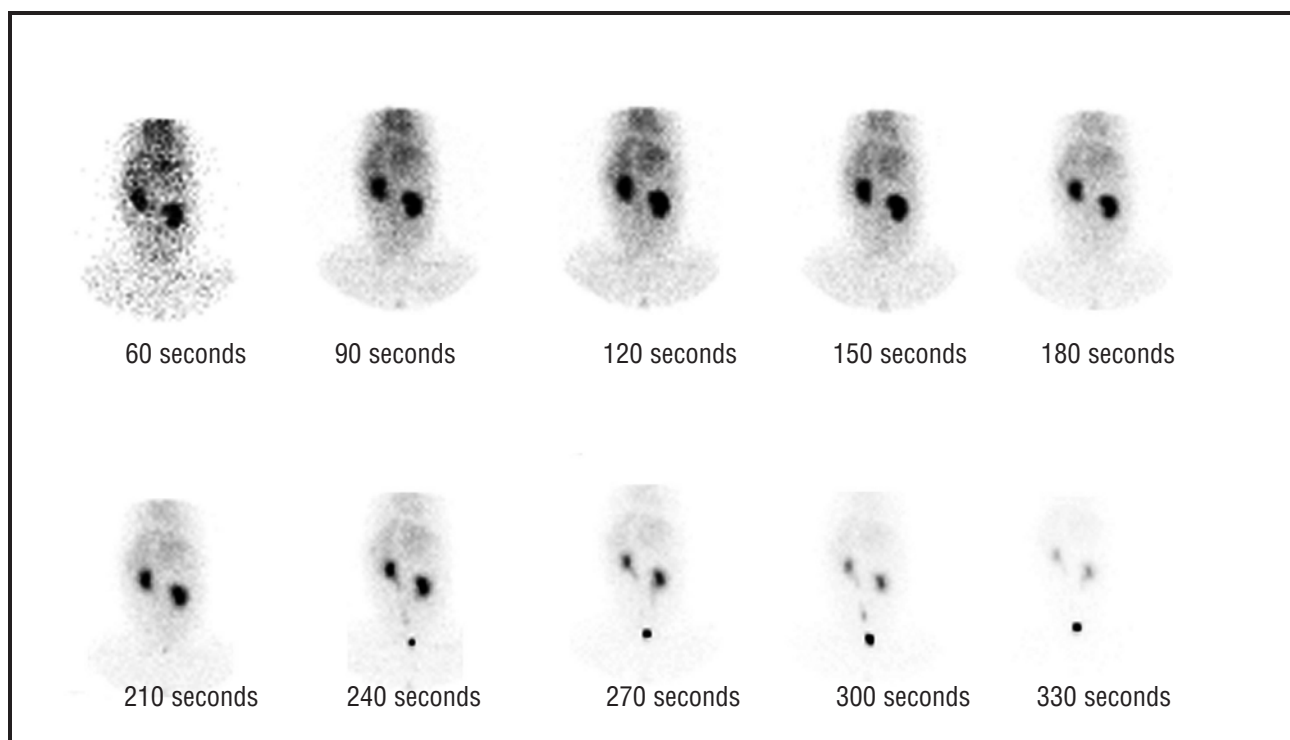


Figure 18.8: Dorsal images of a normal dog following intravenous injection of ^{99m}Tc -MAG3

Note the rapid uptake of the radiopharmaceutical by the kidneys and the subsequent clearance into the urinary bladder. The renal extraction of this radiopharmaceutical is faster than ^{99m}Tc -DTPA.

Table 18.4: Indications for Renal Scintigraphy Using ^{99m}Tc -MAG3 or ^{131}I -OIH

Determine global and individual kidney ERPF.
Determine filtration fraction (when combined with GFR).
Serial ERPFs can be used to evaluate a patient's response to treatment.
Early diagnosis of impaired renal function.
Evaluate function of contralateral kidney prior to nephrectomy.
Identify and determine the severity of subclinical renal disease in an animal receiving nephrotoxic agents (eg, chemotherapeutics or aminoglycoside antibiotics).
Evaluate Kidney following Transplantation.

tigraphy and requires that serial blood samples be taken and the plasma radioactivities determined. Clearance studies do not require a gamma camera and can be performed on dogs, cats, and horses as well as other species.

Blood Sampling and Counting

An accurately known volume of dose solution is injected intravenously at zero time. Suggested doses of the radiopharmaceutical are listed in Table 18.6. Heparinized blood samples, 1 to 2 mL, are drawn at accurately timed intervals from a vein other than the one used for injection. Timing and number of samples drawn are somewhat arbitrary, with a minimum of four to five samples beginning at 5 minutes postinjection. Barthez, et al,¹³ have shown that a minimum of four samples (5 minutes, and 2.5-, 3-, and 4-hours) provides a clearance curve with an acceptable amount of error. The samples should be spaced at increasing intervals through 180 minutes for GFR and 90 minutes for ERPF determination. Samples are then centrifuged and 0.5 to 1 mL of plasma is accurately pipetted into test tubes for

Table 18.5: Imaging Parameter for Renal Scintigraphy Using ^{99m}Tc -MAG3**Radiopharmaceutical** ^{99m}Tc -MAG3 (mercaptoacetyltriglycine)**Dose**

	mCi	MBq
Dog	1-4	37-148
Cat	1-3	37-111

Acquisition Parameters - ^{99m}Tc -MAG3 Scintigraphy for EPRF Evaluation

Animal preparation	Normal State of Hydration.
Dynamic frame acquisition	3 seconds per frame (60 to 100 frames total).
Static frame acquisition	60 second image.
Matrix	128 (64) $\times$ 128 (64) $\times$ 16 (Dynamic) and 256 $\times$ 256 $\times$ 16 (Static).
Collimator	Low-energy, all-purpose.
Time to image	Immediate for Dynamic Acquisition, total imaging time 3-5 minutes. Acquire Lateral static image following the dynamic study.
Positioning	Animal in lateral recumbency with camera centered dorsal to the kidneys (dynamic). Keep animal in same lateral recumbency and position the camera lateral to the kidneys.
Views	Dorsal view for dynamic dorsal acquisition; Lateral view for static image.

counting. From the same solution used to dose the animal, an accurately measured volume (0.1 to 0.5 mL) is diluted and well mixed in a 500 or 1,000 mL volumetric flask. Duplicate counting standards are pipetted from the volumetric flask using the same volume as the plasma samples. All samples, plasma, and counting standards, are counted in a well-type (sodium iodide crystal) detector. Samples should be counted sequentially and without interruption as soon as possible to avoid excessive decay and decay corrections, although ^{131}I with a longer physical half-life of 8 days permits a delay until counting. A 1-minute counting time per sample should give sufficient total counts for adequate counting precision. A probe detector can be used for counting plasma samples, if extreme care is taken to position all samples and standards in exactly the same position relative to the probe. If one is using the probe system, counting efficiency will be lower than in a well detector, thereby requiring larger radiopharmaceutical dosages (two to four times larger). The procedures of calculation of plasma clearance is listed in Table 18.7.

Descriptions of fitting and analyzing plasma clearance curves are given in many texts and articles, including those by Matthews et al¹⁴ and Cohn.¹⁵ Personal computer programs are readily available for such curve-fitting procedures. A mono-exponential model gives GFR clearance values that are very close to the bi-exponential procedure just described. For EPRF, however, the bi-exponential procedure is required.

In humans, ^{99m}Tc -MAG3 clearance is lower than ^{131}I -OIH clearance. It does not directly provide EPRF, but is highly correlated to it ($r = 0.92$).¹⁶ Itkin et al¹⁷ have shown that the reverse is true in the dog; ^{99m}Tc -MAG3 clearance is higher than paraaminohippuric acid (PAH) clearance. Their results from six dogs (18 data points; $r = 0.83$) resulted in the following equation:

$$\text{EPRF mL/min/kg (from PAH)} = 2.17 + 0.49 \times (\text{}^{99m}\text{Tc-MAG3 clearance mL/min/kg})$$

Table 18.6: Radiopharmaceutical Doses Used for Plasma Clearance Studies

Glomerular Filtration Rate - ^{99m}Tc -DTPA		
Species	μCi	MBq
Dog and Cat	25-100	1-4
Horse	3,000-4,000	111-148

Effective Renal Plasma Flow		
^{131}I -Orthoiodohippuran (^{131}I -OIH)		
Species	μCi	MBq
Dog and Cat	25-100	1-4
Horse	300-400	11.1-14.8
^{99m}Tc -MAG3		
Dog and Cat	25-100	1-4
Horse	3,000-4,000	111-148

Clearance rates can also be measured using an external scintillation probe detector, with or without blood sampling.¹⁸⁻²⁰ The fraction of the volume of distribution (V_d) that is cleared per minute during the renal phase is related to the half-life of the renal phase ($T_{1/2b}$) by:

$$0.693/T_{1/2b} = k_{b-\text{min}}$$

Assuming the V_d of ^{99m}Tc -DTPA is (or closely approximates) the extracellular fluid volume (ECFV), then:

$$\text{GFR/ECFV} = k_b$$

and the slope of the renal phase component of the clearance curve is approximately equal to the GFR divided by the ECFV. This relationship is strongest with low GFRs and weakens as the GFR increases and the first component (mixing phase) contributes more to the calculated value.¹⁹

Principles of Interpretation

Radionuclide clearance methods for measuring GFR

Table 18.7: Procedures for Calculating Plasma Clearance

Calculations	
1.	The radioactivity in the dose counting standard (STD) is determined and expressed as counts per minute (cpm). This is multiplied by the dilution factor to determine the total cpm in the dose. Example: 1 mL of dose solution is injected into a dog, and 0.2 mL from the same solution is diluted and well mixed in a 1,000 mL volumetric flask. 0.5 mL plasma samples and 0.5 mL STD from the volumetric flask are counted. $\text{Total Dose} = \text{mCi injected into patient, [cpm]} \times \left[\left(\frac{\text{mCi in 0.2 mL of Dose}}{1,000 \text{ (dilution factor from Flask)}} \right) \times \text{cpm in 0.5 mL Aliquot from Flask} \right]$
2.	Percent injected dose (% ID) per mL of plasma = $\{[(\text{cpm in plasma sample})/(\text{mL plasma counted})]/(\text{total cpm in dose})\} \times 100$
3.	A plasma disappearance curve is produced by plotting the % ID (vertical log scale) per mL versus time (horizontal linear scale) on semilog paper. This curve can usually be resolved (stripped) into 2 separate, straight lines that represent the early "mixing" (A) and the later, renal clearance (B) phases of total plasma clearance (Figure 18.9). Clearance in this 2-compartment model is calculated as: $\text{Plasma clearance (mL/min)} = [0.693 \times \text{Dose}] / [(A_0 \times t_{1/2a}) + (B_0 \times t_{1/2b})]$ where dose = 100%; A_0 and B_0 = zero time intercepts (% dose/mL) of the mixing phase (line A) and renal clearance phase (line B), respectively; $t_{1/2a}$ and $t_{1/2b}$ = half-times of removal (minutes^{-1}) for line A and line B, respectively (times when $A = A_0/2$ and $B = B_0/2$).
4.	Plasma clearance can then be divided by body weight (kilograms) to obtain GFR (using ^{99m}Tc-DTPA) or ERPF (using ^{131}I-OIH) in mL/min/kg.

and ERPF in animals have been reported in numerous papers.¹⁸⁻³⁰ Correlations between radionuclide studies and other methods for measuring GFR and ERPF have been excellent in some cases and less so in others. This is probably because some nonradionuclide assay techniques can be difficult to perform accurately. Because of their relative simplicity, results from radionuclide clearances may be the most precise and, for certain pharmaceuticals, the most accurate.

In the dog, Barthez et al²¹ compared GFRs determined by ^{99m}Tc-DTPA plasma clearance ($r = 0.98$) and image based quantitative renal scintigraphy ($r = 0.86$) to inulin clearance. They concluded that both percentage uptake and plasma clearance of ^{99m}Tc-DTPA give “reasonable estimates of renal function when compared to the standard inulin clearance method.”²¹ Their results suggested that “use of DTPA clearance to estimate total GFR is preferable to percentage uptake, and percentage uptake serves better to estimate the relative function of each kidney.”²¹ They compared the advantages and difficulties of both methods, recognizing that their results should be considered preliminary (small number of dogs and data points). Barbour et al²⁰ obtained excellent correlations between ^{99m}Tc-DTPA ($r = 0.98$), ¹²⁵I-Iothalamate ($r = 0.99$), and inulin clearances in dogs in which the radiopharmaceuticals were injected subcutaneously and steady-state blood levels were maintained; however, urine sampling was required. Moe et al²³ measured iothexol and ^{99m}Tc-DTPA plasma clearances in 18 dogs. There was good agreement between the two agents, although the ^{99m}Tc-DTPA GFR was 15% greater than the Iothexol GFR. Gleadhill et al¹⁹ compared ^{99m}Tc-DTPA and exogenous creatinine clearances in a large number of dogs, measuring ^{99m}Tc-DTPA radioactivity by both blood sampling and counts from an external detector positioned over the head. They advocated normalizing GFR to the extracellular fluid volume (ECFV) rather than to body weight, because “it is the role of the kidney to filter the ECFV and regulate its composition and volume, ... it has the major advantage that the GFR can then be measured directly with the external detector,” and “it also simplifies the mathematics in calculating GFR/ECFV compared with that in calculating GFR/kg.”¹⁹

In the horse, Walsh et al found that ^{99m}Tc-DTPA clearance correlated to inulin clearance ($r = 0.66$).²⁴ Quantitative renal scintigraphy was performed in the

same study and found not to correlate significantly with inulin clearance. In another study by Matthews et al, mean clearance values were statistically the same for ^{99m}Tc-DTPA versus inulin, and also for ¹³¹I-OIH vs PAH.¹⁴ Hood et al measured GFRs of 1.9 ± 0.3 mL/min/kg using ^{99m}Tc-DTPA and ERPFs of 8.2 ± 2.9 mL/min/kg using ¹³¹I-OIH in horses.²⁵ Held and Daniel calculated equine effective renal plasma and blood flows of 6.0 mL/min/kg and 10.7 mL/min/kg using ¹³¹I-OIH.²⁶

In two investigations in the cat, ^{99m}Tc-DTPA clearance has been correlated to endogenous creatinine clearance with $r = 0.71$ and $r = 0.85$.²⁷ Poorer correlations were obtained between ^{99m}Tc-DTPA and inulin clearances.²⁵ Day measured percent dose DTPA uptake to evaluate global and unilateral function in a cat 2 weeks and 8 weeks post-surgery. They felt scintigraphy provided useful information for evaluating the progression of unilateral function following relief of obstruction.²⁸

Obstructive Renal Scintigraphy

The radionuclide renogram can provide information in addition to GFR with slight modification. A commonly encountered clinical problem is the determination of the etiology of a dilated renal pelvis. This determination is critical because, if the cause is due to an obstruction, surgery may be indicated. In humans, this assessment is commonly made by manipulating the renogram time-activity curves mathematically so that various parameters (mean transit time [MTT], time of peak [TOP] radioactivity) are calculated as well as evaluating the clearance data after diuretic administration. Indications for obstructive renography are listed in Table 18.8, and imaging acquisition protocols are given in Table 18.9.

Principles of Interpretation: Diuresis Renal Scintigraphy

There is limited information on diuresis renography in the veterinary literature and it is primarily focused on research situations.⁴ However, it has been used and evaluated extensively in humans. Visual evaluation of the renal time activity curves before and after injection of furosemide is the simplest method used to diagnose obstruction in human medicine.^{31,32} In normal kidneys, furosemide should incite a steep decrease in the renal time-activity curve (Figure

18.10). An obstructed kidney will show no change or may show an increase in the time-activity curve after injection of furosemide (Figure 18.11). There is an indeterminate group that may show some decrease in the time-activity curve but not to the degree considered “normal.”

A quantitative method of determining clearance for diuresis renography is calculation of the clearance half-time. However, a variety of methods can be utilized to calculate the clearance half-time. For instance, the clearance half-time can be determined from the time of injection of the diuretic or from the start of the response. The problem with the latter is that the determination of the start of the response may be difficult to determine if it is not sharp. In one study, normal dogs had a clearance half-time of 9.1 minutes.³³ In humans, a clearance half-time of > 20 minutes regardless of method used is considered diagnostic of obstruction.³⁴

Major problems of interpretation occur with these methods in cases of severe renal insufficiency and severely dilated collecting systems. In both cases, a decrease in the time-activity curve may not be seen and thus provide a false positive diagnosis.³⁴ In addition, dehydration can cause false positive results due to the decreased fluid flux. A full urinary bladder can also delay upper urinary tract emptying (so-called “bladder effect”). Thus, all patients should be well hydrated and have the opportunity to empty the urinary bladder prior to initiation of the study. Furthermore, false-negative results can also be encountered. Barthez et al⁴ found inconsistent results in the response to diuresis in some of their dogs with surgically induced unilateral partial ureteral obstruction. In humans, this can be seen in highly compliant renal pelvises or when there is a high-pressure diure-

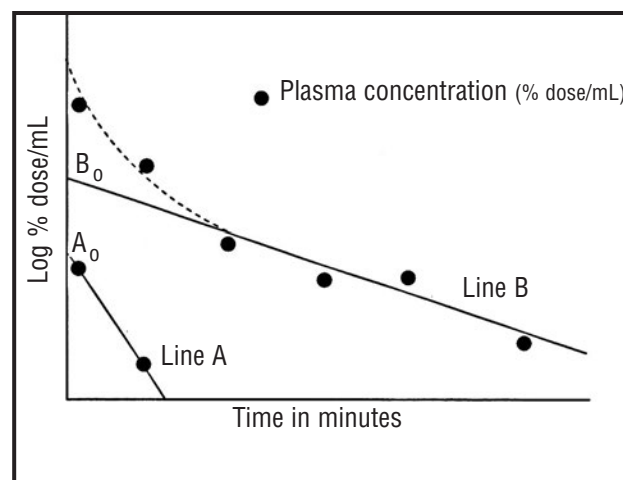


Figure 18.9: Plasma clearance curve showing the total plasma concentration data points (% ID per mL) at the times of blood sampling

The later renal clearance phase line (line B) has been extrapolated to its intercept at time 0 (B_0). The early mixing phase (line A) is obtained by subtracting the points on line B from the early total radioactivity concentrations, with its time 0 intercept being represented by A_0 .

sis through partially obstructed systems.³⁵⁻³⁷

In humans, a standardized procedure has been established for diuresis renography to try to avoid false-negative and false-positive results as previously described. A similar protocol has not been established for veterinary medicine to date.

Mean Transit Time or Time of Peak

The mean transit time and time of peak for the whole (w) kidney and parenchyma (p) of the kidney (wMTT and pMTT and wTOP and pTOP) of the radiopharmaceutical can be calculated from the renal time-activity curve derived from a peripheral intravenous injection (Figure 18.12). MTT can be calculated by various methods involving deconvolution of the renal time-activity curve and the vascular time-activity curve. Deconvolution of these curves allows the derivation of a time-activity curve that simulates a direct arterial injection of radiopharmaceutical into the renal artery. Various methods have been described in the human and veterinary literature. The most common methods are deconvolution using a matrix method and Fast Fourier Transformation

Table 18.8: Indications for Obstructive Renography

Differentiate an obstructed dilated ureter from a dilated nonobstructed ureter.
Evaluate patency of the ureter in patients with hydronephrosis.
To evaluate a patient's response to treatment.
Calculate MTT and TOP renal activity.

Table 18.9 Imaging Parameters for Obstructive Renography**Radiopharmaceutical**^{99m}Tc-DTPA (diethylenetriaminepentaacetic acid).**Dose**

Species	mCi	MBq
Dog	1-4	37-148
Cat	1	37

Acquisition Parameters

Diuresis Scintigraphy	
Animal preparation	Normal state of hydration.
Dynamic frame acquisition	6 seconds per frame for 3 minutes then 3 seconds per frame for 5 minutes (diuresis); inject furosemide (3 mg/kg) at 4.5 minutes radiopharmaceutical injection.
Matrix	128 (64) × 128 (64) × 16 (Dynamic) and 256 × 256 × 16 (Static).
Collimator	Low-energy, all-purpose.
Time to image	Immediate for dynamic acquisition; total imaging time 6-20 minutes. Acquire lateral static image following the dynamic.
Positioning	Animal in lateral recumbency with camera centered dorsal to the kidneys (dynamic). Keep animal in lateral recumbency and position the camera lateral to the kidneys.
Views	Dorsal (dynamic); lateral (static).
MTT and TOP	
Dynamic frame acquisition	10 seconds per frame for 20 minutes.
Static frame acquisition	60 seconds per image.
Matrix	128 (64) × 128 (64) × 16 (Dynamic) and 256 × 256 × 16 (Static).
Collimator	Low-energy, all-purpose.
Time to image	Immediate for dynamic acquisition; total imaging time 6-20 minutes. Acquire lateral static image following the dynamic.
Positioning	Animal in lateral recumbency with camera centered dorsal to the kidneys (dynamic). Keep animal in lateral recumbency and position the camera lateral to the kidneys.
Views	Dorsal (dynamic); lateral (static)

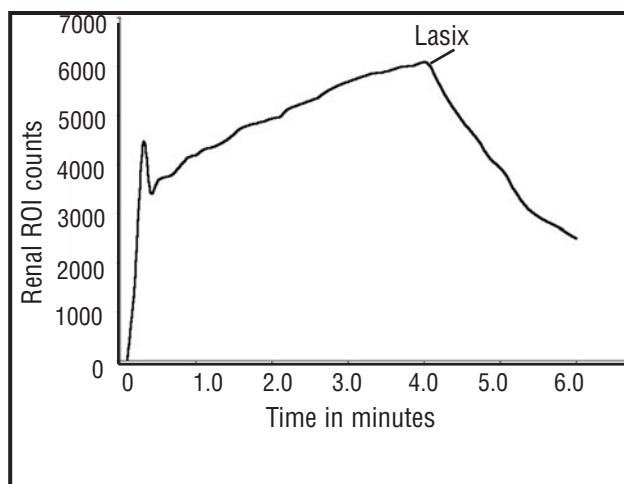


Figure 18.10: Renal time-activity curve in a normal dog

There is rapid decline (clearance) of the renal radioactivity after the injection of furosemide during drug-induced diuresis.

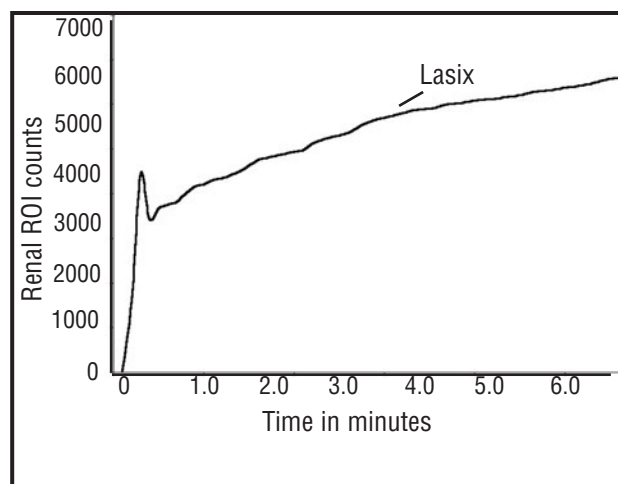


Figure 18.11: Renal time-activity curve in a dog with obstruction of the ureter

There is no clearance of the radioactivity from the kidney after the injection of furosemide, consistent with complete obstruction of the outflow tract.

(Figure 18.12). The mathematics involved is simplified using readily available computer software. These methods should all yield similar numeric MTT values. The previously described methods are outlined in the Appendix.

In one study, the normal wTOP was 230 ± 60 seconds and the pTOP was 208 ± 49 sec. Parenchymal and whole kidney MTT ranged from 137 to 184 seconds. The pMTT was shorter than wMTT.³⁸ In another study, the wTOP, pTOP, pMTT, and wMTT increased in dogs 2 to 9 days after surgically induced partial ureteral obstruction and may be useful in evaluation of upper urinary tract obstruction. The increase in pTOP ranged from two to nine times the baseline value.⁴ In humans, wMTT normally is 3.6 ± 1.1 minutes and a value of > 7.6 minutes is diagnostic of obstruction.³⁹ A definitive value for obstruction has not been established in dogs.

Structural Renal Scintigraphy

Anatomic information, such as size, shape, and position, can be determined from static renal imaging. The radiopharmaceuticals commonly utilized include ^{99m}Tc -DTPA, ^{99m}Tc -MAG3, ^{99m}Tc -GH, and ^{99m}Tc -DMSA. They are transported to the nephron

through the renal arterial circulation and filtered through the glomerulus. Some of these agents are reabsorbed by the tubules (GH and DMSA) and localize there. Thus, tumors, cysts and abscesses that do not contain tubules or areas of decreased blood supply, such as infarcts, will cause areas of decreased radiopharmaceutical uptake ("cold spots"). In addition, the amount of activity retained in the kidney is representative of the relative function. Lists of indications and imaging protocols are given in Tables 18.10 and 18.11.

Principles of Interpretation

^{99m}Tc -DMSA and ^{99m}Tc -GH are filtered by the glomeruli and are reabsorbed and bound to the renal tubules.^{38,39} This allows delayed, static imaging of the functional tubular mass in the renal cortices (Figure 18.13). Imaging is delayed to allow clearance of the unbound radiopharmaceutical from the collecting system. Any alteration in the tubules, such as from tumors, cysts, or abscesses, will cause decreased uptake of these radiopharmaceuticals in those regions (Figure 18.14). Obviously, all these processes could produce similar scintigraphic patterns and are thus relatively sensitive but not specific.⁴⁰ In humans, ^{99m}Tc -DMSA has been used extensively

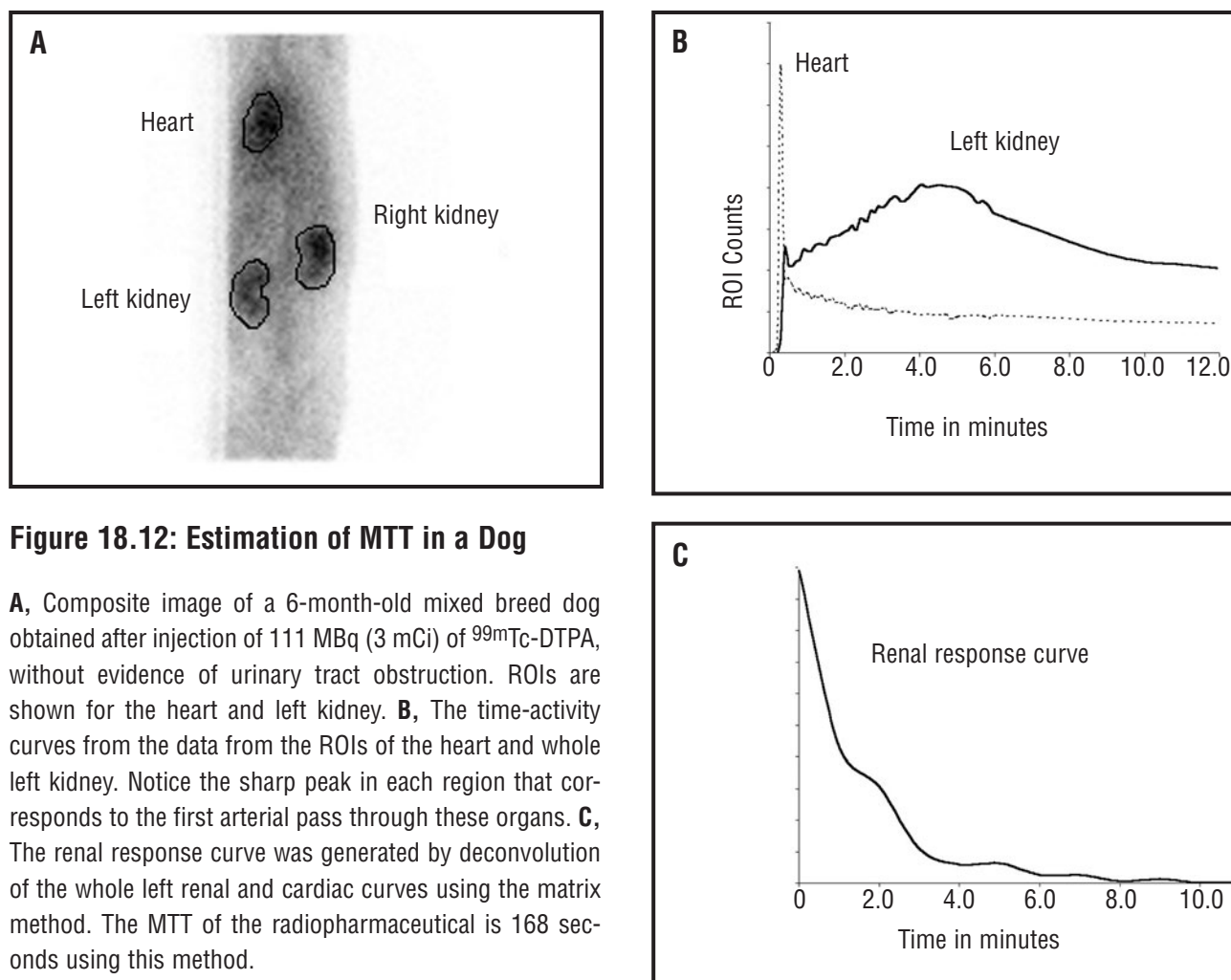


Figure 18.12: Estimation of MTT in a Dog

A, Composite image of a 6-month-old mixed breed dog obtained after injection of 111 MBq (3 mCi) of ^{99m}Tc -DTPA, without evidence of urinary tract obstruction. ROIs are shown for the heart and left kidney. **B**, The time-activity curves from the data from the ROIs of the heart and whole left kidney. Notice the sharp peak in each region that corresponds to the first arterial pass through these organs. **C**, The renal response curve was generated by deconvolution of the whole left renal and cardiac curves using the matrix method. The MTT of the radiopharmaceutical is 168 seconds using this method.

Table 18.10: Indications for Morphologic Renal Imaging

Assess kidney size, shape, and position.
Evaluate suspected renal trauma, tumor, cysts, abscesses, or pyelonephritis.
Evaluate relative renal function of the kidneys.

in evaluation of acute pyelonephritis. Typically, this produces a scintigraphic pattern of multiple photopenic defects in normal to enlarged kidneys. The mechanism responsible for this pattern is likely due to a combination of focal tubular cell dysfunction and ischemia from the acute inflammatory response to the infection. Chronic pyelonephritis appears similar except the kidneys are usually small (Figure

18.15).⁴¹

Relative function can be determined by obtaining the net kidney counts with depth correction and then using the following equation⁴²:

$$\% \text{ Individual relative kidney perfusion} = \frac{(\text{Net depth-corrected kidney counts})}{(\text{Net depth-corrected left Kidney counts} + \text{net depth-corrected right kidney counts})} \times 100$$

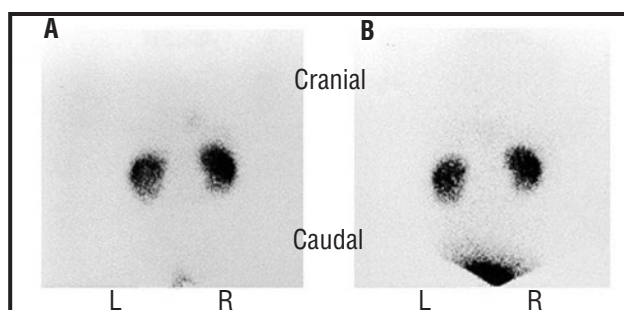
^{99m}Tc -DTPA and ^{99m}Tc -MAG3 are filtered by the glomeruli but not bound to the tubules; and thus, activity in the cortices is transitory. In spite of this, some information can be gained through examination of the summed composite images. Location and size can be easily evaluated. The uniformity of the radioactivity is dependent on the time frame of summed images. However, if summing the first 3

Table 18.11: Imaging Parameters for Morphologic Renal Imaging**Radiopharmaceutical**^{99m}Tc-DMSA (dimercaptosuccinic acid).**Dose**

Species	mCi	MBq
Dog	1-4	37-148
Cat	1	37
Horse	20	740

Acquisition Parameters

Animal preparation	Normal state of hydration.
Static frame acquisition	500,000 counts.
Matrix	256 × 256 × 16 (static).
Collimator	Low-energy, all-purpose.
Time to image	3-4 hours postinjection.
Positioning	Recumbent for small animals with gamma camera under the table. Place the gamma camera over the back of a horse while in a standing position.
Views	Dorsal, right and left lateral and dorsolateral obliques in small animals. Dorsal and dorsolateral obliques in horses.

**Figure 18.13: Dorsal images from a normal dog acquired 1 (A) and 4 (B) hours after injection of ^{99m}Tc-DMSA**

Note the high kidney-to-background ratio. The highest intensity uptake is in the renal cortex.

minutes from a dynamic functional study, the kidney should have uniform activity.

Summary

Renal scintigraphy provides rapid, noninvasive information regarding renal function in dogs, cats and horses. Specifics regarding glomerular filtration can be assessed and used as a method for evaluating a patient's response to therapy. Various mathematical techniques have been shown to be valid for use in veterinary medicine and may help provide further information, although the true clinical impact has yet to be realized.

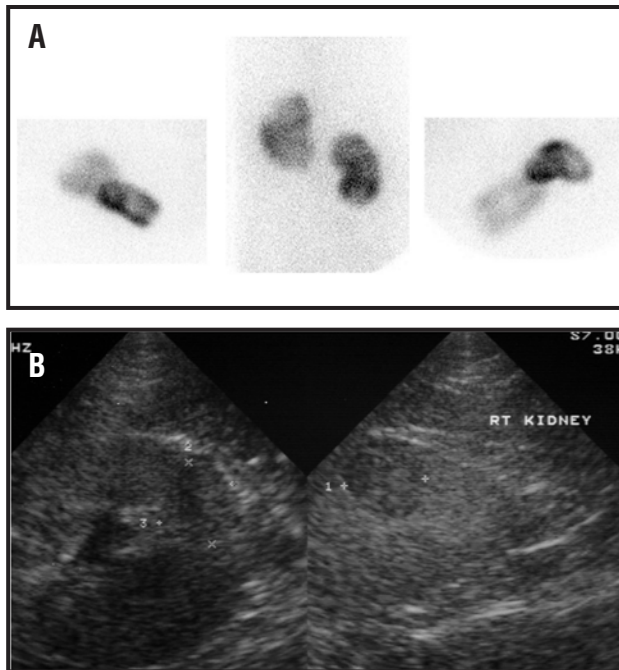


Figure 18.14: Renal morphology scan of a 12-year male-castrated dog with renal metastasis.

A, 3.3 mCi of ^{99m}Tc -DMSA was injected intravenously and static images were acquired 3 hours after injection. The uptake within the kidney is non-uniform. There are several photopenic regions representing the area of metastasis. The tumor cells replace to displace the normal renal tubular cells resulting in the photopenic void. **B**, Ultrasound images of the right kidney in the same dog. A renal cortical metastasis is marked using the electronic calipers.

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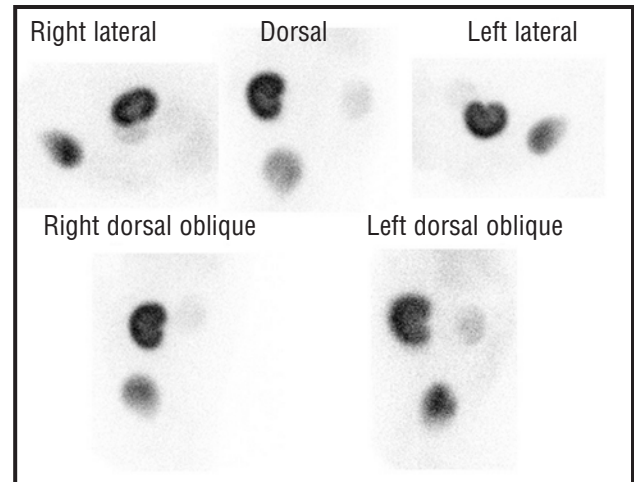


Figure 18.15: Renal morphology scan of a 4-year female-spayed dog with decreased renal function of the right kidney.

3.5 mCi of ^{99m}Tc -DMSA was injected intravenously and static images were acquired 3 hours after injection. Note the poor uptake by the right kidney. By measuring the uptake of ^{99m}Tc -DMSA by the kidney, differential renal function can be determined.

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Appendix: Deconvolution Methods

Fourier Transformation⁴³

Input Function

$$f(x_{\text{kidney}}) \text{ ----> FFT----> } F(u_{\text{kidney}})$$

$$f(x_{\text{blood pool}}) \text{ ----> FFT----> } F(u_{\text{blood pool}})$$

$$F(u_{\text{kidney response}}) = \frac{F(u_{\text{kidney}})}{F(u_{\text{blood pool}})}$$

$$F(u_{\text{kidney response}}) \text{ -----> IFFT-----> } f(x_{\text{kidney response}})$$

where: $f(x_{\text{kidney}})$ = renal time-activity curve
 $f(x_{\text{blood pool}})$ = blood time-activity curve
 $F(u_{\text{kidney}})$ = Fourier Transformation of renal time-activity curve
 $F(u_{\text{blood pool}})$ = Fourier Transformation of blood time-activity curve
 $f(x_{\text{kidney response}})$ = renal response curve
 FFT = fast Fourier transformation and IFFT = inverse fast Fourier transformation

Note: An appended tail is usually applied to the $f(x)$ curves to alleviate high-frequency artifacts using the following equation:

$$\text{Tail} = 0.5 \times N \times (\cos[(i - \text{last frame number}) \div (128 - \text{last frame number})] + 1)$$

where N = renal or blood pool counts at last frame

i = varying time points from last frame number to 128

Matrix Method³⁶

The deconvolution equation can be written in matrix notation as:

$$H = B^{-1} \times R \times (1/\Delta t)$$

Where H = renal response curve

B^{-1} = inverse matrix of Blood pool time-activity curve

R = renal time-activity curve

Δt = difference in time between 0 and t

Mean Transit Time⁴⁴

$$\text{MTT} = \frac{\sum_{t=1}^n H(t)\Delta t}{H(i)}$$

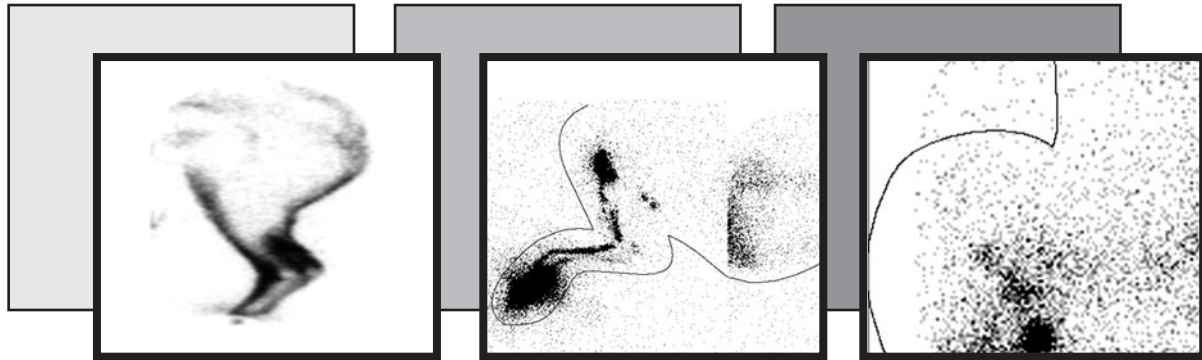
where H = renal response

Lymphoscintigraphy

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Introduction

Lymphoscintigraphy is a rapid, noninvasive diagnostic test for evaluating lymphatic vasculature, associated lymphocenters, and lymph nodes, particularly of the extremities. More recently, lymphoscintigraphy has also been used in combination with intraoperative methods for regional or “sentinel” lymph node localization and selective biopsy in cancer patients with regional metastatic potential. A list of indications for lymphoscintigraphy is given in Table 19.1.

Radiopharmaceuticals Used for Lymphoscintigraphy

Particulate Radiopharmaceuticals

^{99m}Tc is labeled to the inert colloidal compounds sulfur colloid or antimony trisulfide colloid. Because ^{99m}Tc -antimony trisulfide colloid is not currently commercially available in the United States, ^{99m}Tc -sulfur colloid, filtered through a millipore filter to a particle size no greater than 100 nanometers (nm), is most often used for lymphoscintigraphy. Unfiltered ^{99m}Tc -sulfur colloid is not suitable for lymphoscintigraphy due to the much larger and heterogeneous particle sizes. The size of the colloidal particle influences the pattern and rate of absorption into the lymphatic circulation following interstitial injection. Particles < 10 nm can pass through the capillary openings, thereby allowing entrance into the systemic blood vascular circulation such that rapid clearance from the injection site occurs.^{1,2} These small particles cause a high background radioactivity due to their presence in the blood pool. Particles larger than 100 nm are slowly cleared with a high retention at the injection site. Large, colloidal particles accumulate within the mononuclear phagocytic cells of the liver and spleen.² Most lymphoscintigraphy is performed with colloidal particles ranging in size from 15 to 40 nm.^{1,2} In general, ^{99m}Tc -labeled colloids are absorbed slower from the injection site (1 to 3 hours) than ^{99m}Tc -dextran but have less background activity providing superior image contrast for imaging lymph nodes.^{3,4} Although particles that are 15 to 40 nm in diameter have been shown to be the optimal size for peripheral lymphatic uptake, recent studies with other particulate diagnostic imaging agents suggest that particles many times this size

range may be effectively used.⁵

Soluble Radiopharmaceuticals

^{99m}Tc -labeled dextran is a polysaccharide, noncolloidal, nonparticulate radiopharmaceutical that is soluble in lymph fluid.⁶⁻⁸ ^{99m}Tc -labeled dextran provides adequate visualization of lymphatic vessels and is cleared more rapidly than colloids from the injection site.⁶⁻⁸ Dextran is used clinically as plasma substitutes. The molecular weight must be large enough ($> 40,000$ daltons) to prevent entrance into the systemic capillary membrane.^{3,9} Typical molecular weights of dextrans that are used for lymphoscintigraphy range between 70,000 and 100,000 daltons. The ^{99m}Tc -labeled dextran is prepared by dissolving dextran in 0.9% sodium chloride solution. Stannous chloride is added as a reducing agent, and the kits are deoxygenated using a nitrogen gas purge.⁶ Freshly eluted ^{99m}Tc -pertechnetate is added to the vial to complete the labeling procedure.

Mechanism of Localization and Elimination

Following interstitial injection, the colloidal particles migrate into the lymphatic circulation through endothelial gap junctions. The movement of fluid and macromolecules into the lymphatic vessels is not completely understood; but the process is thought to be due to a combination of osmotic gradients and compression by extrinsic forces, such as muscle contraction.^{1,2,9} Other factors that may play a role are increases in interstitial hydrostatic pressure due to the injection volume or postinjection massage of the injection site leading to particulate transit into the lymphatic vessels. Lymphatic propulsion in larger lymphatic vessels is affected by both active contraction of smooth muscle in the lymphatic walls and extrinsic compression by adjacent muscles and organs. Valves within the lymphatic vessels inhibit retrograde flow of lymph.^{1,2,9}

The afferent lymphatic vessel transports the radiopharmaceutical to the regional lymph nodes where a portion of the ^{99m}Tc -colloid is phagocytized by the mononuclear phagocytic cells lining the lymph node sinuses.² A fraction of the radiopharmaceutical will pass through the lymph node into efferent lymphatic vessels to be transported to the next lymph node in

the chain (second-order lymph node). The amount of radiopharmaceutical entering the efferent lymphatic vessel will decrease precipitously following passage through each successive lymph node, making it more difficult to visualize the lymphatic circulation as the distance from the injection site increases.

Visualization of the abdominal duct is possible within 30 minutes following subcutaneous injection of the radiolabeled colloid in the perineal region.^{6,10} In the normal dog, the thoracic duct is usually not visualized.⁶ Transit times, lymphatic morphology and lymph node visualization have been described in the dog.¹¹ The indications for lymphoscintigraphy are summarized in Table 19.2.

Only a small percentage of injected radiopharmaceutical accumulates in the peripheral lymphatics and regional lymph nodes, with a majority of material remaining at the injection site. The radiopharmaceutical is phagocytized by the mononuclear phagocytic cells at the injection site, within the lymph nodes, or by distant macrophages following vascular redistribution. Unbound or dissociated $^{99m}\text{TcO}_4^-$ is removed by the kidneys so that urinary bladder radioactivity can be noted.

Images are acquired immediately following subcutaneous or intradermal injection and then at specified time intervals (every 5 to 10 minutes) for the specific areas of interest, up to 1 to 2 hours postadministration (Table 19.2). Delayed images at 4 to 6 hours postinjection may provide more definitive information regarding regional lymph node location and numbers without interference from lymphatic vascular activity.

Extremity Lymphoscintigraphy

Peripheral lymphatics can be evaluated by injecting 17.5 to 74 MBq (0.5 to 2 mCi) of the radiopharmaceutical, using a tuberculin syringe and a 25-gauge needle, into the interstitial space between the toe webs.^{11,12} It is recommended to aspirate with the syringe prior to injecting to avoid intravascular injection. The volume of injected solution is typically 0.1 to 0.3 mL. Serial static frame mode images are acquired in a $128 (256) \times 128 (256) \times 16$ matrix. Images should be acquired for 1 to 2 minutes to obtain adequate count density. Imaging times may vary depending on the rate of absorption into the efferent lymphatics. Typical imaging times are 0,

5, 10, 15, 20, 30, 45, 60, and 120 minutes. Lateral images of the entire affected limb should be acquired and the normal contralateral limb should be imaged as a basis for comparison in patients with unilateral disease. Additional cranial or caudal images should be acquired when findings on lateral images are ambiguous. A flexible ^{57}Co marker is helpful to outline anatomic regions for precise localization of abnormalities of the extremity. Manipulation of the limb and injection site along with the use of larger injection volumes may increase the rate of radiopharmaceutical absorption.

Lymphoscintigraphy of the Head and Neck

Filtered radiopharmaceutical can be injected into the base of the external ear, the rostral aspect of the mandible, the rostral aspect of the maxilla, or the nasal mucosa to map the regional draining lymph nodes. The imaging agent and injection technique are the same as for extremity lymphoscintigraphy. Because the distance from the injection site to the draining regional lymph nodes is significantly less than for comparable extremity imaging studies, interference from the injection site can obscure nodal uptake. A smaller injection dose of 14.8 to 29.6 MBq (400 to 800 μCi) in a volume of 0.1 mL is recommended to minimize this effect. Serial static frame mode images are acquired in a $128 (256) \times 128 (256) \times 16$ matrix. Images should be acquired for 1 to 2 minutes to obtain adequate count density. Imaging times may vary depending on the rate of absorption into the efferent lymphatics. Typical imaging times are 0, 5, 10, 15, 20, 30, 45, 60, and 120 minutes. Both lateral and ventral images are recommended for lymph node localization.¹²

Sentinel Node Localization

The sentinel node concept has only recently been introduced into the veterinary literature, and no definitive protocol has yet been established. The authors have used 14.8 to 29.6 MBq (400 to 800 μCi) of ^{99m}Tc -sulfur colloid in a volume of 0.1 to 0.3 mL injected subcutaneously or intradermally in a four-quadrant injection pattern around the margins of an externally accessible parenchymal neoplasm. The radiopharmaceutical is administered immediately preoperatively or at the onset of surgery. Perilesional dye injection with isosulfan blue can be used to facilitate identification of draining lymphat-

ics and associated lymph nodes. A handheld gamma probe (Neoprobe Corporation, Dublin, Ohio) is used intraoperatively to localize radiopharmaceutical uptake in the first order or “sentinel nodes” receiving lymphatic drainage from the tumor basin. Because of the “spillover” of radiopharmaceutical from first-order to second-order lymph nodes, the differential in radioactivity counts is greatest soon after injection.^{12,13}

Abdominal and Thoracic Wall Lymphoscintigraphy: Evaluating for Lymphatic Metastasis

Lymphatic drainage from the ventral body wall can be assessed by injecting 17.5 to 37 MBq (0.5 to 1 mCi) of the radiopharmaceutical into the rectus abdominus muscle 1 cm caudal to the costochondral margin and 1 cm lateral to midline.^{7,8} Additional injections can be made into the subcutaneous tissues lateral to the caudal abdominal mammary glands. Serial static frame mode images are acquired in a 128 (256) × 128 (256) × 16 matrix. Additional ventral and lateral images of the abdomen and thorax are acquired 2 to 4 hours following ^{99m}Tc-colloid injection and at 15-minute intervals following ^{99m}Tc-dextran injection. The images can be acquired for either 60 seconds or 300,000 counts.

Evaluation of the Thoracic Duct

The thoracic duct can be evaluated by injecting 37 to 74 MBq (1 to 2 mCi) of the radiopharmaceutical into two sites in the perineal region.⁴ The injection volume should be between 0.1 and 0.3 mL. Serial static images are acquired in a 128 (256) × 128 (256) × 16 matrix. Serial images are taken at 0, 5, 10, 30, 60, 90, 120, 180, and 240 minutes following injection. The images can be acquired for either 60 seconds or 300,000 counts.

Principles of Interpretation — Normal

Extremity Lymphoscintigraphy

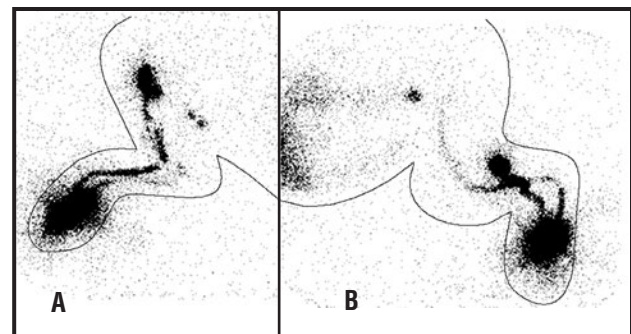
The lymphatics of the pelvic limb of dogs can be loosely divided into communicating deep and superficial systems with the superficial lymphatics further subdivided into medial and lateral compo-

nents. These multiple collecting systems provide some degree of redundancy to prevent obstruction of lymphatic drainage of the limb. Superficial lymphatics originate in the distal extremity, and those of the deep system appear to arise proximal to the tarsus. Lymphatic vessels distal to the stifle drain to the popliteal node with two to four trunks continuing proximally as afferent lymphatics to the medial iliac lymph node group.¹⁵ Lymphatic anatomy can vary considerably, and unexpected lymphatic drainage patterns occasionally result in radiopharmaceutical uptake in inguinal or other pelvic lymph nodes.

The radiopharmaceutical is usually seen lymphatic vessels within 5 minutes following injection. Single or multiple discrete linear bands of activity are seen extending proximally from the injection site. With radiocolloid, activity is confined to the site of injection and the discrete lymphatic vessels while the interstitium of the leg remains relatively devoid of radioactivity. In the pelvic limb, the distal limb lymphatics and the popliteal lymph node are easily visualized in normal animals following radiopharmaceutical injection. Detection of more proximal lymphatics and the medial iliac lymph nodes is vari-

Figure 19.1: Normal lateral lymphoscintigrams of the left thoracic limb (A) and the left pelvic limb (B) following subcutaneous injection of filtered ^{99m}Tc-sulfur colloid into the interdigital spaces

The large foci of activity in the distal extremities represent the injection sites. Afferent lymphatic vessels to the cervical and popliteal lymph nodes are evident in the thoracic and pelvic limbs. Two small foci of activity caudal to the cervical node represent uptake in the accessory axillary lymph node. A faint focus of activity proximal to the popliteal node represents medial iliac node uptake. Lymphatics from the proximal and distal limb are faintly visible coursing to the sublumbar node.



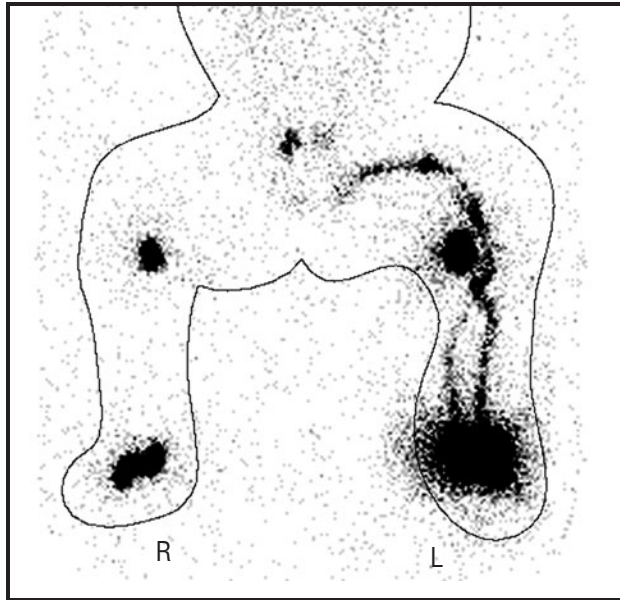


Figure 19.2: Normal ventral lymphoscintigram of the pelvic limbs of a dog

The left side was injected 1 hour before this acquisition, and the right was injected 24 hours previously. The large foci of activity in the distal extremities represent the injection sites. Lymphatic vessels are seen in both the distal and proximal aspect of the left pelvic limb, as are the popliteal lymph node and a smaller more proximal femoral or inguinal node. The right popliteal and medial iliac nodes are also evident.

able (Figures 19.1 and 19.2). In the thoracic limb, the superficial cervical lymph node is seen in most normal dogs; but the time from injection to visualization of the lymph node is longer than that for the popliteal node of the rear leg due to the longer transit distance from the injection site. The superficial cervical nodes are relatively large in most dogs and may be multiple. The accessory axillary lymph node, which is relatively small, may also accumulate activity in some dogs.¹¹

Abnormal Patterns of Distribution in Lymphoscintigraphy

Differentiating Lymphatic from Vascular Causes of Limb Edema

In addition to systemic causes, limb edema may be due to venous or lymphatic obstruction or stasis. The

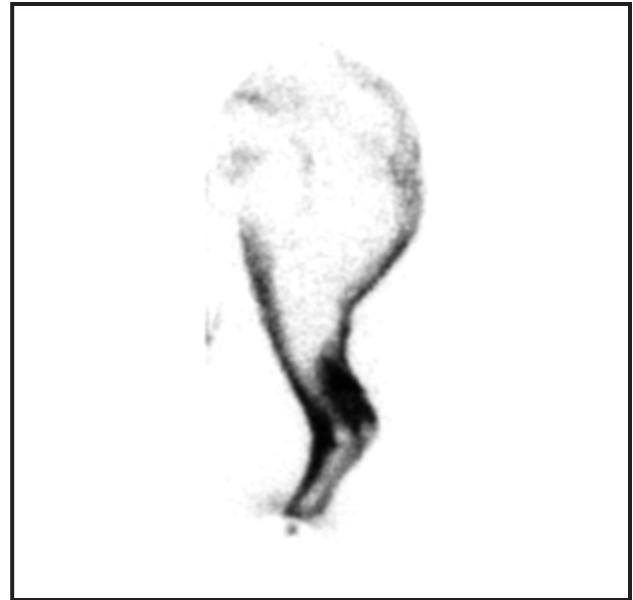


Figure 19.3: Lymphoscintigram of the left pelvic limb of a dog with unilateral lymphedema

This patient presented with lymphedema of the entire left pelvic limb and pelvis. The radiopharmaceutical was slow to move from the injection site, and the radioactivity slowly diffused proximally in the subcutaneous tissues. Lymphadenic ducts were not visualized. This pattern is consistent with primary lymphedema.

source for accumulation of interstitial fluid can often be determined by performing lymphoscintigraphy in conjunction with venous angiography. If venous obstruction is ruled out by angiography, lymphoscintigraphy can be used to define the pathways of lymphatic drainage, verify and localize the origin of lymphatic obstruction or leakage, and identify regional lymph nodes.

Primary Versus Secondary Lymphedema

Primary lymphedema is an uncommon disorder caused by abnormal development of the lymphatic system. Aplastic, hypoplastic, hyperplastic, and lymphangiectatic forms are described and may be associated with regional lymph node aplasia. In dogs, clinical signs of primary lymphedema appear shortly after birth. Secondary lymphedema is an acquired disorder caused by obstruction resulting in lymphatic stasis. Differentiating primary versus secondary lymphedema is not always possible due

Table 19.1: Indications for Lymphoscintigraphy

Differentiate lymphatic from vascular causes of limb edema.
Evaluate primary or secondary lymphedema.
Determine the location of obstruction or leakage of lymphatic vessels.
Document the pathways of lymphatic drainage, and localize sentinel lymph nodes for selective node biopsy or for radiation treatment planning.
Evaluate lymph nodes for the presence of metastasis.
Evaluate leakage of lymph from the thoracic duct.

to similarities of scintigraphic abnormalities seen in both conditions.^{2,14-16} However, primary lymphedema has been characterized by slow absorption and reduced visualization of lymphatic vessels and regional lymph nodes; and secondary lymphedema is characterized by dilated lymphatic vessels, collateral vessels, and interstitial accumulation and retention of the radiopharmaceutical (Figures 19.2, 19.3, 19.4, and 19.5).^{2,16}

Lymphoscintigraphy of the Head and Neck

Lymphatic drainage patterns and localization of regional lymph nodes of the head and neck can be defined using lymphoscintigraphy (Figure 19.6). Such studies can play an important role in surgical node dissection and radiation treatment planning as actual lymphatic drainage patterns may differ from established pathways.¹³ Nodes that accumulate radiophar-

Table 19.2: Imaging Parameters for Lymphoscintigraphy

Radionuclide

^{99m}Tc-sulfur colloid (filtered to small particle size of 40 to 100 nm).

^{99m}Tc-antimony trisulfide colloid (3 to 12 nm particle size; not available in the USA).

^{99m}Tc-dextran.

Dose

Species	mCi	MBq	Vol (mls)
Dog	0.5 - 2	18.5 - 74	0.1 - 0.25
Cat	0.5 - 2	18.5 - 74	0.1 - 0.25

Acquisition Parameters

Animal preparation	None.
Static frame acquisition	Time-based acquisitions of 1 to 2 minutes per image.
Matrix	256 x 256 x 16 or 128 x 128 x 16.
Collimator	Low-energy, all-purpose, high-sensitivity or high-resolution.
Time to image	0, 5, 10, 15, 20, 30, 45, 60, and 120 minutes following injection. 4 to 6 hour images (optional).
Positioning	Lateral recumbency over the gamma camera.
Views	Lateral images of the affected and normal limb. Dorsal or plantar/palmar images are optional.

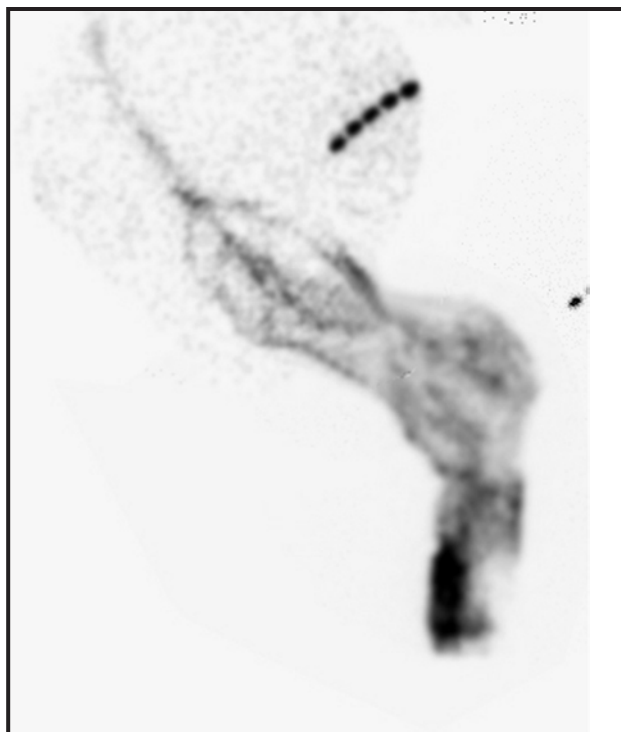


Figure 19.4: Lymphoscintigram of the left pelvic limb of a dog with unilateral lymphedema

This patient presented with lymphedema of the entire left pelvic limb and pelvis. The radiopharmaceutical diffused in the interstitial tissue. There were many dilated and torturous lymphatic ducts that eventually converged into a single duct proximal to the stifle. The pattern is consistent with secondary lymphedema.

maceutical following external ear-base, mandibular, maxillary, and nasal mucosal deposition include the mandibular, medial retropharyngeal, parotid, buccal, superficial cervical and anomalous nodes.¹² One or more afferent lymphatics are typically seen extending from the injection site to the first-order node group. More distant lymphatic vessels and second-order lymph nodes are usually seen and the pattern of lymphatic flow can often be determined from the expanding pattern of radiopharmaceutical distribution on serial static images.

Sentinel Node Localization

Sentinel lymph nodes are defined as the first node or nodes encountered by afferent lymphatic draining a specific anatomical site such as a parenchymal neoplasm. Lymphatic metastasis is assumed to occur

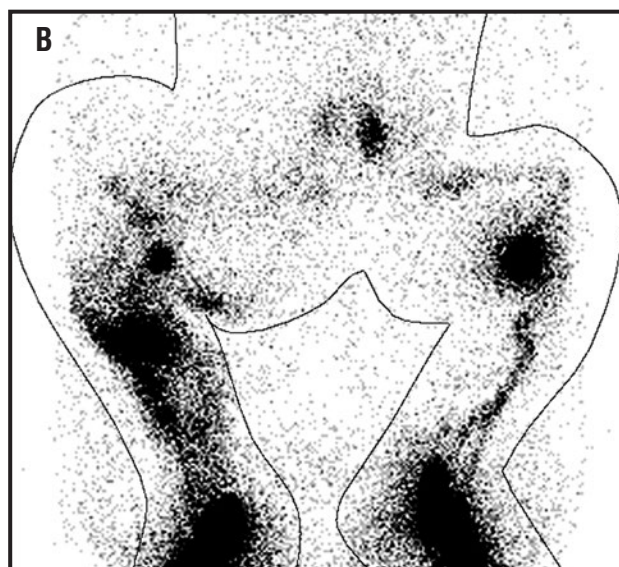
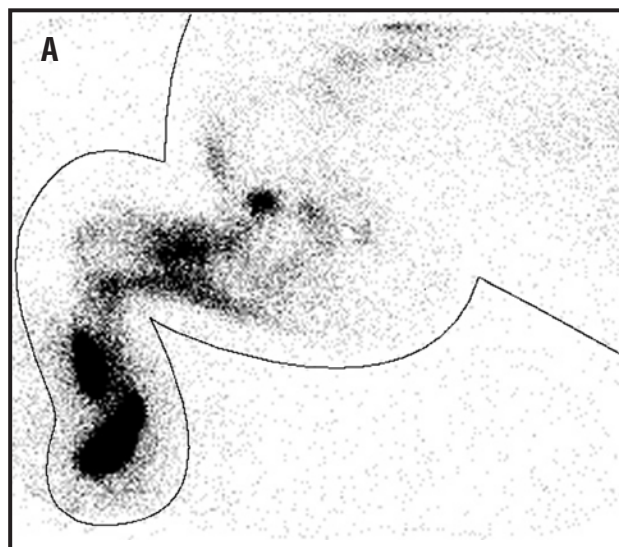


Figure 19.5: Lymphoscintigram of the pelvic limbs of a dog with unilateral lymphedema

A, This patient presented with lymphedema of the entire right pelvic limb and pelvis. Right lateral pelvic limb and **(B)** ventral images of the pelvis and pelvic limbs are shown. A venogram of the affected limb was normal. Accumulation of radioactivity in the interstitial extracellular tissues surrounding the tibia is evident along with deep lymphatic channels, indicating complete lymphatic obstruction was not the cause of the edema and that edema was more likely caused by extravasation from increased lymphatic permeability. Biopsy of the subcutaneous tissues revealed lymphangiosarcoma.

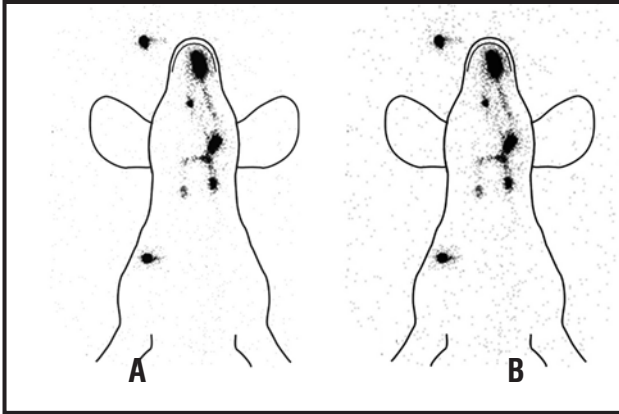


Figure 19.6: Ventral view of a normal dog 40 minutes (A) and 120 minutes (B) after subcutaneous injection of 400 µCi of filtered ^{99m}Tc -sulfur colloid into the rostral mandible

Intermandibular, mandibular, and medial retropharyngeal lymph nodes and associated lymphatic vessels are evident. The two foci of activity on the left represent external markers.

in an orderly fashion and therefore the status of the sentinel lymph node should be representative of the remaining regional lymph nodes.¹⁷ Although variable, sentinel node activity is at least twice that of regional second-order lymph nodes and can be one to two orders of magnitude greater.^{12,13} Following surgical excision in humans, sentinel nodes are evaluated for the presence of metastatic disease by intraoperative frozen-section microscopy. If the node is negative, other regional nodes are also presumed to be negative. If the sentinel node is positive for metastasis, other regional lymph nodes are presumed to be positive and a more aggressive lymph node dissection or follow-up radiation therapy is employed.¹⁷

Diagnosis of Lymph Node Metastasis

Lymphoscintigraphy for diagnosis of metastasis is of limited value as compared to cross-sectional imaging modalities, such as ultrasound, computed tomography, and magnetic resonance imaging. Lymph node metastasis is characterized by a diminished or lack of visualization of regional lymph nodes.^{2,8} Due to the normal variability of lymph node appearance, if this technique is used, it is recommended that bilateral evaluation be done to enable direct comparison.

Thoracic Duct Evaluation

Evaluating the thoracic duct by lymphoscintigraphy is currently of limited value. In experimental canine models where the thoracic duct had been transected, direct visualization of the thoracic duct was not possible on scintigraphic images.⁶ Animals with chylothorax secondary to occlusion of the cranial vena cava will have diffuse uptake in the thoracic cavity. Lymphangiography, though more invasive, provides superior morphologic images of the thoracic duct.

Summary

Lymphoscintigraphy provides a rapid, noninvasive imaging technique for evaluating the lymphatic vasculature and associated lymphocenters. More recently, lymphoscintigraphy has also been used in combination with intraoperative methods for regional or “sentinel” lymph node localization and selective biopsy in cancer patients with regional metastatic potential. The use of lymphoscintigraphy for sentinel nodal evaluation has yet to be realized in veterinary medicine.

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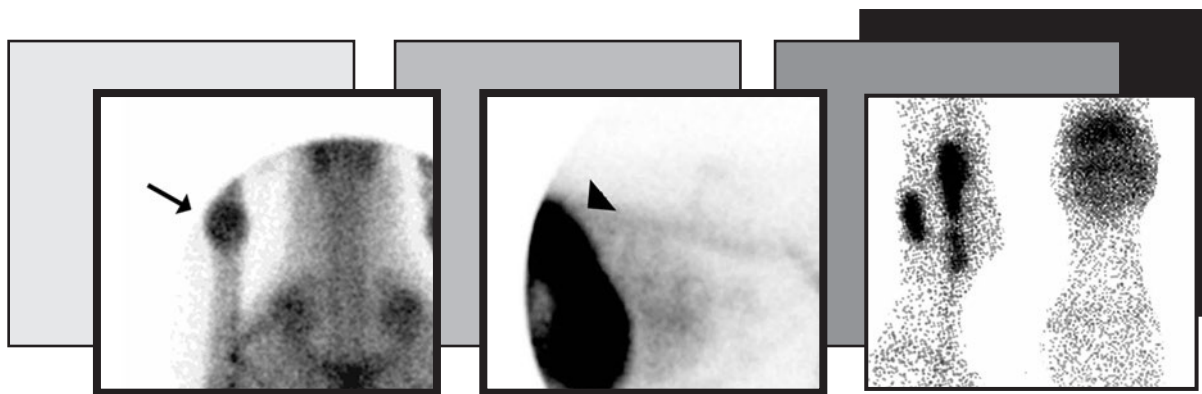
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Scintigraphic Imaging of Inflammation and Infection

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Introduction

Radiographic or ultrasonographic imaging of focal infection usually requires gross morphologic changes for detection. The radiographic signs of infection may not be discernible at the time of clinical presentation or maybe nonspecific, making the early diagnosis of infection difficult.^{1,2} Detecting the infection early will influence patient management, and may improve therapeutic response. Identifying specific areas of interest for biopsy or monitoring is a primary goal for using an imaging modality to evaluate infection.

Radionuclide studies can serve as a sensitive screening process for inflammatory or infectious diseases.¹⁻²⁰ Conventional scintigraphic studies, such as bone or brain scans, can detect an inflammatory or infected focus, however their findings are nonspecific, (Figure 20.1). One of the primary physiologic responses to infection is the movement and active migration of leukocytes, proteins, and antibodies into sites of inflammation.^{2,18,20-22} Radiolabeling these blood constituents could be a diagnostic aid for identifying or confirming an inflammatory lesion in a noninvasive manner. Additionally, radionuclide scans targeting inflammation or infection may help determine the activity or progression of confirmed lesions.^{2,12-14} Results of scintigraphic studies specific for imaging sites of inflammation could also provide prognostic information and may directly impact the treatment. The indications for inflamma-

tory scintigraphy are listed in Table 20.1.

^{99m}Tc-labeled leukocyte, ¹¹¹Indium chloride, and ⁶⁷Gallium citrate are radiopharmaceuticals currently used for scintigraphic imaging of inflammation and infection, but they are nonspecific. These radiopharmaceuticals reflect the magnitude of the physiologic inflammatory (blood flow and vascular permeability) responses on which their accumulation is dependent.^{2,18-24} As many disease processes (eg, neoplasia) incite an inflammatory response, the interpretation of scintigraphic studies should be made within the context of the available patient information. Current research is focusing on antibody labeling, both nonspecific immunoglobulins (IgG or F(ab')₂ fragments)^{5,11,18} and antibodies directed against cells or products present in high concentrations at sites of infection (eg, antigranulocyte antibodies).^{6,9,27}

Radiolabeled Leukocytes

Radiolabeled leukocytes are particularly useful in cases of pyogenic infections or acute inflammation characterized by an accumulation of a high number of granulocytes at the site of infection. ¹¹¹Indium oxine and ^{99m}Tc-Hexa-Methyl-Propylene-Amine Oxime (^{99m}Tc-HMPAO) are the most common radiopharmaceuticals used for leukocyte labeling.^{2,8,11,16,17,28,31-33} Table 20.2 lists the advantages and disadvantages of each. Agents that have been used in the past but no longer utilized include ¹¹¹In-tropolone, ^{99m}Tc-pyrophosphate and ^{99m}Tc-sulfur colloid.

Separation of Leukocytes

The first step in radiolabeling of leukocytes is the collection of whole blood and separation of the blood into its respective components. Sterility must be maintained during the handling of blood, any blood products to be re-injected, and labeling reagents. Careful isolation technique must be practiced to avoid activation or damage to the leukocytes and their surface receptors. It is essential to maintain the chemotactic response of the leukocytes to enable normal physiologic migration to active sites of

Figure 20.1: ^{99m}Tc-MDP planar bone scintigraphy soft tissue phase ventral images from a dog with polyarthritis

There is multifocal, increased radioactivity involving multiple joints (arrows).

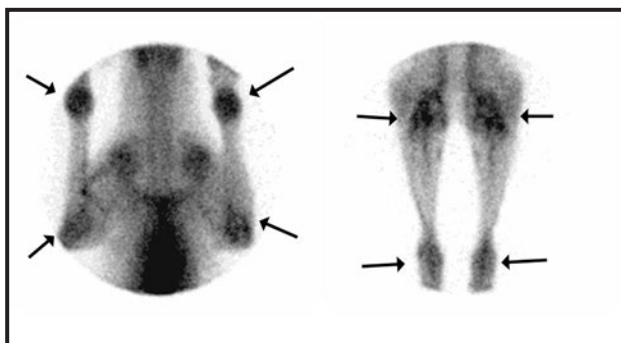


Table 20.1: Indications for Inflammatory Scintigraphy

Identifying or localizing any inflammatory or septic focus in animals with known or suspected inflammatory disease.
Septicemia or multisystemic infection.
Inflammatory bowel disease.
Osteomyelitis, septic arthritis, discospondylitis.
Rheumatoid arthritis.
Evaluate animals with fever of unknown origin.
Evaluate surgical sites or surgical implants.
Delayed unions.
Drainage at a surgical site.
Excessive pain or swelling.
Acute onset of postoperative pain or swelling.
Febrile postoperative patients.
Evaluating loosening or infection of orthopedic prosthesis.
Evaluate lesions identified on other imaging studies.
Lytic or lucent regions in bone.
Soft tissue masses.
Areas of increased pulmonary opacity on thoracic radiographs.
Evaluate disease progression at known sites of infection.
Response to antibiotic and/or antiinflammatory therapy (eg, osteomyelitis, inflammatory bowel disease)
Predicting cure for cessation of long-term therapy (eg, osteomyelitis, tuberculosis)
Monitoring regional or distant disease extension

inflammation and infection. A list of materials commonly used for white blood cell isolation is included in Table 20.3, and the outline of the isolation procedures is included in Table 20.4.

White Blood Cell Labeling

All handling of radionuclides, radiopharmaceuticals, and labeled cells is performed with appropriate shielding, lab coats and rubber gloves. The procedures for radiolabeling the leukocytes with indium-111 is in Table 20.5 and for the technetium-99m labeling of leukocytes is provided Table 20.6.

Mechanisms of Localization

Diffuse accumulation of labeled leukocytes in the liver, spleen, and bone marrow is considered normal.^{2,17,27} This is due either to the mononuclear phagocytic systems removal of damaged cells or normal margination of granulocytes in the vascular spaces of these organs. A transient increase in pulmonary activity is also seen. Cell damage from the labeling procedure or abnormal leukocyte aggregation could prolong the normal pulmonary transit time. Pulmonary activity should decrease by 4 hours, while hepatic, splenic, and bone marrow activity should increase. Radiolabeled cells in the horse and cat may be permanently removed from circulation by the mononuclear phagocytic cells in the lung. In the dog, the liver and spleen remove damaged white blood cells. Twenty-four-hour delayed images result in a pattern similar to that at 4 hours, with activity also present in the colon and urinary bladder.¹⁷ Complete description of factors influencing leukocyte migration and accumulation at sites of infection or inflammation is beyond the scope of this chapter. Properly labeled neutrophils will maintain normal migratory and phagocytic properties.

Elution of the ^{99m}Tc-HMPAO radiolabel or a by-product occurs over time. The radiolabel by-products are excreted by the kidneys and gastrointestinal tract. Normal accumulation of radiopharmaceuticals in the kidney, urinary bladder, and intestinal tract may compromise abdominal scan interpretation.

Principles of Interpretation

Focal accumulations of the radiolabeled leukocytes in locations other than those listed previously are consistent with inflammatory disease. In humans,

Table 20.2: Advantages and Disadvantages of ^{111}In -oxine Versus $^{99\text{m}}\text{Tc}$ -HMPAO

Advantages of ^{111}In -oxine	Advantages of $^{99\text{m}}\text{Tc}$ -hexa-methyl-propylene-amine oxime ($^{99\text{m}}\text{Tc}$ -HMPAO, also called exametazime or Ceretec)
High labeling efficiency and label retention.	Lipophilic compound with stable intracellular trapping in white blood cells (granulocytes).
Long half-life ($T_{1/2} = 2.82$ days) of ^{111}In allows for delayed imaging.	Selectively labels and remains bound to granulocytes better than monocytes.
Decays by electron capture resulting in the release of two gamma emissions.	Provides superior imaging characteristics due to the high photon flux of the $^{99\text{m}}\text{Tc}$ label.
Disadvantages of ^{111}In -oxine	Disadvantages of $^{99\text{m}}\text{Tc}$ -HMPAO
Relatively expensive per-unit dose.	Urinary and intestinal excretion may compromise diagnostic accuracy.
Low photon flux requires long acquisition times.	Variable labeling efficiency.
Requires the use of a medium-energy collimator with decreased camera resolution (relative to $^{99\text{m}}\text{Tc}$)	The radiopharmaceutical kit is expensive.*
Long half-life delays patient release.	Short shelf-life of radiopharmaceutical after reconstitution (30 minutes).

*Note: The expense and short shelf-life can be offset by fractionating the reconstituted kit into multidose aliquots and storing for extended periods of time. Fractionated aliquots should be prepared with reduced amounts of $^{99\text{m}}\text{Tc}$. **33-35**

Table 20.3: List of Commonly Used Reagents for White Blood Cell Isolations

Acid citrate dextrose (ACD) solution. Use 2 mL per 10 mL of blood collected.
Hydroxyethyl starch 6% solution (Hespan). Use 4 mL of Hespan® per 15 mL of blood.
15 or 50 mL sterile, pyrogen free polypropylene centrifuge tube.
Earle's Balanced Salt Solution (EBSS) or Physiologic Buffered Saline Solution (PBSS).

radiolabeled WBC accumulation has been useful in diagnosing acute or chronic soft tissue infection, rheumatoid arthritis, inflammatory bowel disease, acute osteomyelitis, septic arthritis, graft or implant infection, and sterile abscesses.^{2,11} Reports in veterinary medicine have been limited.^{8,17,28,29} The use of radiolabeled leukocytes in veterinary medicine could include: identifying septic joints, osteomyelitis, deep-seated infections, abdominal abscesses, pyelonephritis, evaluating postsurgical fracture sites or implants, and evaluating patients with fever of unknown origin (Figures 20.2 to 20.5). The accuracy of these methods,

and comparison with other techniques is still being evaluated in veterinary medicine. The sensitivity of ^{111}In -labeled leukocyte imaging for detecting experimentally induced pyelonephritis in dogs was 89% during the acute phase of infection.²⁸ Chronic pyelonephritis was not evident in this same experimental group of dogs using ^{111}In -leukocytes. False-positive radiolabeled leukocyte scans have been reported in humans with open fractures, neoplasia, and loose (but not infected) orthopedic implants. False-negative studies have also been reported with chronic osteomyelitis in humans who have low granulocyte

numbers. Poor labeling technique can activate the granulocytes that limit the number of cells available for migration into the areas of inflammation or result in low labeling efficiency and decreased cellular viability. These factors will degrade the diagnostic quality and sensitivity of the procedure. The acquisition parameters for imaging ^{99m}Tc -WBC, ^{99m}Tc -HMPAO, $^{111}\text{InCl}_3$ and ^{111}In -WBC imaging are summarized in Tables 20.7 and 20.8.

^{111}In Indium Chloride Scintigraphy

Mechanisms of Localization

^{111}In indium chloride ($^{111}\text{InCl}_3$) and ^{67}Ga gallium citrate (^{67}Ga) exhibit many similarities in biodistribution and localization.^{21,22,24} After intravenous injection,

$^{111}\text{InCl}_3$ binds rapidly to plasma transferrin. $^{111}\text{InCl}_3$ will also bind to cells expressing transferrin membrane receptors. These cells then take up the $^{111}\text{InCl}_3$ by receptor-mediated endocytosis. Increased vascular permeability and expanded extracellular fluid space present at inflammatory sites are important for localization. For this to take place, $^{111}\text{InCl}_3$ need not be unbound from transferrin, but only leaked into the extravascular space. Transferrin is present in inflammatory lesions, but at a low concentration. Lactoferrin, secreted from lysosomes by stimulated or dead neutrophils, is usually present at high concentrations in sites of inflammation. Because of the higher binding affinity of ^{111}In to lactoferrin, ^{111}In is transferred from transferrin to lactoferrin at the inflammatory focus. This causes sufficient radionuclide accumulation for gamma imaging.

$^{111}\text{InCl}_3$ is normally taken up by erythropoietic tissues. Approximately one third of the intravenously injected dose localizes in erythroid marrow, one third within the liver, and one third throughout the remainder of the body, primarily bound to transferrin. Renal and fecal excretion are minimal.

Principles of Interpretation: Normal

Progressive uptake of radioactivity within the liver, spleen, and erythroid marrow is considered normal. The pattern of hepatic activity should be uniform. Erythroid marrow activity (except in geriatric patients) is usually symmetric and predominantly

Figure 20.2: Radiographs and bone scan from a 7-year-old, warmblood mare that presented for acute left thoracic limb lameness

Oblique radiographs (A and B) of the left metacarpophalangeal joint. There are focal regions of osteolysis within the axial aspect of both proximal sesamoids (arrows). Lateral (C) and palmar (D) scintigraphic images of this joint were acquired 4 hours following injection of autologous ^{99m}Tc -WBCs. There is significant activity in the region of the proximal sesamoid bones and the metacarpophalangeal joint. Cytology of the joint fluid revealed purulent inflammation. Though not confirmed with cultures, septic osteomyelitis involving the proximal sesamoids was suspected. (Images courtesy of the Center for Imaging Science, School of Veterinary Medicine, University of California, Davis.)

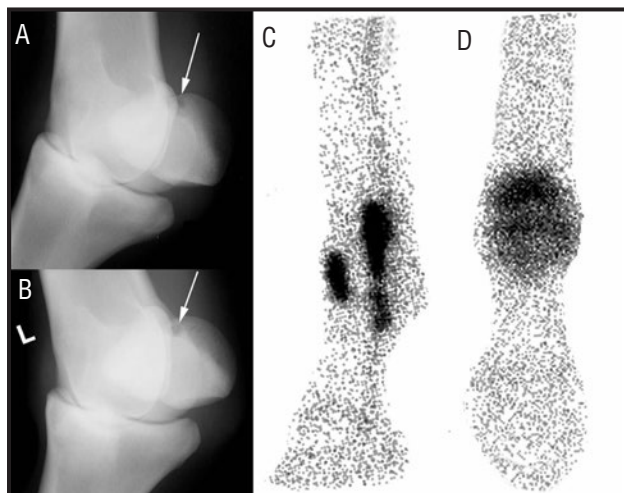


Figure 20.3: Dorsal views centered over the thorax and abdomen from an autologous labeled ^{99m}Tc -WBC scan of a dog with pyelonephritis

There is abnormal uptake noted within both kidneys (arrows). There is also activity in the left ureter and bladder (arrowheads). R = right, L = left.

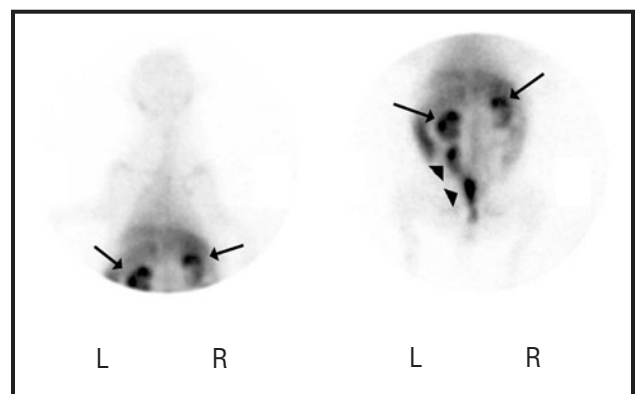


Table 20.4: Procedures for Isolation of White Blood Cells.

1. Collect venous blood in a syringe containing the specified amount of ACD. A large-bore butterfly catheter (18 gauge) works best. The needle is placed and a good blood flow is established. The syringe is attached to the butterfly catheter, and the blood is slowly withdrawn as the syringe is inverted to ensure mixing with the ACD. - Horse: 15 mL - Dog and cat: 10 to 15 mL
2. The specified amount of hydroxyethyl starch solution (6%) is added to the syringe and inverted several times. The syringe is clamped in position with the needle end pointed upward. A small extension set is attached to the inverted syringe.
3. Allow white blood cells to sediment out at room temperature for 45 to 60 minutes.
4. Collect the leukocyte rich plasma (LRP) into the sterile centrifuge tube by slowly advancing the plunger until the red cell layer is at the needle hub, thus avoiding red blood cell contamination.
5. LRP is centrifuged at 500 g for 5 minutes.
6. The supernatant is collected is now leukocyte-poor plasma (LPP) and is saved for resuspension of cells. Four mL of the EBSS or PBSS per mL of LPP is used to make a "20% plasma wash."
7. For ^{111}In -oxine labeling, rewash the cells with 10 mL of EBSS and pellet by centrifugation at 250 g for 10 minutes.
8. Immediately resuspend the cell pellet in 2 mL "20% plasma wash (for $^{99\text{m}}\text{Tc}$ -HMPAO) or 2 mL of EBSS (for ^{111}In -oxine). Mix gently.
9. Cells are now ready for labeling with the radionuclide. Time is critical because cell viability and function, radionuclide purity, and labeling efficiency are time dependent.

Table 20.5: Procedure for Labeling Leukocytes with ^{111}In -Oxine.

1. Add 11-37 MBq (0.3-1.0 mCi) of ^{111}In -oxine to the 2 mL cell suspension (from step 8 above).
2. Incubate for 15 minutes at room temperature, agitating occasionally.
3. Add 2 mL of the 20% plasma wash.
4. Centrifuge at 500 g for 5 minutes.
5. Collect supernatant and count activity.
6. Resuspend cells in 5 mL of EBSS. Mix gently.
7. Count activity in cell suspension.
8. Determine cell labeling efficiency. Labeling efficiency (%) = (activity in cells)/(activity in cells + activity in supernatant) $\times$ 100. - A labeling efficiency of greater than 50% is desirable. - Cell viability and function testing (optional). - Perform a trypan blue dye exclusion cell viability test. - The cell phagocyte function test is not practical for clinical uses.

Table 20.6: Procedure for Labeling Leukocytes with ^{99m}Tc -HMPAO

Follow directions provided by the manufacturer for kit labeling and quality control. Use the radiolabeled kit within 30 minutes of reconstitution; the lipophilic nature of the primary compound changes with time. If fractionated aliquots of the commercial kit are used, reduce the activity of ^{99m}Tc to be added to the aliquot. ³³⁻³⁵	
1. Add 37-1110 MBq (10-30 mCi) of ^{99m}Tc -HMPAO preparation to the cell suspension. Mix gently and incubate for 15-30 minutes at room temperature, agitating the suspension occasionally.	
2. Centrifuge at 500 g for 5 minutes.	
3. Collect the supernatant and count the radioactivity in the supernatant.	
4. Resuspend cells in 5 mL of "20% plasma wash." Mix gently.	
5. Count the radioactivity of the cell suspension.	
6. Determine the labeling efficiency as described; 25% to 50% or greater is desirable.	

Table 20.7: Imaging Parameters of Radiolabeled Leukocytes**Radionuclide** ^{99m}Tc -HMPAO (hexa-methyl-propylene-amine oxime) ^{111}In -oxine**Dose**

The dose injected into the animal is dependent on the labeling efficiency. The labeling efficiency of HMPAO is variable. Typically 20-30 mCi of ^{99m}Tc -HMPAO is added to the cell suspension in a hope to have 5-10 mCi of radiolabeled cells. Due to price, typically 17.5 to 74 MBq (0.5 to 2.0 mCi) of ^{111}In -oxine is added to cell suspension. Because indium has a higher and more consistent labeling efficiency, the administered dose of radiolabeled leukocytes is typically 17.5 to 54.5 MBq (0.5 to 1.5 mCi).

Acquisition Parameters

Animal preparation	Intravenous catheter for injection.
Static frame acquisition	150,000 to 500,000 counts. These will be long acquisitions for ^{111}In (3 to 5 minutes).
Matrix	256 × 256 × 16.
Collimator	Low-energy, all-purpose for ^{99m}Tc -WBC and medium-energy, parallel-hole for ^{111}In -WBC.
Time to image	0.5, 1, 2, and 4 hours. Follow-up images at 24 hours can be obtained for the ^{111}In -WBC.
Positioning	Camera under table, animal in recumbent position.
Views	Orthogonal views of the extremities. Ventral, dorsal, and opposite laterals for the body cavities.

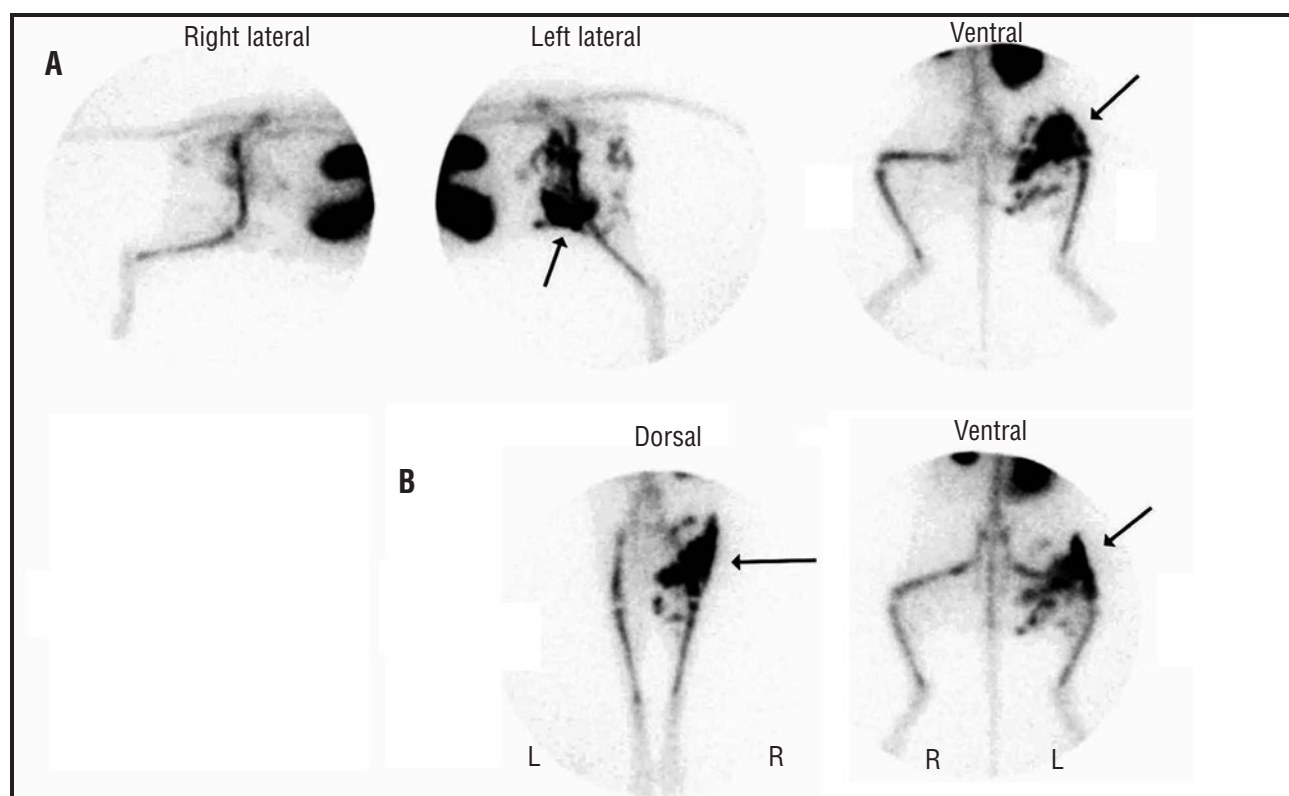


Figure 20.4: Ventral, left and right lateral views taken at 4 hours (A) and ventral and dorsal views at 24 hours (B) after injection autologous labeled ^{99m}Tc -labeled granulocyte scintigraphy in a cat. Twenty hours post-administration of the ^{99m}Tc -HMPAO labeled granulocytes there is a diffuse accumulation of the radio-labeled leukocytes in the are of a draining tract in the left pelvic limb (arrows), (R = right, L = left).

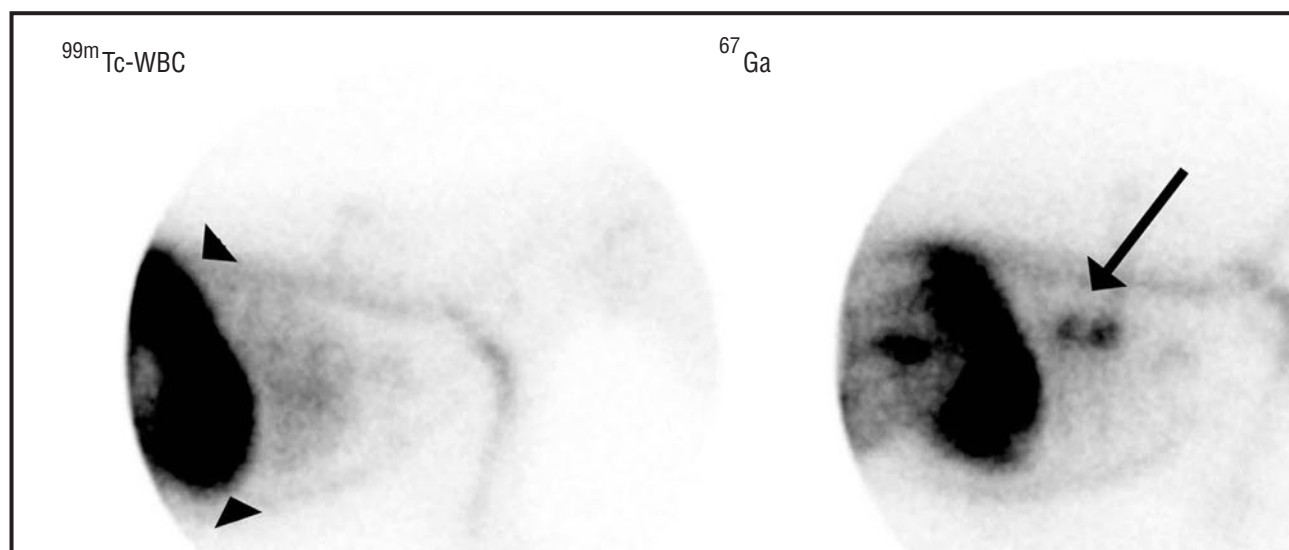


Figure 20.5: Right lateral views of an autologous labeled ^{99m}Tc -HMPAO granulocyte study (left) and a ^{67}Ga citrate scan (right) in a dog with a fever of unknown origin and a chronic cough

The ^{99m}Tc -HMPAO granulocyte study illustrates a negative thoracic scan with marked hepatic uptake (arrowheads). The ^{67}Ga scan demonstrates focal uptake within the central region of the thorax (arrow) corresponding to the tracheobronchial lymphadenopathy. In addition, there is hepatic and intestinal radioactivity noted. This dog was confirmed to have coccidiosis.

Table 20.8: Imaging Parameters of $^{111}\text{InCl}_3$ **Radionuclide**

$^{111}\text{InCl}_3$ supplied as carrier-free $^{111}\text{InCl}_3$ at an acid pH. This can be diluted in saline to a desired volume of 1 to 3 mL. Physical half-life of 2.82 days (67 hours) and decays by electron capture.

Dose

Species	mCi	MBq
Dog or Cat	0.5 - 2	18.5 - 74
Foal	2 - 5	74 - 185

Acquisition Parameters

Animal preparation	Intravenous catheter for injection.
Camera preparation	15% windows centered on the 174 and 247 keV photopeak. If only a single peak is selected, the 174 keV photopeak provides the best resolution.
Collimator	Medium-energy, parallel-hole, (suitable for the 174 and 247 keV photopeaks).
Static frame acquisition	100,000 to 250,000 counts. Images are normally acquired for 3-5 minutes. Sedation or general anesthesia may be required to avoid motion artifacts.
Matrix	256 × 256 × 16.
Time to image	1, 4, and 24 hours postinjection. Delayed images obtained at 72 hours in humans appear to offer little advantage over the 24-hour images.
Positioning	Camera under table; animal in recumbent position.
Views	Orthogonal views of the extremities. Ventral, dorsal, and opposite laterals for the body cavities.

within the vertebrae. Activity in the pelvis, proximal humerus, and distal femur was routinely found in 1 to 2-year-old beagles, consistent with active erythropoiesis in red marrow spaces.¹ Faint bowel activity within the colon and rectum may be seen on delayed images (24 hours or greater).^{1,3} The indications for $^{111}\text{InCl}_3$ scintigraphy are summarized in Table 10.9.

Abnormal: Localizing Sites of Inflammation or Infection

With the exceptions already mentioned, accumulation of $^{111}\text{InCl}_3$ is indicative of inflammation. Definitive differentiation between infected and non-infected sites of inflammation is not possible. The activity and, thus, the detectability of a lesion is influenced by the magnitude of the inflammatory response, the blood supply to the affected region,

Table 20.9: Indications for $^{111}\text{InCl}_3$ Scintigraphy

Evaluate early bone infection, where $^{99\text{m}}\text{Tc}$ -MDP scans may be falsely negative for the first 1 to 4 days of infection.
Evaluate fracture sites for infection.
Chronic infections or infections where low granulocyte numbers are expected.

and the size of the area involved. Infectious processes often have a very strong inflammatory component resulting in focal intense accumulations, while less intense accumulations suggests noninfectious origin. In an experimental setting, an infected bone accumu-

lated twice the amount of $^{111}\text{InCl}_3$ when compared to a sham-operated noninfected bone.¹ Areas of $^{111}\text{InCl}_3$ accumulation can occur within soft tissues at the sites of intramuscular injections of sedatives or analgesics.

Evaluating Surgical Sites

Normal postoperative inflammation should decrease by 1 to 2 weeks postsurgery, depending on the degree of tissue trauma prior to and during surgery. Focal intense accumulation of activity at a fracture site, or increasing activity at a fracture or implant site over time is consistent with an active infection. Interpretation of radioactivity is hindered in bone fractures with active erythroid marrow. The contralateral limb may be used to evaluate for the normal radioactivity expected to be present in active erythroid marrow.

Evaluating Disease Progression

In humans with osteomyelitis, a normal ^{111}In -leukocyte scan pattern following treatment positively predicts successful treatment and complete recovery.^{12,13} In one study, patients treated for osteomyelitis who had persistent abnormalities on $^{111}\text{InCl}_3$ scan, also had clinical recurrence of infection within 2 years of the $^{111}\text{InCl}_3$ scan.¹² This finding has not been confirmed experimentally or clinically in animals.

^{67}Ga Gallium Citrate Scintigraphy

^{67}Ga Gallium citrate (^{67}Ga), is commonly used in humans as a screening test for infection or inflammation. There has been limited use of ^{67}Ga in veterinary nuclear medicine imaging. ^{67}Ga scintigraphy is useful in chronic nonpyogenic processes, including granulomatous and lymphocyte-mediated disease. ^{67}Ga is also used in humans for imaging lymphoma and other neoplasms.

There are disadvantages of ^{67}Ga scintigraphy. There is nonspecific radionuclide accumulation resulting in possible false-positive diagnoses in some cases of tumors, healing fractures, noninfected prostheses; and there has be uptake in previously treated, culture negative sites of osteomyelitis. False-negative studies are possible early in the infectious process, especially in osteomyelitis. ^{67}Ga has inferior imag-

ing characteristics due to the multiple high-energy and medium-energy gamma ray emissions and a low photon flux. The long physical half-life with urinary and colonic excretion makes isolation of the animal and waste containment difficult. ^{67}Ga does not provide prognostic information after antibiotic therapy, as has been proven with $^{111}\text{InCl}_3$. Delayed images at 48 and sometimes 72 hours are occasionally necessary to increase target-to-background ratios.

Mechanisms of Localization and Image Interpretation

^{67}Ga Gallium citrate has biodistribution kinetics similar to iron and $^{111}\text{InCl}_3$.^{19,23,24} After intravenous injection, ^{67}Ga binds primarily to transferrin with delayed soft tissue clearance over 24 hours. Approximately, 15% to 25% of the ^{67}Ga is excreted by the kidneys during the first 24 hours. After 24 hours, the major route of excretion is intestinal. The biologic half-life of ^{67}Ga is 25 days. The normal tissues that accumulate ^{67}Ga include: liver, lacrimal glands, salivary glands, nasopharynx, bone marrow, and spleen. The liver normally metabolizes both lactoferrin and transferrin resulting in a high accumulation of liver radioactivity. ^{67}Ga localizes to sites of inflammation within neutrophils by similar mechanisms discussed for $^{111}\text{InCl}_3$ (Figure 20.5). Some tumors have a large transferrin receptor population located on the cell membrane. ^{67}Ga accumulation therefore relates to cell binding and, in some cases, receptor-mediated endocytosis. Tumor types that accumulate ^{67}Ga in humans include: lymphoma, melanoma, lung carcinoma, and primary hepatomas. ^{67}Ga has also been used for detecting abscesses and localizing diffuse pulmonary inflammatory processes, such as *Pneumocystis carinii* interstitial pneumonia. The

Table 20.10: Indications for ^{67}Ga Gallium Citrate Scintigraphy

Chronic non-pyogenic processes including granulomatous and lymphocyte-mediated diseases.
Fever of unknown origin patient with a chronic history where neoplasia or chronic infection with inflammation are likely to be identified.
Neutropenic patients.

Table 20.11: Acquisition Parameters of ⁶⁷Gallium citrate.**Radionuclide**

⁶⁷Gallium citrate (⁶⁷Ga). Supplied as a cyclotron produced carrier free ⁶⁷Gallium citrate. ⁶⁷Ga has a physical half-life of 3.26 days (T_{1/2} = 78.2 hours) and decays by electron capture.

Gamma emissions of ⁶⁷Gallium citrate:

Photon emission	keV	% abundance
Gamma 1	91.3	3
Gamma 2	93.3	38
Gamma 3	184.6	24
Gamma 4	209.0	2
Gamma 5	300.2	16
Gamma 6	393.6	4
Gamma 7	494.3	0.1
Gamma 8	703.6	0.01
Gamma 9	794.7	0.06
Gamma 10	888.0	0.15

Dose

Species	mCi	MBq
Dog or Cat	1-4.0	37-148
Horse	4-10	149-370

Acquisition Parameters

Camera preparation	15% windows centered on the 93, 185, and 300 keV photopeak. If only a single peak is selected, the 174 keV photopeak provides the best resolution.
Animal preparation	Intravenous catheter for injection.
Static frame acquisition	100,000 to 250,000 counts. Images will take 3 to 5 minutes to acquire. Sedation or general anesthesia may be required to avoid motion artifacts.
Matrix	256 × 256 × 16.
Collimator	Medium-energy or high-energy, general-purpose.
Time to image	24, 48, and 72 hours postinjection.
Positioning	Camera under table; animal in recumbent position.
Views	Orthogonal views of the extremities. Ventral, dorsal and opposite laterals for the body cavities.

inflammatory activity of generalized interstitial lung diseases has been documented using ^{67}Ga scintigraphy in humans.

^{111}In -transferrin may be used for evaluating inflammatory bowel disease. In normal dogs, radioactivity is not identified within the bowel prior to 24 hours after intravenous injection of the ^{111}In -transferrin. In dogs with inflammatory bowel disease, radioactivity will be present in the small bowel 2 to 4 hours after injection. Following treatment and clinical improvement, ^{111}In -transferrin scans return to normal. ^{111}In -labeled transferrin accumulation from noninflammatory bowel conditions, including other causes of protein losing enteropathy, have been seen in a limited number of cases. The indications for ^{67}Ga -scintigraphy are summarized in Table 20.10. The acquisition parameters for ^{67}Ga -scintigraphy are summarized in Table 20.11.

Blood Pool Agent and Vascular Permeability Scintigraphy

Inflammatory changes cause an increase in vascularity and vascular permeability. A variety of non-specific radiopharmaceuticals can be used to reflect these processes.¹⁹ Intravenous injection of non-specific radiopharmaceuticals that remain in the systemic circulation will reflect blood flow to the area during its first-pass and equilibrium phases. Although not specific for inflammation, these agents image the physiologic process that accompanies inflammation. This focal accumulation of a radiotracer is non-specific, because hyperemia and increased capillary permeability may be present in other disease conditions, including neoplasia.

Sodium pertechnetate can be used to evaluate both the vascular and extracellular fluid compartments (first and second phases of bone scintigraphy). Vascular phase images are obtained from the first pass of $^{99\text{m}}\text{TcO}_4^-$ through the tissues. "Soft tissue" images reflective of the extracellular fluid compartment may be obtained from 2 to 20 minutes after intravenous administration.

Radiopharmaceuticals that are excreted by the kidneys (eg, $^{99\text{m}}\text{Tc}$ -DTPA) have large molecular sizes limiting their distribution to the intravascular space and are useful in identifying hypervascularity. Such molecules may also leak and accumulate in extravas-

cular spaces at an inflammatory site. This is because of increased capillary permeability or endothelial damage, vascular permeability imaging has been used for brain scintigraphy based on the disruption of the normal blood-brain barrier by tumor invasion and neovascularization.

Summary

Use of radiolabeled cells and blood products for inflammatory imaging has been a mainstay in human medicine for the work up of occult infections. Due to the radiolabeling procedure, inflammatory imaging using labeled blood cells has not become a routine imaging technique in veterinary medicine. Use of other radionuclides (such as ^{111}In Indium Chloride and ^{67}Ga Gallium) may provide useful information regarding occult or acute inflammatory conditions that are difficult to image using other modalities.

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Receptor, Monoclonal Antibody, and Peptide Imaging

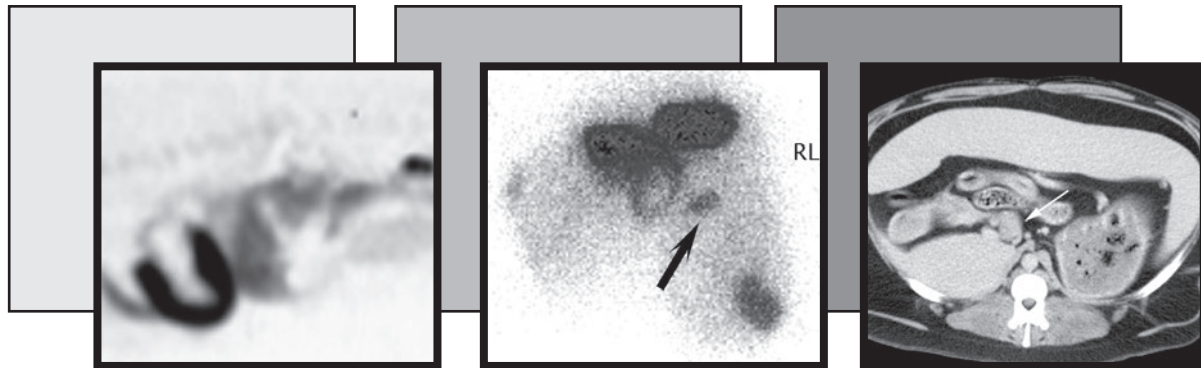
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Introduction

True receptor imaging has been key to the radiotracer concept since the conception of the Anger camera. One can see that nearly all of radiopharmaceutical localization is a result of some form of receptor binding or cellular transportation into the cell occurring at the level of the cell membrane, specific cellular proteins, intracellular receptors, or proteins in the extracellular matrix. The radiopharmaceutical binding is specific to organic or inorganic molecules so that localization will occur within the extracellular or intracellular compartment. Specifically targeted cell membrane receptors of normal tissues and/or tumors have been a focus of nuclear medicine research for the past 20 years. The hope is that if one is able to target a specific tumor receptor, systemic radiotherapeutic agents can then be developed for use in systemic radiotherapy. Tumor targeting began with different radionuclides (^{123}I , ^{125}I , ^{131}I , ^{201}Tl , ^{67}Ga) that were found to have avidity for a variety of different tumors. In these cases, however, the specificity for a given tumor was poor; and, in fact, other disease processes, such as inflammation, would also localize these radionuclides. The next step in receptor research involved the development of radiolabeled antibodies and antibody fragments for imaging specific tumor types. Aside from complex chemistry in order to make this happen (and lack of being able to use $^{99\text{m}}\text{Tc}$ in most antibody-labeled products), the labeled antibodies were found to have prolonged residual blood pool. If systemic radiotherapy were to work, then rapid clearance of the blood pool with specific localization to the target organ or tumor would be a necessity. This would ensure tumoricidal dosages with relative sparing of other organ systems. As biochemistry has advanced, specific tumor membrane proteins have been discovered and thereby a host of new cellular targets found that can be used for imaging and systemic radiotherapy.

Another form of receptor binding studies relates to the intracellular evaluation of specific metabolic pathways. Once normal has been determined, the possibility for evaluating various disease states and alterations in these metabolic pathways could be documented, possibly leading to novel treatment considerations. The purpose of this chapter is to review common types of receptor imaging scintigraphy currently available in human and veterinary medicine. Even though this area has not been explored

in the clinical setting to a large degree in veterinary medicine, there is a place for this type of imaging. Research imaging using these types of studies has been described in the literature and should serve as a basis for clinical imaging.

Neuroendocrine Imaging

Embryology, Anatomy, and Physiology

The basic mechanism of neuroendocrine imaging depends on specific cell membrane receptors that are embryologically derived from neuroectoderm or neural crest cells.¹ In the developing embryo, the neural folds arise from the neural plate. The ectodermal cells within the neural folds proliferate and expand creating a neural groove within the center. The neural folds then fuse to form the neural tube starting at the level in the cervical region, proceeding in both cranial and caudal directions. Prior to neural tube formation, a series of neuroectodermal cells along the lateral aspect of the developing neural folds (called the neural crest) begin to dissociate from the neural folds.¹ These cells migrate away from the neural crest early during embryologic development and are incorporated into various structures and organs forming a part of the neuroendocrine cells specific to an organ. The cells from the neural crest will migrate and become functional cell lines of melanoblasts, spinal ganglia (sympathetic nervous system), paraganglia (adrenal medulla), islet and delta cells of the pancreas, chromaffin bodies, amine precursor uptake and decarboxylation (APUD) cells, and the leptomeninges.²⁻⁵ These cells have the capability of taking up amine precursors and decarboxylating them into various end products (pro-hormones and hormones). An example is L-tyrosine being taken up by the adrenal medullary chromaffin cells. The L-tyrosine is converted in the cytosol by tyrosine hydroxylase to L-dihydroxyphenylalanine (L-DOPA). The L-DOPA is then decarboxylated by the enzyme, amino acid decarboxylase to L-dopamine. The term APUD has been applied to these neuroendocrine cells because of this specialized cellular metabolic handling of the amino acid L-tyrosine. On transmission electron microscopy, cellular derivatives of the neural crest have a large population of secretory granules or storage vesicles within the cytoplasm. Differentiated neural crest tumors produce excessive amounts of various hormones and neurosecretory products, such

as epinephrine, norepinephrine, dopamine, insulin, serotonin and calcitonin.

APUD cells secrete a number of biogenic amines, including dopamine, norepinephrine, epinephrine, serotonin, and peptides, such as somatostatin, substance P, insulin, and glucagon. Several features of APUD cells and other cells of neural crest origin include the presence of specific secretory proteins within the storage vesicles, called chromogranins A, B, and C and synaptophysin. Additionally, the enzyme neuron-specific enolase is present as another marker of neuroendocrine origin and differentiation. Neuroendocrine tumors typically present with clinical signs related to the secretion of the various biogenic amines that were previously listed.

Benzyl Guanidine Derivatives: Imaging of Pheochromocytomas

One form of neuroendocrine tumor imaging is based on analogs which will trace modifications of the amino acid L-tyrosine that take place during the biochemical synthesis of epinephrine and norepinephrine. Once the L-DOPA has been formed in the cytosol of the adrenal medulla, there is uptake into intracellular, cytoplasmic secretory granules where the L-dopamine is converted to norepinephrine by dopamine- β -hydroxylase. The epinephrine is then transported back into the cytosol where it is converted by an enzyme present only in the adrenal medulla, phenylethanolamine-N-methyltransferase. The epinephrine is then transported back into the secretory granule by the same transport mechanism (catecholamine- H^+ exchanger called vacuolar-type H-adenosine triphosphatase 1 or VMAT-1) as described for the uptake of the L-DOPA. These secretory granules act as storage centers and are then released under appropriate sympathetic stimulation.^{6,7}

Neural crest tumors that have been described in humans include: pheochromocytoma, neuroblastoma, carcinoid, paraganglionoma, chemodectoma, medullary thyroid carcinoma, islet cell neoplasia, gastrinoma, and melanoma. From this list potential applications in veterinary medicine would include pheochromocytomas, chemodectomas, insulinomas, melanoma, gastrinoma and carcinoid tumors.³ Although each of these tumor types is uncommon (with the exception of melanoma), identification of these tumors and potential metastatic disease using a noninvasive technique, such as scintigraphy, is

appealing.

The most common neural crest tumor seen in veterinary medicine is the pheochromocytoma, which usually originates in the adrenal medulla. Pheochromocytomas have a variable presentation, but retrospective studies have shown that incidental (nonclinical) pheochromocytomas are found between 28% and 57% of the time in the specific canine populations evaluated.⁷⁻⁹ Although, a pheochromocytoma has been reported in a cat, it is extremely rare.⁷ Canine pheochromocytomas have been shown to contain chromogranin A, synaptophysin, vasoactive intestinal peptide and adrenomedullin using immunohistochemical techniques.⁷ In humans, 85% of pheochromocytomas are adrenal in origin and 10% of those tumors are bilateral.⁵ Pheochromocytomas produce clinical signs secondary to the secretion of high levels of catecholamines including systemic hypertension, retroperitoneal masses with hemorrhagic diathesis, cardiopulmonary or non-specific clinical signs. Pheochromocytomas can invade the phrenicoabdominal vein and the caudal vena cava. Distant metastatic disease has been reported to be 13% to 24%.^{8,9} A high frequency of concurrent tumors (including other endocrine tumors) has been reported at 54% (37 out of 61 dogs).⁸

Extra-adrenal pheochromocytomas are rare, but have been reported.⁷ Extra-adrenal chromaffin tissue is present adjacent to the thoracic and abdominal aorta and can be found extending from the neck (region of the carotid bodies) to the pelvis with the highest concentration of the tissue being in the sympathetic chain in the thorax and in a central position medial and caudal to the renal position. Tumors originating from this extra-adrenal chromaffin tissue are called paraganglionomas or extra-adrenal pheochromocytomas. In humans, 10% of the pheochromocytomas have been associated with familial neurocristopathic syndromes (neurofibromatosis type-I, von Hippel-Lindau disease, multiple endocrine neoplasia type-IIA and type-IIB) with an autosomal dominant genotype and variable phenotypic expression.¹⁰

Scintigraphic evaluation of pheochromocytomas was originally performed in humans at the University of Michigan. In 1981, Wieland reported on the first pheochromocytoma imaged using ¹³¹I-metaiodobenzylguanidine (MIBG).² MIBG is synthesized by combining the benzyl group of bretylium and the guanidine group from guanethedine with a substituent.

tion reaction for the radiolabeling with ^{123}I or ^{131}I .² By 1984, other tumor types that were neuroendocrine in origin were imaged using ^{131}I -MIBG in humans these included neuroblastomas, carcinoid, medullary thyroid carcinomas, and paraganglionomas. The indications for imaging suspected neuroendocrine tumors are the same in both veterinary and human medicine (Table 21.1).

Mechanism of Localization

The mechanism of localization for MIBG is receptor uptake specific to catecholamines. These receptors are found on the cell membrane of neuroendocrine cells/tumors as well as on the intracytoplasmic membranes of the secretory granules (VMAT-1). Normal biodistribution of MIBG seen in humans includes salivary glands, heart, liver, adrenal medulla, and urinary bladder excretion when imaged at 24 hours. The target organ appears to be the liver, with an estimated absorbed dose of 0.89 mGy per MBq injected. Studies have shown that uptake is proportional to the number of secretory granules present and the re-uptake mechanism of catecholamines (called uptake-1) at the cellular membrane, specific to the synaptic sympathetic terminal or the adrenal medulla. ^{123}I -MIBG has been shown to have a sensitivity of 88% for identifying pheochromocytomas and potential metastatic lesions in humans.² There are cases, however, where pheochromocytomas will not avidly take up the ^{123}I -MIBG or ^{131}I -MIBG. Possible explanations for this include the lack of the differentiated receptor found at the cell membrane specific to the uptake-1 mechanism or lack of secretory granules for appropriate uptake and storage of the MIBG. In

either case, accumulation of the MIBG within the tumor does not occur. One study has shown ^{18}F -FDG PET to be complementary to ^{123}I -MIBG imaging and identified several patients where the ^{123}I -MIBG was negative yet uptake of ^{18}F -FDG was noted within the pheochromocytoma.^{12,13}

MIBG Scintigraphy and PFBG Positron Emission Tomography

MIBG imaging for pheochromocytomas in veterinary medicine has been limited to a single case report, (Figure 21.1). The acquisition parameters for ^{123}I -MIBG are summarized in Table 21.2. Localization and uptake of the ^{123}I -MIBG was present within 4 hours postintravenous injection of 37 MBq (1 mCi).¹⁴ Positron-emitting tracers have also been developed, including ^{18}F -parafluorobenzyl guanidine (PFBG). PFBG uptake and retention characteristics have been documented in the isolated rat heart and in the dog.¹⁴⁻¹⁷ In both of these species there is specific neuronal uptake (uptake-1) and nonspecific myocardial uptake (uptake-2). Within 5 minutes, PFBG was shown to have significant cardiac retention along with adrenal medullary uptake in the dog (Figure 21.2).^{15,16} PFBG has also been used to describe several dogs with known pheochromocytomas documenting the full extent of the disease process using PET imaging (Figure 21.3). In one dog, tumor thrombus could be seen to the level of the right atrium on the PFBG study, that was confirmed using echocardiography.¹⁷

In humans, high dosage ^{131}I -MIBG radiotherapy has been used effectively for controlling primary and metastatic pheochromocytomas and paraganglionomas.¹⁸ Palliative treatment for metastatic pheochromocytoma has been shown to have mixed results.¹⁸ Sixty percent of patients responded with temporal relief of tumor burden and symptoms, however, total remission was not achieved. In dogs, where caudal vena cava invasion is a common finding with invasive pheochromocytomas, there might be a role for ^{131}I -MIBG radiotherapy. Surgical reports in the veterinary literature have shown a high intraoperative morbidity (15%) and perioperative morbidity (51%) or mortality (22%).¹⁹ These reports have also shown that the presence of tumor thrombus has not been shown to be a negative predictor of intraoperative and perioperative complications in dogs with pheochromocytomas and adrenal cortical adenocarcino-

Table 21.1: Indications for Neuroendocrine (MIBG or Octreotide) Scintigraphy

Determine the presence of a pheochromocytoma or extra-adrenal paraganglionoma.
Determine the presence of an insulinoma.
Document the presence of macroadenomas of the pituitary gland (somatostatin tumors), although not proven in veterinary medicine.
Document the presence of other neuroendocrine tumors.

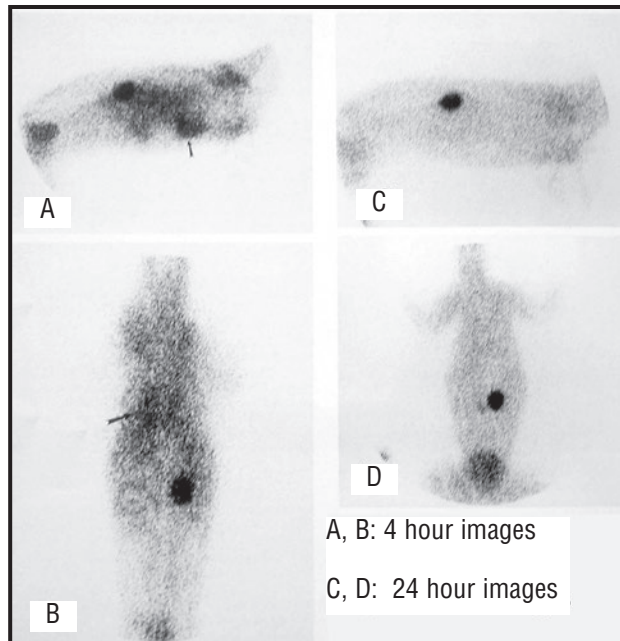


Figure 21.1: Right lateral and dorsal images obtained from a dog 4- and 24-hours after the intravenous injection of ^{123}I -MIBG

There is ^{123}I -MIBG uptake noted in the heart (arrow), the liver region and the urinary bladder. In addition, there is an intense area of uptake noted in the right adrenal gland. The left adrenal gland is not visualized and there is radioactivity within the urinary bladder noted on the dorsal image consistent with normal excretion. A pheochromocytoma was removed involving the right adrenal gland at surgery. Berry CR et al, *Vet Radiol.* 1993;34(1):52-55, reprinted by permission.

mas.¹⁹ Surgical resection might be possible after decreasing the overall tumor and thrombus size. This would need to be explored in the future. The major disadvantage is the handling of large dosages of ^{131}I (3.7 GBq based on the human literature). Bone marrow suppression in high repeated ^{131}I -MIBG dosages in humans can be irreversible.

^{131}I -MIBG has also been reported for imaging carcinoid tumors.²⁰ Carcinoid tumors originate from the neuroendocrine cells of the gastrointestinal tract (Kulchitsky cells or D cells). These tumors secrete serotonin as part of their paraneoplastic syndrome.²⁰ Carcinoid uptake of the ^{131}I -MIBG has been variable in humans. Carcinoid tumors may also originate

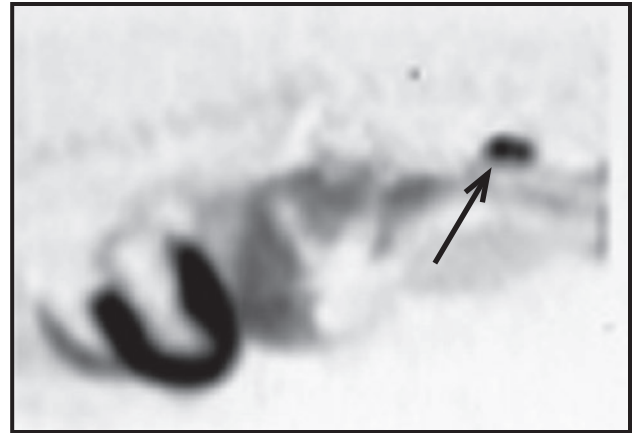


Figure 21.2: Reconstructed single sagittal plane image obtained from a dog 20 minutes after the intravenous injection of 175 MBq of ^{18}F -PFBG

There is uptake within both the right and left ventricular walls and right adrenal medulla (arrow).

in the lung parenchyma or bronchial wall. To date, there are no clinical reports of dogs being imaged with MIBG for a carcinoid tumor.

Somatostatin Analogs

Normal Physiology

Another avenue of neuroendocrine receptor imaging that developed concurrently with the initial ^{131}I -MIBG, was the formulation and evaluation of somatostatin analogs in combination with common radionuclides used for scintigraphic imaging. Cell membrane receptors specific to neuroendocrine tumors have a specific avidity for binding specific proteins, such as somatostatin. Somatostatin is a short-chain (14 or 28 amino acids) peptide hormone that is released by two primary sources within the body.²¹ The paraventricular region of the hypothalamus produces somatostatin, the peptide that is 14 amino acids in length. The somatostatin is released into the hypophyseal portal circulation and exerts inhibitory effects on the somatotroph cells of the adenohypophysis, specifically blocking the release of growth hormone.^{22,23} The mechanism of action involves inhibition of a second messenger system. The somatostatin binds to a specific somatostatin

Table 21.2: Scintigraphic Parameters for Small Animal Imaging Using ^{123}I -MIBG or ^{131}I -MIBG.**Radionuclide** ^{123}I -Metaiodobenzyl guanidine (MIBG). ^{131}I -MIBG.**Dose in Small Animals (Dogs and Cats)**

Radionuclide	mCi	MBq
^{123}I -MIBG	3 - 5	111 - 185
^{131}I -MIBG	0.5 - 1	17.5 - 37

Acquisition Parameters

Animal preparation	None required. Sedation may be necessary in order to get total count images of 250,000 counts. General anesthesia is recommended if using ^{131}I -MIBG.
Acquisition parameters	Static frame mode with a minimum number of total counts for 250,000 per image (lateral and ventral images) for ^{123}I -MIBG and 100,000 for ^{131}I -MIBG. To acquire a 100,000 count image using ^{131}I -MIBG may require between 15 and 20 minutes so general anesthesia is recommended.
Matrix	$256 \times 256 \times 16$.
Collimator	Use the low energy all-purpose collimator for ^{123}I -MIBG and the medium energy collimator for ^{131}I -MIBG. Be sure to adjust the pulse height analyzer (PHA) to the 159 keV photopeak of ^{123}I with a 20% window. Adjust the camera PHA to 364 keV photopeak of ^{131}I .
Time of imaging	For imaging ^{123}I -MIBG, static images are acquired at 2, 4 and 24 hours. If a positive study is obtained at any of these imaging time points, one does not have to proceed. If both right and left adrenal glands are identified on the 2 hours images, one does not have to continue with the later time points. The later time points are included to decrease the background radioactivity (which may be more important if ^{131}I is used). For ^{131}I -MIBG, acquire images 4, 24, and 48 hours post injection.
Positioning	The patient is positioned in lateral recumbency on the imaging table with the gamma camera positioned underneath the table.
Views	Right lateral, left lateral and dorsal images of the thorax. Right lateral, left lateral and dorsal images of the abdomen.

cell membrane receptor on the somatotroph. This binding activates the inhibitory G protein that blocks ATP from forming cAMP. By blocking the cAMP, protein kinase A will not allow for the opening of calcium channels, thereby inhibiting calcium influx into the intracellular space. It is the intracellular calcium that stimulates the somatotroph to release preformed growth hormone. When the somatotroph is receiving GHRH (growth hormone releasing hormone) and somatostatin, the inhibitory influence of the somatostatin will prevail.

Other neuroendocrine cells, including the pancreatic islet δ cells and D cells of the gastrointestinal tract, secrete somatostatin.^{21,22} This form of somatostatin is the 28-amino acid form and primarily mediates specific aspects of gastrointestinal physiology by inhibiting gastric secretion and the parietal cells of the stomach from releasing hydrochloric acid. Somatostatin will also increase fluid absorption and decrease fluid secretion by the small intestine, increase smooth muscle contraction of the small intestine, and decrease bile flow and exocrine and

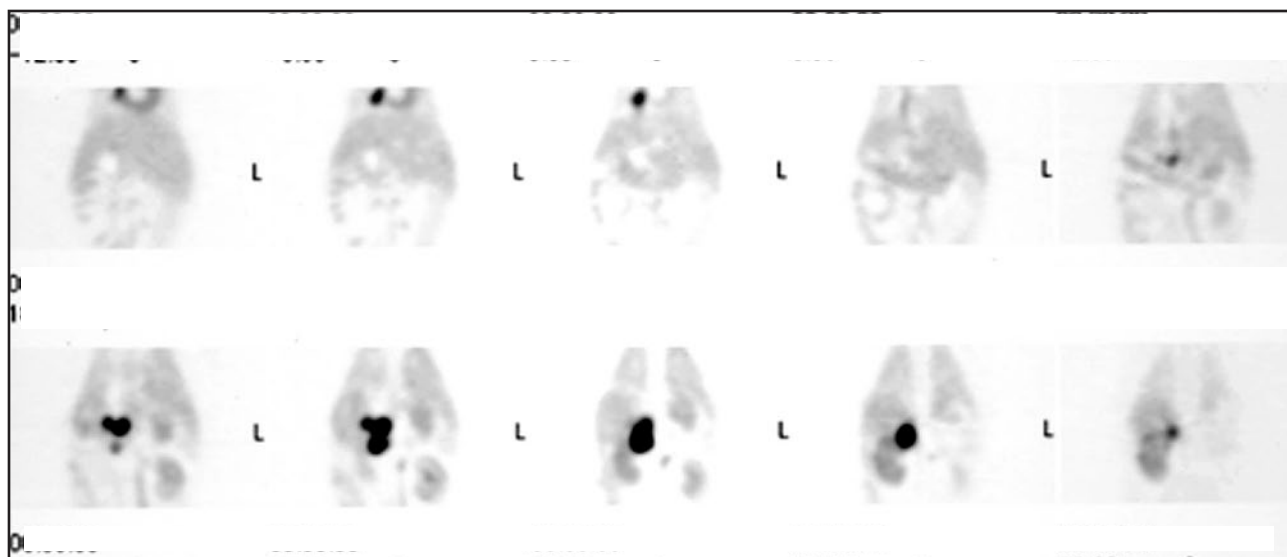


Figure 21.3: Reconstructed dorsal plane images obtained from a dog 30 minutes after the intravenous injection of 175 MBq of ^{18}F -PFBG.

There is intense uptake within the right adrenal medulla. A right adrenal pheochromocytoma was removed at surgery.

endocrine pancreatic secretions.²² Somatostatin has been shown to be useful as an adjuvant to chemotherapy in the treatment of tumors that are expressing somatostatin receptors.³ This is because somatostatin has antiproliferative effects on tumors, which include the induction of somatostatin receptors (inhibits the release of growth hormone [GH], insulin, glucagon, and gastrin); promotion of tyrosine phosphatase (reverses the growth promotion as seen by oncogenes via the tyrosine kinase group); inhibition of the release of specific growth factors (GH and insulinlike growth factor I [ILGH-I]); and inhibits angiogenesis, thereby limiting tumor blood supply.^{3,24}

Somatostatin has a very short biological half-life (less than 2 minutes); so radiolabeling the somatostatin molecule is impractical. In 1982, octreotide was developed as an eight-chain amino acid peptide that was shown to be a somatostatin analog. Octreotide has three amino acids in common with somatostatin, but the remaining amino acids are different.³ Octreotide has a longer biological half-life, thereby allowing for better imaging characteristics. Initial radiolabel of the octreotide was by replacement of the third amino acid with tyrosine so that the tyrosine could be labeled with ^{123}I (^{123}I -Tyr3-octreotide). However, significant hepatobiliary clearance prohib-

ited specific evaluation of abdominal tumors located in the superior abdomen from being identified in humans. The second formulation for a radiolabel involved the original octreotide molecule with the synthetic addition of a DTPA molecule that provides four carboxyl groups for binding metals and forming stable complexes. This molecule was called pentetreotide. The radionuclide that showed the highest affinity without dissociation was ^{111}In . OctreoScan (^{111}In -DTPA-D-Phe1-octreotide) is commercially available for imaging tumors that express the somatostatin receptor.

Within the body, there have been at least five different somatostatin receptor subtypes (SSRTs). ^{111}In -DTPA-octreotide binds most readily to SSRT-2 and to a lesser extent SSRT-5. Once ^{111}In -DTPA-octreotide binds to the somatostatin receptor, it is internalized with the receptor. This vacuole binds with a lysosome resulting in enzymatic degradation with the release of ^{111}In -DTPA-D-Phe from the original molecule. The ^{111}In -DTPA-D-Phe cannot pass through either the lysosomal membrane or the cell membrane, so the ^{111}In -DTPA-D-Phe is effectively trapped within the cell at this point. In humans, the ^{111}In -DTPA-octreotide is rapidly cleared from the blood pool and excreted by the kidneys so that 60% to 80% is excreted in the urine by 24 hours. Normal

biodistribution includes uptake in the thyroid, pituitary, urinary bladder, and to a lesser extent the liver and spleen. The kidneys are the target organs receiving an absorbed dose of 0.45 mGy per MBq injected. Patients undergoing ^{111}In -DTPA-octreotide (planar and SPE[C]T) scintigraphy are imaged at 4, 24, and 48 hours postinjection. If the images are considered positive at 24 hours, 48-hour images are not necessary.

Tumors that have been imaged with ^{111}In -DTPA-

octreotide in humans include: APUDomas, meningiomas, gastrinomas, insulinomas, paraganglionomas, and functional pituitary adenomas or adenocarcinomas (Table 21.3).^{3,24} However, there are some inflammatory diseases that will also avidly bind the OctreoScan, including tuberculosis, sarcoid granulomas, systemic lupus erythematosus, and rheumatoid arthritis.³ Attempts to image somatostatin receptor positive tumors in a more rapid fashion have resulted in the development of a PET agent and more recently two $^{99\text{m}}\text{Tc}$ agents.²⁸⁻³⁰ The $^{110\text{m}}\text{In}$ -

Table 21.3: Tumors and Disease Processes That Have Somatostatin Receptors and Have Been Shown to be Visualized Using ^{111}In -DTPA-D-Phe1-Octreotide in Humans

Adenohypophysis
a. Adenomas (GH, TSH-secreting tumors)
Adrenal Medulla
a. Pheochromocytoma
b. Neuroblastoma
c. Extramedullary pheochromocytomas
Paraganglia
a. Paraganglionomas
Thyroid Neoplasia
a. Papillary adenoma
b. Medullary carcinoma
Skin
a. Merkel cell carcinomas
b. Melanomas
Pancreatic Islet Cell Tumors
a. Insulinoma
b. Glucagonoma
GI Endocrine Tumors
a. Carcinoids
b. Gastrinoma
c. Undifferentiated neuroendocrine carcinomas

Bronchopulmonary
a. Carcinoid
b. Small cell carcinoma
Miscellaneous Sites
a. Larynx
b. Paranasal sinuses
c. Salivary gland
d. Chemodectoma, carotid body tumors
Leptomeninges
a. Meningiomas
Glial Cells – CNS
a. Well-differentiated astrocytomas or oligodendrogliomas
Activated Leukocytes
a. Autoimmune diseases
b. Granulomas
c. Lymphoma

DTPA-D-Phe1-octreotide is the PET equivalent of the ^{111}In -DTPA-octreotide molecule.²⁸ Because of the inherent resolution advantages of PET, one study has shown the tumor detection rates were greatly enhanced using the PET radiotracer. Also, quantitative uptake patterns and response to therapy could be done using the $^{110\text{m}}\text{In}$ -DTPA-D-Phe1-octreotide PET radiotracer. However, even though the researchers have shown the use of a commercial labeling kit for $^{110\text{m}}\text{In}$ -DTPA-D-Phe1-octreotide, only one patient was studied, so further clinical trials are necessary.²⁸

The first $^{99\text{m}}\text{Tc}$ -labeled product with a somatostatin receptor affinity was developed and called $^{99\text{m}}\text{Tc}$ -P829.²⁹ This radiotracer has a poor sensitivity when compared with the ^{111}In -DTPA-D-Phe1-octreotide. The second $^{99\text{m}}\text{Tc}$ -labeled product had a higher sensitivity when compared with ^{111}In -DTPA-D-Phe1-octreotide.³⁰ $^{99\text{m}}\text{Tc}$ -hydrazinonicotinyl-Tyr3-octreotide holds promise for the future because of the better imaging characteristics inherent to $^{99\text{m}}\text{Tc}$ imaging as well as a single acquisition protocol at 4 hours post injection, that would simplify patient imaging over the course of 2 days as with ^{111}In -DTPA-D-Phe1-octreotide.

The original chemical modification made to the octreotide molecule has been useful for labeling with the beta emitter ^{90}Y trium. The somatostatin analog, ^{90}Y -[DOTA]0-Tyr3-octreotide has entered into Phase 1 clinical trials.³¹ Limitations may be related to renal uptake, although pre-treating patients with positively charged amino acids has been shown to decrease the degree of renal uptake of ^{111}In -DTPA-D-Phe1-octreotide.³¹

^{111}In -DTPA Octreotide Imaging in Veterinary Medicine

Imaging using ^{111}In -DTPA-D-Phe1-octreotide has been limited to two case reports.^{31,32} This has included a pancreatic insulinoma (with gastric lymph node metastasis) that had increased uptake of ^{111}In -DTPA-D-Phe1-octreotide identified at 4 and 24 hours post intravenous injection. In the second case, a dog with a right atrial mass was shown to have ^{111}In -DTPA-D-Phe1-octreotide avid paraganglionoma at necropsy. Imaging was done at 4 and 24 hours. Due to the limited number of cases in the veterinary literature, the true sensitivity and speci-

ficity for ^{111}In -DTPA-D-Phe1-octreotide imaging is not known. Normal abdominal biodistribution of the ^{111}In -octreotide uptake is seen in the liver, gallbladder, kidneys, urinary bladder and on later images, some small intestinal radioactivity may be seen.

As there is limited experience with ^{111}In -DTPA-D-Phe1-octreotide, the proposed imaging protocols (Table 21.4), may need future modifications based on future investigations. Clinical applications could easily include imaging of dogs suspected to have insulinomas (Figures 21.4 and 21.5) or cats suspected of having insulin diabetes mellitus resistance secondary to functional adenomas of the adenohypophysis with a proposed mechanism of excessive GH or ACTH release.³³

Additional applications could include evaluation of brain tumors (meningiomas) before and after radiation therapy to assess individual patient response. Use of the ^{111}In -DTPA-D-Phe1-octreotide for imaging autoimmune disorders and inflammatory processes may also show future promise. The advent of the $^{99\text{m}}\text{Tc}$ product, however, holds the most promise depending upon the pricing of the radiopharmaceutical, once it becomes commercially available. The authors have imaged one veterinary patient with this agent ($^{99\text{m}}\text{Tc}$ -NeoTect) (Figure 21.6). In this dog, the

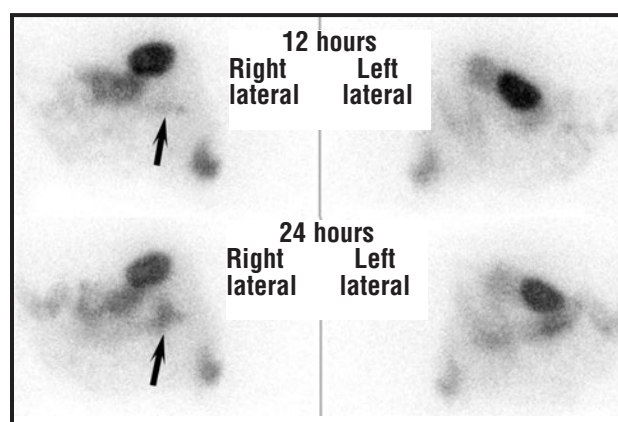


Figure 21.4: ^{111}In -octreotide study in a dog with an insulinoma.

Right lateral and left lateral images obtained at 12 and 24 hours after the injection of 74 MBq (2 mCi) of ^{111}In -octreotide. Abnormal accumulation within the right dorsal abdomen is seen. An insulinoma was removed at surgery.

Table 21.4: : Scintigraphic Imaging Parameters Using ^{111}In -Octreotide**Radionuclide** ^{111}In -octreotide, (OctreoScan). $^{99\text{m}}\text{Tc}$ -pentatide (NeoTect).**Dose in Small Animals (Dogs and Cats)**

Radionuclide	mCi	MBq
^{111}In -octreotide	1 - 4	37 - 148
$^{99\text{m}}\text{Tc}$ -pentatide	2 - 4	74 - 148

Acquisition Parameters

Animal preparation	None required. Sedation may be necessary.
Acquisition parameters	Static frame mode with a minimum number of total counts for 300,000 per image (lateral and ventral images) for ^{111}In -octreotide. This may require 3 minutes for a total count acquisition of 300,000. The dorsal image, obtained for the same time period (3 minutes) may only yield a 150,000-count image.
Matrix	256 × 256 × 16.
Collimator	Use a medium-energy collimator for ^{111}In -octreotide and a low-energy, all-purpose collimator for $^{99\text{m}}\text{Tc}$ -pentatide. Be sure to adjust the pulse height analyzer to 172 and 247 keV photopeaks of ^{111}In with a 20% window. Adjust the camera PHA to 140 keV photopeak of $^{99\text{m}}\text{Tc}$.
Time of imaging	For imaging ^{111}In -octreotide, static images are acquired at 4, 24, and 48 hours. If a positive study is obtained at any of these imaging time points, one does not have to proceed. For $^{99\text{m}}\text{Tc}$ -NeoTect, static images are acquired at 30 minutes and 1, 2, 3, and 24 hours after injection.
Positioning	The patient is positioned in lateral recumbency on the imaging table with the gamma camera positioned underneath the table.
Views	Right lateral, left lateral, and dorsal images of the thorax. Right lateral, left lateral, and dorsal images of the abdomen.

study was negative, although the biodistribution was similar to that described for ^{111}In -octreotide. This dog died from other causes and an insulinoma was not found at necropsy.

Tumor Cell Receptor Imaging: Labeled Choline Analogs

A new PET analog for choline receptors has also been described.^{35,36} Various carcinomas express a high density of choline receptors and choline kinase. It has been shown that there is up-regulation of the number of choline receptors on the cell membranes of certain tumors. In addition, choline is taken up and phosphorylated at a more rapid rate in certain tumor

types. ^{18}F -fluoromethyl-dimethyl-2-hydroxyethyl-ammonium is a fluorinated analog of choline.^{35,36} In vitro studies have shown similar uptake rates for the fluorinated choline analog when compared with ^{18}F -FDG. Choline receptor blockade resulted in a 90% decrease in binding in cultured prostatic carcinoma cells.³⁵ When compared with C-14-labeled choline, there is similar uptake in a tumor-bearing mouse model with similar prominent hepatic and renal uptake. Imaging of human patients with the fluorinated choline analog has resulted in increased uptake within the primary as well as osseous and soft tissue metastatic lesions.³⁵ Preliminary studies have shown increased radiotracer uptake in metastatic breast adenocarcinoma.³⁶

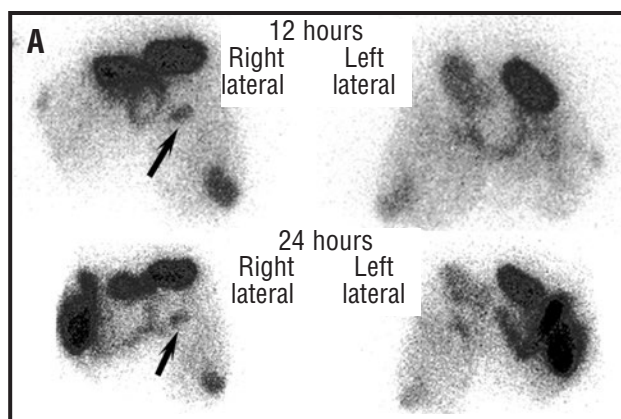


Figure 21.5: Right lateral and left lateral images obtained from an 8-year-old German Shepherd dog at 12 and 24 hours after the intravenous injection of 74 MBq (2 mCi) of ^{111}In -octreotide

A, Abnormal accumulation is seen within the right dorsal abdomen. **B**, Single transverse computed tomographic image from the same dog prior to surgery. A focal nodule is present in the head of the pancreas. An insulinoma was removed at surgery. The area of radiopharmaceutical accumulation along the ventral and cranial margin of the liver is the gallbladder.

Monoclonal Antibodies

Radiolabeled monoclonal antibodies that bind leukocytes are being investigated.^{37,38} Several antibodies to human neutrophils have excellent labeling efficiency. ^{123}I or ^{131}I , $^{99\text{m}}\text{Tc}$, and ^{111}In radiolabels have been used with comparable results. These antibodies bind neutrophils in the circulation, marginating neutrophil pools, and extravascular sites of inflammation. Granulocyte antibody labeling has not affected neutrophil function. The most promising of the initial human leukocyte labels, however, will not cross-react with neutrophils of other animal species (including dogs). Monoclonal antibodies have also been developed against specific infectious agents (eg, *Candida albicans*). These antibodies show promise in imaging specific infectious etiologies, and allow imaging in a variety of species. Low target-to-background ratios and slow in vivo localization currently limits the usefulness of these methods.

Antibodies and Antibody Fragments

In addition to the specific antibodies mentioned previously, polyclonal antibody imaging for infection and inflammatory disease (eg, rheumatoid arthritis) is currently a major research emphasis.³⁷⁻⁴² Radiolabeled polyclonal human or murine IgG have

excellent early results in localizing infection in a variety of laboratory animals and humans. Complete antibodies or antibody fragments can be used in combination with $^{99\text{m}}\text{Tc}$, $^{111}\text{InCl}_3$, or radioiodine labels. Reports of clinical applications of polyclonal antibodies in animals have not yet appeared.

Radiolabeled Particles

Nanocolloid

Nanocolloid labeled with $^{99\text{m}}\text{Tc}$ consists of small serum albumin colloids with a particle size of < 100 nm. Like all colloids, mononuclear phagocytic cells located in the liver, spleen, and bone marrow will take up the radiolabeled nanocolloid. As a result, after intravenous injection the product clears very rapidly from the blood pool. Because the nanocolloid leaks nonspecifically into a focus with enhanced vascular permeability, only poor accumulation in inflammation foci is observed.⁴³

Liposomes

Liposomes are microscopic lipid vesicles consisting of one or more concentric phospholipid bilayers enclosing discrete aqueous spaces. Liposomes have been investigated extensively as carriers for drugs in attempts to achieve selective deposition

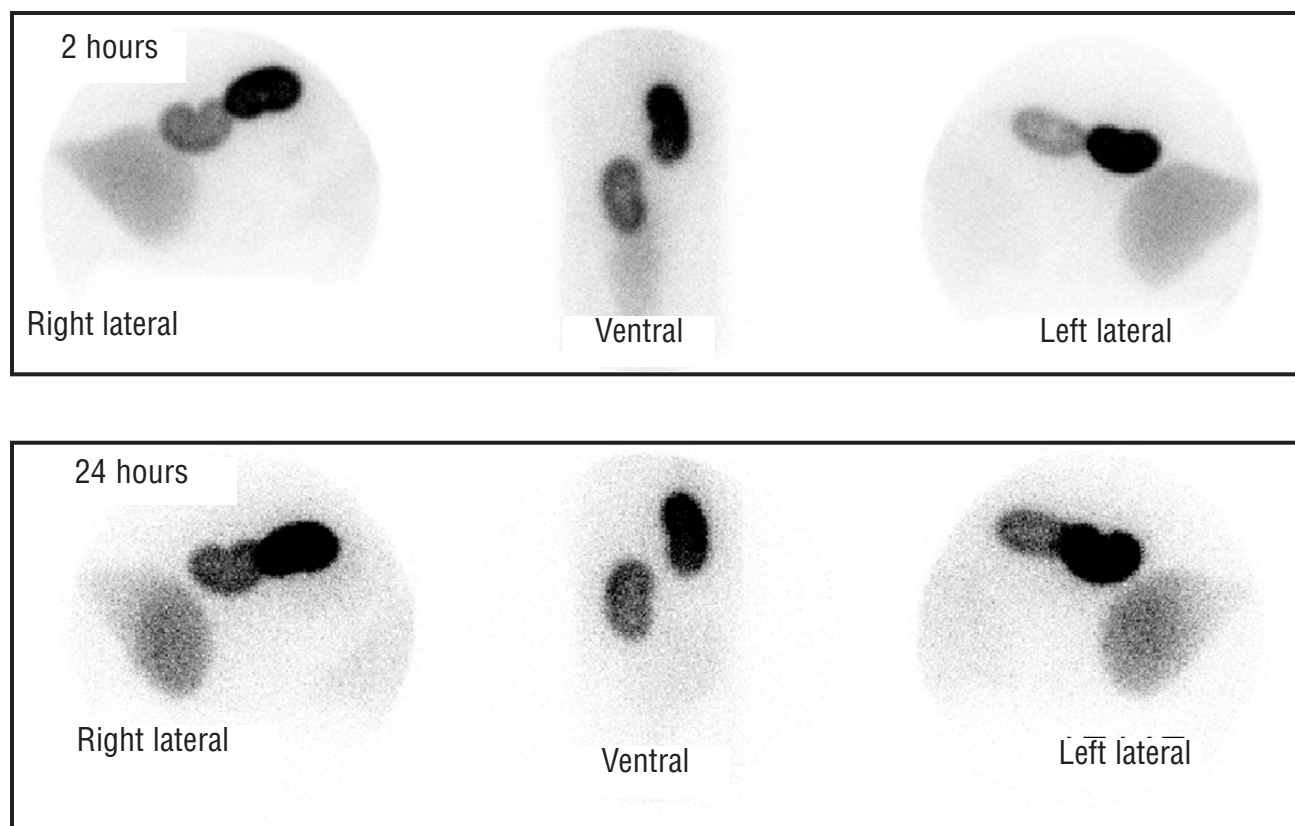


Figure 21.6: Static right lateral images from a dog suspected of having an insulinoma obtained after intravenous injection of 111 MBq of ^{99m}Tc -Neotect.

A, Right lateral, left lateral, and dorsal images obtained at 2 hours postinjection. Each image was obtained for 500,000 counts. There is normal biodistribution of the radiopharmaceutical in the kidney and urinary bladder. There is absence of radioactivity in the area of the pancreas. **B**, Right lateral, left lateral, and dorsal images obtained at 24 hours. The study was interpreted as normal.

and/or controlled release of drugs.⁴⁴ The biodistribution and kinetics can be influenced by changing the composition of the bilayer itself by varying the phospholipid components, the charge, or the size of the liposomes.⁴⁵ Given the enhanced vascular permeability in inflammation, liposomes extravasate to the interstitial space.⁴⁶ Thus liposomes have been proposed as vehicles with which to target infectious and inflammatory foci. Reports of clinical applications of radiolabeled particles in animals have not yet appeared. A review of potential applications of liposomes, including detection of infection and inflammation in animal models, has been reported.⁴⁴

Labeled Receptor-Specific Small Proteins and Peptides

Chemotactic Peptides

N-formyl-methionyl-leucyl-phenylalanine (fMLF) is a bacterial product that acts as a potent leukocyte chemotactant peptide. Recently analogues that can be radiolabeled with ^{111}In have been developed.⁴⁷ Studies in animals have shown evidence of binding to leukocytes *in vivo* and localization at sites of infection. A major advantage of such small peptides is their fast clearance from circulation. This could facilitate imaging early after injection. In

rabbits, a ^{99m}Tc -labeled fMLF derivative yielded target-to-background ratios greater than or equal to those achievable with ^{111}In -labeled leukocytes.⁴⁸ Unfortunately use of these biologically potent peptides can result in a transient but severe leukopenia even at relatively low doses.

Interleukins

Interleukins (ILs) are an expanding group of bioactive substances that initiate and mediate the inflammatory response by facilitating communication of leukocyte subsets with other cells and tissues.^{49,50} Various IL receptors are expressed on different leukocyte subsets. First reports on labeled cytokines described the potential of iodinated IL-2 to depict infiltrations of activated lymphocytes, by autoradiography in the pancreas in experimental diabetes specifically.⁴⁹ In humans, various autoimmune responses that are characterized by activated lymphocytic infiltration with up-regulated IL-2 receptor levels have been visualized.

Another approach is the use of radiolabeled IL-1 a potent pro-inflammatory cytokine. IL-1 receptors are expressed on a wide range of leukocytes, such as monocytes and neutrophils.⁵¹

Drawbacks of the use of such a biologically active protein include fever and hemodynamic and hematologic side effects, occurring even at very low concentrations, making it difficult to produce a clinically safe agent.⁵² Reports of clinical applications of radiolabeled receptor-specific small proteins and peptides in animals have not yet appeared.

Radiolabeled Antibiotics: Ciprofloxacin

In an attempt to achieve bacteria specificity, a modified version of the fluoroquinolone ciprofloxacin was radiolabeled with ^{99m}Tc and used for infection imaging.⁵³ Sensitivity in first clinical studies was relatively low. Nevertheless, this agent may have some role in the differential diagnosis between infectious and sterile inflammation. Reports of clinical applications of radiolabeled antibiotics in veterinary patients have yet to be published.

Summary

Neuroendocrine, monoclonal antibody, and peptide receptor imaging have yet to be realized in veterinary medicine, partly because of expense and partly because of inadequate radiopharmacy facilities (and training/expertise) for preparation of labeled compounds. MIBG and octreotide are commercially available, however, cost between \$750 and \$1,500 for a single dose when purchased through a distributing radiopharmacy. This limits the availability to the veterinary market. Newer commercial products that are ^{99m}Tc labeled may provide for a cheaper alternative that makes practical use of these radiopharmaceuticals in veterinary medicine.

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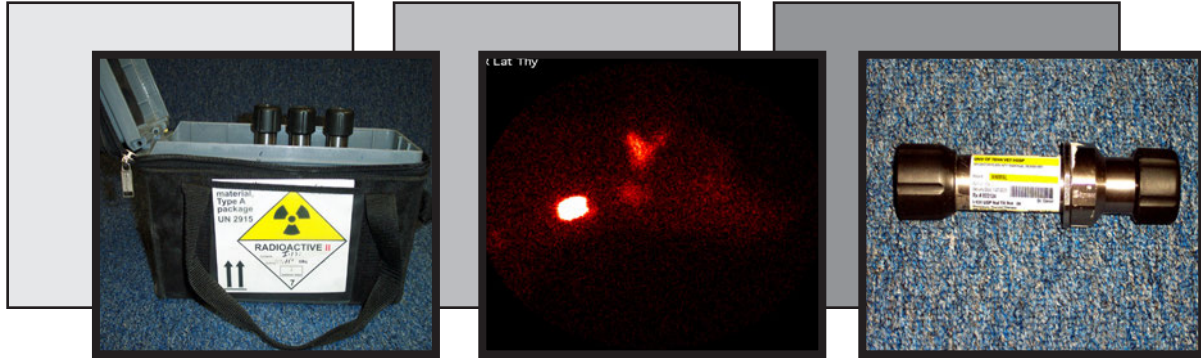
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Thyroid Radiotherapy: Iodine-131

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Introduction

Iodine-131 radiation therapy is an effective treatment for animal and human patients with thyroid neoplasms or hyperplasia. This chapter discusses the role of ^{131}I treatment, potential complications, and current thoughts on dosage regimens for dogs and cats with thyroid cancer. ^{131}I undergoes β^- radioactive decay with multiple beta and gamma emissions (Table 22.1). The physical half-life is 8.06 days. The specific gamma ray constant is 2.2 R/mCi-hr at 1 cm. The half-value layer of the 364 keV gamma emission is 3 mm lead equivalent.

Mechanism of Localization

Iodide is trapped by follicular epithelial cells of the thyroid gland, oxidized to iodine, actively transported into the follicular colloid and bound to tyrosine residues within thyroglobulin molecules. Additionally, iodide is concentrated but not protein bound by the stomach and salivary glands. The kidney eliminates unbound iodide within the blood pool.

The use of ^{131}I for treating thyroid neoplasia is based on its property of thyroid tissue localization, relatively short effective half-life ($T_{\text{eff } 1/2} = 2$ days) and radiation emissions. Iodine-131 will emit beta particles that transmit 90% of their total energy to a sphere within 1 mm from the decaying ^{131}I atom, resulting in cell kill in the area of emission. Approximately 90% of local radiation effect is due to beta radiation and the remaining 10% due to gamma radiation.

Treatment and Dosage

Feline Adenomatous Hyperplasia

The empirical dose for the treatment of cats is 148 to 185 MBq (4 to 5 mCi) given intravenously or subcutaneously.¹⁻¹⁰ The radioiodine dose (mCi) can be calculated based on an initial percent iodine uptake study by the thyroid tumor. The calculated ^{131}I dose is based on peak radioactive iodine uptake (RAIU) obtained from a radionuclide tracer scintigraphic study. The formula requires calculating the RAIU effective half-life of ^{131}I in the patient and estimating the weight of the thyroid gland. A typical target dose for the thyroid gland is 150 to 200 Gy. A standard formula for calculating a target dose to the thyroid is found in Table 22.2.

Feline Thyroid Carcinoma

The empirical dose for the treatment of thyroid carcinoma in the cat is between 1,110 and 1,480 MBq (30 to 40 mCi) given intravenously. The empirical dose ranges that are listed are used by the author based on experience and extrapolation from treatment of thyroid tumors in humans. At this time, an optimal dose has not been established for treating functional thyroid carcinomas in the cat. Radioiodine dose (in mCi) can also be calculated from the percent radioactive iodine uptake by the thyroid tumor. The target dose necessary for thyroid ablation of a normal human thyroid gland is 500 Gy.¹¹ A tumoricidal target dose has not been established in the cat.

Table 22.1: Physical Decay Characteristics of I-131

Radiation	Mean Percentage per Disintegration	Mean Energy (keV)
Beta-1	2.0	69.1
Beta-2	6.6	96.4
Beta-3	89.8	191.6
Gamma-1	2.6	80.1
Gamma-2	5.8	284.3
Gamma-3	82.0	364.4
Gamma-4	6.5	636.7

The empirical dose for the treatment of thyroid carcinoma in the dog is between 2,775 and 4,625 MBq (75 and 125 mCi) given intravenously. The empirical dose ranges that are listed are used by the author based on experience and extrapolation from treatment of thyroid carcinomas in humans. At this time, an optimal dose has not been established for treating functional thyroid carcinomas in the dog. Radioiodine dose (in mCi) can also be calculated from the percent radioactive iodine uptake by the thyroid tumor. A tumorcidal

target dose for the treatment of thyroid carcinoma has not been established in the dog.

The debate between an empirical dosage and an individualized dose calculation based on percent iodine uptake (RAIU) in administering radioiodine continues.^{1,2,7,12-14} In practice, most doses are given empirically. Proponents of individualized calculation based on percent iodine uptake contend that customized dosimetry permits adequate dose to tumors that less efficiently concentrate iodine and prevent

Table 22.2: Formula for Calculating ^{131}I Dose to be Delivered

$$^{131}\text{I} (\mu\text{Ci}) = \frac{[(\text{Target dose, cGy/g}) \times (\text{Thyroid gland weight, g})]}{[(1200 \text{ cGy-g}/\mu\text{Ci}) \times (\text{peak RAIU, \%}) \times \text{Teff}_{1/2}]}$$

where $1/\text{Teff}_{1/2} = 1/\text{Tbio}_{1/2} + 1/\text{Tphys}_{1/2}$, ($\text{Teff}_{1/2}$ = effective half-life, $\text{Tbio}_{1/2}$ = biological half-life and $\text{Tphys}_{1/2}$ = physical half-life); and RAIU = percent radioactive iodine uptake (%).

Table 22.3: Indications for Radioiodine Therapy

Treatment of benign adenoma or adenomatous hyperplasia of the thyroid gland resulting in hyperthyroidism in cats. ¹⁻⁶
Treatment of functional thyroid carcinoma in the cat and dog. ⁷⁻¹¹ The term functional as used in this chapter refers to the ability of the neoplasm to trap and organify radioactive iodine and not its hormonal secretory characteristics.
Ablation of normal thyroid tissue to facilitate the detection of recurrent, incompletely excised, or disseminated thyroid carcinoma in the dog and cat. ¹¹

Table 22.4: Parameters for Radioiodine Therapy Radionuclide

Sodium ^{131}I iodine, oral solution, USP.

Dose

Feline Adenomatous Hyperplasia
Empirical dosage: 148-185 MBq (4-5 mCi) IV or SQ.
Feline Thyroid Carcinoma
Empirical: 1,110-1,480 MBq (30-40 mCi) IV.
Canine Thyroid Carcinoma
Empirical: 2,775-4,625 MBq (75-125 mCi) IV.

^{131}I Characteristics

Physical Characteristics
^{131}I undergoes β^- decay with resultant beta and gamma emissions.
The physical half-life is 8.06 days.
The specific gamma ray constant is 2.2 R/mCi-hour at 1 cm.
The half-value layer in lead is 3 mm.

overdosage in those tumors that effectively concentrate iodine. The proponents using empirical dose calculation(s) point to the high percentage of successful outcomes and acceptable complication rates using standardized doses, as well as the inherent errors and inconsistencies involved in percent iodine uptake dosimetry.

Preparation and Administration

One measures the radioactivity of the dose using a dose calibrator set for ^{131}I . Due to the volatility of $\text{Na } ^{131}\text{I}$ solution, the decanting and transfer should be done under an exhaust hood that has been approved for use with radioactive materials (portable hoods are available in a cost range of \$1,000 to \$3,000). The radiopharmaceutical is supplied as a nonsterile oral solution. Intravenous or subcutaneous injection of this material has not resulted in complications, but filtration using a Millipore may be performed. One places the dose within a shielded syringe. Subcutaneous injection is uncomplicated, but care should be used to avoid leakage of radioiodine solution from the injection site and to avoid accidental needle placement through both layers of tented skin, resulting in injection of radioiodine on the skin surface. Stabilizing (EDTA in water) and diluting (sodium thiosulfate) solutions are used when dealing with ^{131}I . Additionally, the ^{131}I solution is acidic and stings if not pH adjusted. For subcutaneous injection, an insulin or 3.0 mL syringe can be used and the 4 mCi of the ^{131}I is diluted to 0.4 to 0.5 mLs total injected dose. This type of syringe setup is used to reduce the percent of the dose that is left in the syringe as residual radioactivity. For intravenous administration, an over-the-needle or butterfly catheter with an attached 3-way stopcock and flush syringe is used to ensure venous access, facilitate dose administration, and minimize personnel exposure. One attaches the shielded syringe to the three-way stopcock, injects the radioiodine, and then flushes the catheter. One measures the residual radioactivity within the injection apparatus in the dose calibrator to determine the actual dose given, (actual dose = preinjection radioactivity minus postinjection radioactivity). The indications for radioiodine therapy are summarized in Table 22.3. The parameters for radioiodine therapy are summarized in Table 22.4.

Excretion

The kidneys excrete a majority of the ^{131}I , with lesser amounts being eliminated in the feces and saliva. Approximately 3% of the injected dose is isolated to the area of thyroidal hyperplasia.

Radiation Safety/Patient Isolation

As a result of gamma emissions from ^{131}I within the thyroid gland and urine excretion of the ^{131}I , isolation of the treated animals and their excreta is required following treatment. The isolation time varies according to the ^{131}I dose administered, the effective half-life of ^{131}I within a given patient, and applicable state and/or federal regulations. Typically, cats injected with 4 mCi will measure greater than 200 mR per hour at the surface site of injection and between 1.2 and 1.5 mR per hour at 1 meter. Within 48 hours, the radioactive iodine is absorbed from the subcutaneous injection site and the largest percentage excreted in the urine. Solid and liquid wastes (consisting of any bedding or contaminated material containing urine, saliva, or feces) should be handled as radioactive waste in accordance with local regulations. In most cases, this means the collection of the radioactive wastes and storage for 10 physical half-lives (3 months) prior to elimination in public waste facilities. Radiation detectors at garbage dump sites are sensitive enough to pick up μCi amounts of ^{131}I from waste material that has been prematurely released. After 48 hours, the cats usually measure (on average) between 150 and 200 mR per hour at the surface and less than 0.5 mR per hour at 1 meter. Based on the release criteria established for the end radiation user, some cats with detectable radiation exposures can be discharged to owners. In these circumstances, written instructions limiting contact with the pet and the pet's excreta during the first month following treatment should be given to the owner.

Species Differences

There are no known differences in the trapping and organification of iodine by canine and feline thyroid glands. A difference between the species is the secretory nature of canine and feline thyroid neoplasms.

Feline tumors typically produce increased amounts of biologically active thyroid hormones. The majority of dogs with thyroid carcinoma are euthyroid or hypothyroid, with less than 5% of dogs having increased serum thyroid hormone concentrations.⁶ Most canine thyroid carcinomas contain follicular elements¹⁵ and are capable of trapping and organifying radioiodine. Judging the “functional” ability of a tumor and whether radioiodine is a rational option for treatment based only on hypersecretion of thyroid hormones is inappropriate. This is because canine thyroid carcinomas are capable of trapping and organifying iodine without hypersecretion and some tumors secrete biologically inactive thyroid hormones that are not detected using routine thyroid hormone assays. In humans, a “functional” tumor refers to the ability of the tumor and its metastases to trap and organify radioiodine.^{14,16-19} Determining tumor “function” can only be done accurately using radioiodine scintigraphy (see Chapter 10).

Role of Scintigraphy in Radioiodine Treatment

Radionuclide imaging of the abnormal thyroid gland (see Chapter 10) is integral to staging and assessing appropriate treatment of feline and canine thyroid neoplasia as well as calculating the dose when the RAIU technique is used.^{4,8,11,12,20-22} In feline hyperthyroidism, imaging using $^{99m}\text{TcO}_4^-$ serves as a screening procedure to discriminate between adenoma/adenomatous hyperplasia and thyroid carcinoma. It also detects local extension and distant metastasis of thyroid malignancy or the presence of ectopic thyroid tissue in the thoracic cavity. Similarly, $^{99m}\text{TcO}_4^-$ scintigraphy in the dog identifies a cervical mass as thyroid in origin and can also give morphologic information regarding the primary tumor and presence of local extension or distant metastasis. Imaging using radioiodine (^{123}I or ^{131}I) determines the “functional” (eg, capable of trapping and organifying radioiodine) nature of these tumors, and metastasis aids in the detection of distant metastases not identified clinically, radiographically, or with $^{99m}\text{TcO}_4^-$ imaging, and can be used to calculate the RAIU. Post treatment radioiodine thyroid scintigraphy performed by imaging residual radioiodine confirms uptake within known tumor and detects tumor foci not identified on low activity pretreatment scans.^{23,24}

Follow-up scintigraphy after treating canine and feline thyroid carcinoma is important in evaluating response to therapy. In animals treated surgically, scintigraphy is useful in assessing the surgical bed for incomplete tumor resection. In animals treated with radioiodine, scintigraphy localizes residual functional tissue or documents effective thyroid ablation. Follow-up imaging is performed 4 to 6 weeks following treatment and then at 3- to 6-month intervals to document regression or recurrence. Imaging in the post-treatment period is ideally done under conditions that maximize radioiodine uptake in the primary tumor, tumor bed or metastasis. This principle is the rationale for radioiodine thyroid ablation that, by inducing hypothyroidism, maximizes endogenous TSH production. As TSH enhances iodine uptake within functional thyroid tissue, hypothyroidism optimizes conditions for tumor detection and treatment. For this reason, animals receiving exogenous thyroid hormones as maintenance therapy should have their medications discontinued prior to imaging. In humans, T_4 supplements are withdrawn at 6 weeks and T_3 supplements are withdrawn at 3 weeks. Exact withdrawal times have not established for veterinary patients.

Patient Factors

The uptake and resident time of therapeutic amounts of ^{131}I for a given patient depend on many factors. Probably chief among these is the ability of the hyperplastic/neoplastic lesion and associated metastases to trap and organify iodine, a factor best determined by pretreatment scintigraphy. However, other factors are recognized to substantially modify radioiodine uptake. Routinely used antithyroid drugs, including propylthiouracil and methimazole have been shown to decrease radioiodine resident time within the thyroid gland in humans.⁶ Patient intake of stable iodine, including intravenous radiographic contrast media and iodine based surgical solutions prior to treatment has significantly reduced radioiodine uptake.^{14,25,26}

Endogenous plasma thyrotropin (TSH) concentrations also play an important role. Maximizing these concentrations is a key consideration in the scintigraphic detection and treatment of differentiated thyroid neoplasia in humans. Thyroid ablation therapy directed at making the patient hypothyroid maximizes pituitary secretion of TSH and enhances radio-

iodine uptake. Investigation of the role of TSH in the treatment of thyroid neoplasia in dogs has been hampered, until recently, by the lack of a reliable assay for this hormone. The role of TSH concentrations is probably less important in the hypersecretory conditions that result in hyperthyroidism, where increased uptake and organification of iodine occurs in spite of suppressed circulating levels of TSH.

Rationale/Goals for Treatment of Adenomatous Hyperplasia in Cats

The hyperfunctioning tissue responsible for hypersecretion of thyroid hormone will preferentially trap the radioiodine. As a result of this localization and the relatively short penetration of the β^- emissions of ^{131}I , this hyperplastic tissue is destroyed, sparing normal thyroid tissue. Most patients become euthyroid following a single treatment.

Rationale/Goals for the Treatment of Functional Thyroid Neoplasia

Surgical excision is the treatment of choice for primary thyroid carcinomas. However, evaluation of patient factors, local tumor extension, and distant metastasis, may make surgical excision infeasible or inappropriate. In such cases, the use of ^{131}I as an adjunct or primary treatment may be indicated. Critical to this application is determining the ability of the tumor(s) to trap and organify iodine through scintigraphy. Goals are determined by the stage of the tumor.

Rationale/Goals for Thyroid Ablation Therapy

^{131}I ablation of normal thyroid tissue as an adjunct to the treatment of malignant thyroid neoplasia has received little attention in the veterinary literature and continues to be controversial in humans. The rationale for this treatment is based on the concept of maximizing the detection and the treatment of malignant thyroid neoplasia by creating a state of hypothyroidism. By removing all normal endogenous sources of thyroid hormones, imaging and treatment can be performed under conditions of maximum TSH stimulation. This, in turn, maximizes radioiodine uptake by functional thyroid tumors and their metastasis. This therapy is advocated in cases of complete tumor excision, to detect recurrence or subsequent metastasis. A further benefit may be

in the destruction of undetected functioning micro-metastases that are below the imaging threshold of scintigraphic or radiographic detection.

Complications

The major complication of low-dose radioiodine therapy of feline adenomatous hyperplasia is iatrogenic hypothyroidism.^{1,2,4,5} The major potential complications using higher-dose radioiodine therapy for treatment of thyroid carcinoma in humans include acute and chronic myelosuppression, radiation pneumonitis, sialoadenitis, thyroiditis, neck pain, gastrointestinal injury, preleukemic syndromes, and leukemia when multiple large doses are used.^{14,27-31} In dogs treated with high dose radioiodine for thyroid carcinoma, the major complication was transient myelosuppression.¹¹

Summary

Radioiodine therapy remains a viable form of treatment of thyroid hyperplasia, adenomas, and carcinomas in select dogs and cats. A thorough understanding of thyroid physiology and pathophysiology is required for adequate treatment of veterinary patients with thyroid neoplasms.

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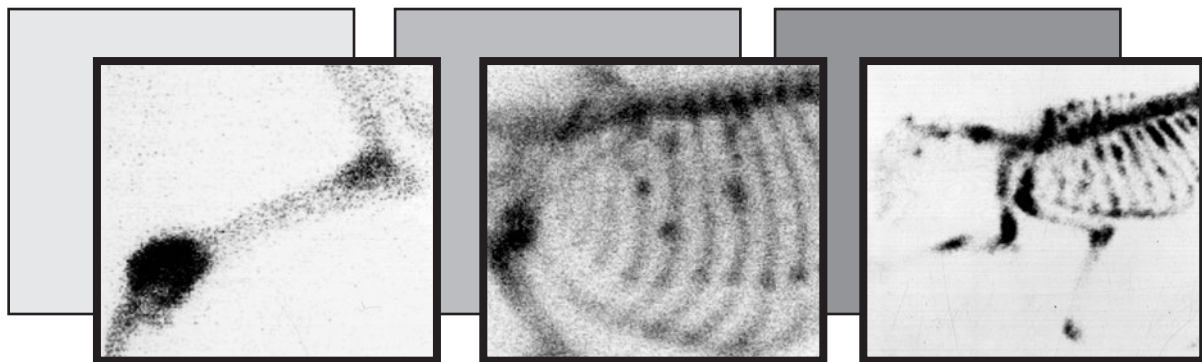
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Primary or Metastatic Bone Tumor Therapy Using Samarium-153-EDTMP

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Introduction

Primary bone tumors in dogs involves either the appendicular or axial skeleton with a bimodal peak age incidence of 1.5 and 8 years.^{1,2} Primary bone tumors in cats are rare.² An effective form of curative therapy for canine appendicular osteosarcoma has not been found.² External beam radiation therapy has been used with some success for palliation of bone pain associated with solitary appendicular sites of osteosarcoma.³ The overall incidence of gross metastatic lesions is noted to be less than 15% at presentation. Pulmonary micrometastatic disease is assumed at presentation, in the face of negative thoracic radiographs; and 90% of the dogs have died or been euthanized within 1 year when limb amputation is used.² Novel methods for treatment of primary osteosarcoma are always being evaluated; but to date, previous therapeutic regimens have not prolonged survival in dogs with osteosarcoma.² It has been shown that 7% of the dogs will have skeletal metastases at presentation and previous reports have recommended survey radiographs of long bones as well as skeletal scintigraphy using ^{99m}Tc-MDP for the evaluation of skeletal metastatic disease.^{2,4} Forrest et al, found that the larger the size of the radiographic lesion, high pretreatment ratios of tumor to adjacent nontumor bone ratios of ^{99m}Tc-MDP uptake and the ratio of the pre-post treatment (intra-arterial cisplatin prior to limb-sparing surgery) tumor/nontumor ratios were correlated with earlier metastatic disease. Also, the presence of skeletal metastases either at or within 6 months of presentation was correlated to poor outcome and decreased long-term survival.⁵ The true incidence of skeletal metastasis secondary to other primary tumors in dogs is not known, but urogenital and pulmonary carcinomas have been shown to metastasize to the appendicular and axial skeleton, with the initial presenting clinical sign being associated with bone pain from the metastatic disease.^{1,2}

In humans with aggressive appendicular osteosarcoma, similar patterns of treatment failure have been seen. Skeletal metastatic disease from a variety of carcinomas results in extreme bone pain and decreased quality of life prior to succumbing to systemic tumor burden. ¹⁵³Sm-EDTMP (ethylenediaminetetramethylene phosphonic acid, Lexitronam or Quadramet) has been shown to be effective for the control of bone pain associated with skeletal metas-

tases.^{6,7} ¹⁵³Sm-EDTMP has a high affinity for skeletal tissues where it concentrates in areas of increased osteoblastic activity by the process of chemisorption to exposed hydroxyapatite crystals.^{6,7}

Another therapeutic radiopharmaceutical that has been developed and evaluated is ¹⁸⁸Rhenium hydroxyethylidene diphosphonate (¹⁸⁸Re-HEDP). ¹⁸⁸Re is a product of a ¹⁸⁸W/¹⁸⁸Re generator, making delivery of the radionuclide easy and efficient. The physical decay characteristics, advantages, and disadvantages along with dose rates provided in humans are summarized in Table 23.1.¹ ¹⁸⁸Re-HEDP is similar to ¹⁵³Samarium-EDTMP in that both decay by β^- and gamma emissions. The gamma emissions have imaging characteristics that favors the use of an external gamma camera, which can then be used to follow localization of the radiopharmaceutical during treatment. Both therapeutic agents also have been shown to have similar skeletal tumor: non-tumor uptake patterns as ^{99m}Tc-MDP.^{8,9} ¹⁸⁸Re-HEDP has been shown to cause mild myelosuppression in humans with the nadir of platelet and leukocyte suppression at 2 to 4 weeks postadministration. The mean effective half-life ($T_{eff1/2}$) of ¹⁸⁸Re-HEDP for the whole body has been shown to be 11.6 hours, and the $T_{eff1/2}$ for skeletal metastatic lesions is 16 hours. Dose estimates for ¹⁸⁸Re-HEDP within skeletal lesions are 3.8 mGy/MBq and 41% of the ¹⁸⁸Re-HEDP is excreted in the urine within the first 8 hours. As with other diphosphonates, ¹⁸⁸Re-HEDP and ¹⁵³Samarium-EDTMP localization is dependent upon local blood flow and the rate of osteogenesis.^{8,9} The standard dosages used in humans for both of these radiopharmaceuticals have ranged from 1.0 to 2.5 mCi/kg or 37 to 93 MBq/kg. Both agents have similar response rates for the relief of bone pain associated with metastatic disease.

¹⁵³Samarium-EDTMP has been used in dogs. Initial studies in normal beagle dogs have shown that acute bone marrow suppression is seen within 2 weeks of injection; however, hematologic parameters returned to normal within 6 weeks. Additionally, 40 dogs with spontaneous skeletal tumors (appendicular and axial primary bone tumors as well as secondary bone invasion from soft tissue tumors and metastatic skeletal tumors) showed a variable response to treatment using 37 MBq/kg of ¹⁵³Sm-EDTMP. This study found that the appendicular tumors, in general, did not respond to therapy. Appendicular primary

Table 23.1: Comparison of Physical and Decay Characteristics and the Results of Human Studies

Radionuclide	Decay Mode	Physical Half-Life	Beta Minus Energy (% Abundance)	Gamma Energy	Beta Minus Range in Tissue	Mechanism of Localization	Dose Estimates	Advantages	Disadvantages
Ortho-P ³²	β^- only	14.3 days	$E_{\max} = 1.71$ MeV	NA	8 mm in soft tissue and 3 mm in bone	Chemisorption to hydroxyapatite	15-63 rad/mCi (0.004 cGy/MBq to 0.02 cGy/MBq)	79% response rate for skeletal metastases	Bone marrow suppression and pancytopenia (4-5 weeks postinjection); no imaging ability
⁸⁹ Strontium chloride	β^- only	50.6 days	$E_{\max} = 1.46$ MeV	NA	6 mm in soft tissue and 2 mm in bone	Calcium analog / exchange	850 rad/mCi (0.23 cGy/MBq)	78% response rate for skeletal metastases	No imaging capability
¹⁵³ Sm-EDTMP	β^- and gamma emissions	1.9 days	$E_{\max} = 0.81$ MeV $\beta_1 = 0.81$ (20%); $\beta_2 = 0.71$ (50%); $\beta_3 = 0.64$ (30%)	103 keV (29% abundance)	0.83 mm in soft tissue.	Chemisorption to hydroxyapatite	20-32 rad/mCi (0.005 cGy/MBq to 0.009 cGy/MBq)	76% response rate (skeletal metastases); can image for localization; rapid urinary clearance	Transient myelo-suppression (leukocytes and platelets) seen 2-4 weeks postinjection
¹⁸⁶ Re-HEDP	β^- and gamma emissions	3.8 days	$E_{\max} = 1.07$ MeV	137 keV (9% abundance)	1.0 mm in soft tissue and 0.5 mm in bone	Chemisorption to hydroxyapatite	NA	76% response rate; excellent correlation with ^{99m} Tc-MDP; capable of imaging for localization	Transient myelo-suppression
^{117m} Sn-DTPA	Beta minus and gamma emissions	13.6 days	0.16 MeV	159 keV (87% abundance)		Chemisorption to Hydroxyapatite	204 rad/mCi to tumor (0.06 cGy/MBq)	Imaging for localization.	Bone marrow transient suppression

bone tumors associated with substantial ossification (based on survey radiographs) exhibited a transient response to therapy, while large tumors with minimal bone formation tended to respond poorly. Small bone lesions with minimal lysis, metastatic lesions and axial skeletal lesions appeared to have a more favorable response. In another study, 9 dogs with primary bone tumors of the appendicular skeleton showed no clinical evidence of pain control in 8 of 9 dogs using a single injection of ^{153}Sm -EDTMP at a dose rate of 37 MBq/kg. In one dog, a tumor of scapula was shown to have undergone complete involution and was considered disease free for 20 months after injection. ^{153}Sm -EDTMP has been shown to have a deleterious effect on normal cartilage develop and maturation in immature rabbits.¹⁰ Other applications of ^{153}Sm -EDTMP therapy has included use of intra-articular injections for radiation synovectomy in advanced cases of osteoarthritis.¹¹⁻¹³

The potential role of ^{153}Sm -EDTMP in the treatment of bone tumors in small animals is discussed in the remaining sections. The dosage and potential complications associated with ^{153}Sm -EDTMP are included. The indications for radiotherapy using ^{153}Sm -EDTMP include treatment of bone pain associated with primary or metastatic bone lesions are summarized in Table 23.2.

^{153}Sm -ethylenediaminetetramethylene phosphonic acid (Lexidronam or Quadramet)

Physical Characteristics

^{153}Sm -EDTMP is a radiopharmaceutical that decays via β^- and gamma decay. Multiple medium-energy beta particles are emitted including: β_1 with an E_{max} of 0.81 MeV (20% abundance), β_2 with an E_{max} of 0.71 MeV (50% abundance), and β_3 with an E_{max} of 0.64 MeV (30% abundance). These β^- have a range of 0.83 mm in soft tissue and are responsible for localized cell damage. The physical half-life of the ^{153}Sm is 46.8 hours. In addition, a 103 keV gamma photon is emitted (28% abundance) allowing for imaging of the distribution of the radiopharmaceutical within the patient after injection using a standard planar gamma camera.¹⁴⁻¹⁶

Mechanism of Localization

^{153}Sm -EDTMP localizes to the trabecular and cortical bone by binding to exposed hydroxyapatite crystals. ^{153}Sm -EDTMP has been shown to correlate with $^{99\text{m}}\text{Tc}$ -MDP so that tumor-nontumor uptake in a group of human patients was shown to be 4.04 ± 2.6 for ^{153}Sm -EDTMP and 4.012 ± 1.9 for $^{99\text{m}}\text{Tc}$ -MDP.¹ Therefore, a $^{99\text{m}}\text{Tc}$ -MDP study should be done on all potential candidates for therapy and a negative $^{99\text{m}}\text{Tc}$ -MDP scintigraphic study would preclude the use of ^{153}Sm -EDTMP for systemic radiotherapy. In humans, there is rapid excretion of the ^{153}Sm -EDTMP, with reports of 9% to 64% excretion of the injected dose within 10 hours based on the tumor burden and degree of ^{153}Sm -EDTMP skeletal uptake.¹ Dose estimates for the tumor with ^{153}Sm -EDTMP uptake have been in the range of 20 to 32 rad/mCi injected or 0.05 to 0.09 cGy/MBq injection.¹

Dosage

Multiple dosing schedules were originally evaluated. These included single and multiple dosing schedules of the ^{153}Sm -EDTMP. Currently, the protocol is a single injection of ^{153}Sm -EDTMP at a dose of 37 MBq (1.0 mCi)/kg to be given intravenously.^{17,18} This dose will deliver approximately 40 Gy to any given bone lesion with ^{153}Sm -EDTMP uptake and an estimated dose of 250 cGy to normal bone and bone marrow.^{15,18,19} The results of all cases treated at the College of Veterinary Medicine University of Missouri, between 1993 and 2003, are summarized in Table 23.3.

Table 23.2: Indications for Treatment with ^{153}Sm -EDTMP

Treatment of primary or metastatic bone neoplasms in dogs, cats, and horses.
Treatment of soft tissue tumors with associated bone invasion.
Treatment of benign bone tumors of the dog, cat and horse.
May alleviate pain associated with severe degenerative joint disease. ¹⁻³

Table 23.3: Information About Patient's Treated With ^{153}Sm -EDTMP (1994-2003)

Patient	Age (years)	Location(s) of Tumor	Tumor Type	Tumor Staging (T1/T2/T3)	Time to Recurrence
C, DP	8.75	Pelvis	Osteosarcoma	NA	14 months
C, LR	6.25	Distal tibia	Osteosarcoma	T2	18 months
C, MX	5.75	Distal radius	Osteosarcoma	T3	7 months
C, MX	10	Skull, orbit	MLO	NA	14 months
C, DP	6.33	Distal radius	Osteosarcoma	T2	7 months
C, MX	5.7	Distal radius	Osteosarcoma	T2	6 months
F, British Blue	12	Maxilla	SCC	T3	6 months
C, MX	14	Mandible	Osteosarcoma	T3	NA
F, MX	15	Mandible	SCC	T3	2 years
C, LR	11	Distal radius	Osteosarcoma	T3	4 months
C, ES	11	Femoral head/neck	Osteosarcoma	T3	2 yrs
EQ, QH	5	Mandible	Ameloblastoma	T2	6 months
C, MX	4	Skull	MLO	T3	2 years
C, BMF	6	Distal tibia	Osteosarcoma	T2	5 months
C, BMF	0.67	Skull	MLO	T2	3 years
C, MX	6	Proximal tibia	Osteosarcoma	T3	NA
C, MX	8	Distal radius, distal tibia	Osteosarcoma	T2	6 months
C, DP	7	Proximal humerus	Osteosarcoma	T2	2 months
C, WH	13.25	Ulnar, spine, sacral, pelvis	TCC	T2	1 month
C, EN	15.8	Proximal humerus	Osteosarcoma	T2	1 month
C, LR	3.5	Frontal bone, zygomatic arch	MLO	T2	1.5 years

Table 23.3 continued: Information About Patient's Treated With ^{153}Sm -EDTMP (1994-2003)

C, MX	unknown	Distal femur	Osteosarcoma	T2	2 months
C, GS	8	Distal radius	Osteosarcoma	T2	2 months (pathologic fracture)
C, GR	5	Proximal humerus	Osteosarcoma	T3	6 months
C, IR	7.4	Proximal humerus	Osteosarcoma	T2	NA
C, RO	5.9	Retroorbital	MLO	T2	1 yr
C, GD	8.5	Proximal humerus	Osteosarcoma	T2	NA
C, MX	10	Distal tibia	Osteosarcoma	T3	6 months
C, GD	7	Distal radius	Osteosarcoma	T2	1 month
C, SB	9	Humerus	Osteosarcoma	T2	6 weeks
C, SB	8	Distal radius	Osteosarcoma	T2	7 months
F, DSH	7	Maxillary, frontal	Osteosarcoma	T2	7 months
C, MX	12	Palatine	Fibrosarcoma	T2	6 months
C, BS	2.5	Frontal bone	MLO	T2	3 months
C, LR	8	Distal radius, sternum, pulmonary metastases	Osteosarcoma	NA	4 months
C, CC	11	Maxilla	Osteosarcoma	T3	3 months
C, LR	6.4	Zygomatic arch, mandible	MLO	T3	NA
C, GR	9	Proximal humerus	Osteosarcoma	T2	NA
C, LR	13.7	Maxilla, tibia, radius/ulna	Osteosarcoma	T3	1 month
C, DM	6	Zygomatic arch	NA	T3	2 months
C, SB	8.7	Distal radius	Osteosarcoma	T2	1 month
C, LR	11.9	Proximal humerus	Osteosarcoma	T2	1 month
C, MX	12	Frontal bone	Osteochondrosarcoma	T2	2 years

Table 23.3 continued: Information About Patient's Treated With ^{153}Sm -EDTMP (1994-2003)

C, MX	14	Humeral diaphysis	Osteosarcoma	T3	6 months
C, LR	NA	Frontal bone, orbit	Chondrosarcoma	T2	2 yrs out
EQ, ARB	NA	Nasal	Osteoma	T2	1 month
C, GR	14	Proximal humerus	Osteosarcoma	T3	6 months
C, BT	7	Distal radius and tibial tuberosity	Osteosarcoma	T2	1 year
C, GS	11	Occipital bone	Osteosarcoma	T3	1 year
C, MX	9	Distal tibia	Osteosarcoma	T3	1 month
C, RO	10	Ischium and acetabulum	Osteosarcoma	T2	4 months
C, RO	9	Distal tibia	Osteosarcoma	T2	5 months
C, DP	8	Distal radius	Osteosarcoma	T2	4 months
C, MX	9	Maxilla	Osteosarcoma	T3	2 months
C, MX	8	Frontal	Osteosarcoma	T2	3 months
C, RO	11	Proximal and midhumerus	Osteosarcoma	T2	4 months
C, LR	11	Acetabulum	Osteosarcoma	T2	8 months
C, BCO	9	Distal radius	Osteosarcoma	T2	5 months
C, GD	5	Distal tibia	Osteosarcoma	T2	5 months
F, MX	6	Mandible	Osteoma	T2	3 months
C, NF	5	Distal radius	Osteosarcoma	T2	4 months
C, GP	7	Distal tibia	Osteosarcoma	T3	4 months
C, GR	3	Distal radius	Osteosarcoma	T3	4 months
C, BMF	7	Third metatarsal	Osteosarcoma	T3	10 months
C, MX	4	Mandible	Osteosarcoma	T3	6 months
C, ST	10	Temporal, occipital	MLO	T3	7 months

C = canine, F = feline, EQ = equine; SCC = squamous cell carcinoma, MLO = multilobular tumor of bone; T1 = no cortical involvement, T2 = cortical involvement, T3 = cortex broken through; NA = not available; TCC = transitional cell carcinoma. Breeds include: GD = Great Dane, MX = mixbreed; ST = standard poodle; GP = Great Pyrenes; NF = Newfoundland; BMF = Bull Mastiff; BCO = Border Collie; LR = Labrador Retriever; DP = Doberman Pincher; RO = Rottweiler; GS = German Shepherd; DP = Doberman Pinscher; IR = Irish Setter; ARB = Arabian; ES = English Setter; DSH = Domestic ShortHair; ES = English Sheepdog; SB = St. Bernard; DM = Dalmation; CC = Chow Chow; BS = Brittany Spaniel; WH = West Highland Terrier; EN = English Springer Spaniel; QH = quarter horse; GR = golden retriever.

Preparation and Administration

$^{152}\text{Sm}_2\text{O}_3$ is obtained as 99.06% enriched $^{153}\text{Sm}_2\text{O}_3$. The ^{153}Sm is prepared by neutron irradiation of ^{152}Sm -oxide target in a nuclear reactor, using thermal and resonance flux. The $^{152}\text{Sm}_2\text{O}_3$ is flame sealed into a quartz vial under a vacuum and then welded into an aluminum can. The sample is irradiated then opened and dissolved in hydrogen chloride and deionized water to a concentration of 1.2×10^{-3} M. To form the ^{153}Sm complex 20 to 85 mg/mL of ligand is used. The ^{153}Sm stock and carrier solution are added so that the final $[\text{Sm}]$ is 3×10^{-4} M with a specific activity of 1 to 10 mCi/ml (37 to 370 MBq/mL). The pH is adjusted to > 10 and the solution is heated to 60°C for approximately 30 minutes to facilitate chelation of the ^{153}Sm and the EDTMP. The final pH is adjusted to 7.0 with 4 to 5 M HCl.

The chelated ^{153}Sm -EDTMP and uncomplexed ^{153}Sm is separated with the use of a Sephadex cationic exchange column. The column is then eluted with isotonic saline. The elutions of ^{153}Sm are counted and the ^{153}Sm -EDTMP yield calculated from the formula:

$$^{153}\text{Sm}\text{-EDTMP}(\%) = (1 - \text{column counts/total counts}) \times 100.$$

The complex yields are reported to be have been shown to be 98% for ^{153}Sm -EDTMP, whereas other ligands have shown lower binding rates (^{153}Sm -NBTP [95.8%]; ^{153}Sm -MDP [97%], and ^{153}Sm -HDP [93%]).^{15,20}

Excretion

The excretion of unbound ^{153}Sm -EDTMP is via the kidneys. Blood clearance has been reported as 2% at one hour, postintravenous administration in rats and 1% of the injected dose at 5 hours in humans.^{4,5,10} Excretion via the kidneys and is complete by 96 hours. The ^{153}Sm -EDTMP complex binds to the inorganic matrix of bone and is very slowly released.

Radiation Safety/Patient Isolation

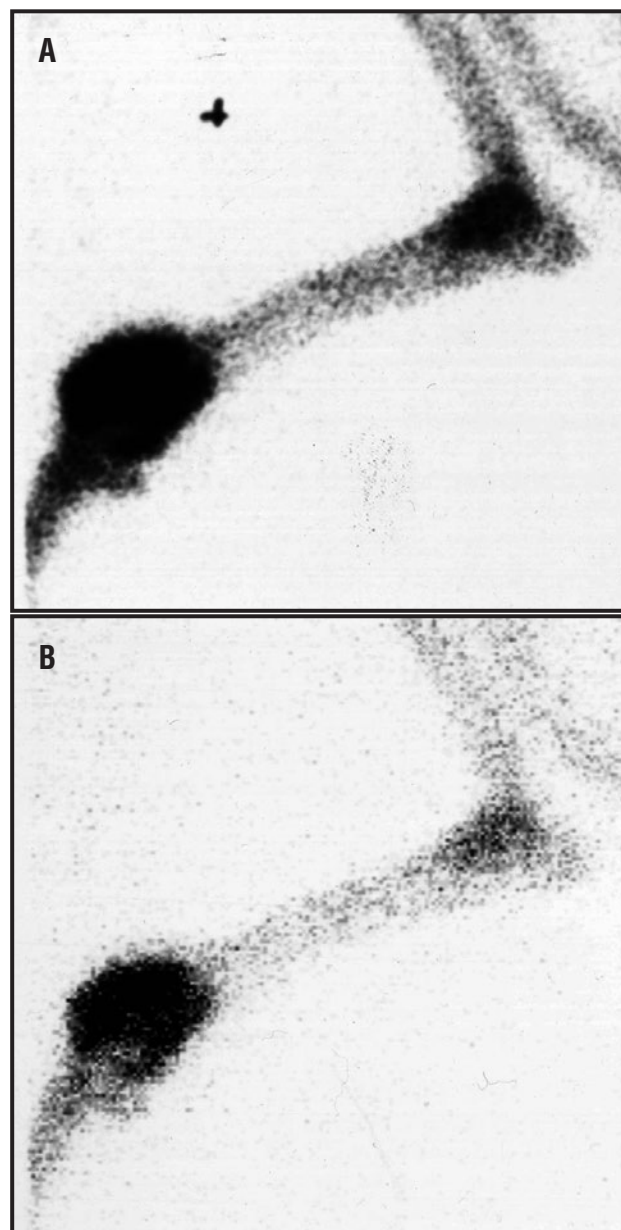
Veterinary patients are isolated for an average period of 5 days at the University of Missouri College of Veterinary Medicine, with a release criteria of 5 mR/hr at 1 meter. This is dependent on the injected dose, rate of excretion (biological half-life), and the specific release criteria for the College. Patients are housed in a radiation isolation area with waste

handled appropriately in bags marked for radioactive materials, which are disposed of after being allowed to decay to background for 10 physical half-lives (20 days).

Species Differences and Complications

Figure 23.1: Comparison of $^{99\text{m}}\text{Tc}$ -MDP skeletal scintigraphy (A) done prior to therapy and a ^{153}Sm -EDTMP scintigraphic bone scan (B) done 2 days after intravenous administration of 740 MBq (20 mCi, B)

There is intense uptake of both radiopharmaceuticals within the distal left radius. The radiographic changes are consistent with an osteosarcoma.



Dogs have a dramatic myelosuppression that is seen between 2 and 4 weeks postintravenous administration.¹⁵⁻¹⁸ Humans and horses that have been treated with ¹⁵³Sm-EDTMP have shown a drop in white blood cell and platelet counts, but most patients do not exhibit clinical signs of the lowered cell counts.¹⁵ Cats that have been treated with ¹⁵³Sm-EDTMP do not exhibit a decrease in white blood cell counts or platelet counts.

Role of Skeletal Scintigraphy in Radiotherapy

¹⁵³Sm-EDTMP uptake has been shown to correlate extremely well with the uptake of ^{99m}Tc-HDP and ^{99m}Tc-MDP used in bone scintigraphy (Figure 23.1).⁴ Skeletal scintigraphy should be done prior to treating animals with ¹⁵³Sm-EDTMP to ensure tumor localization of the ^{99m}Tc-MDP. Two days after administration of the ¹⁵³Sm-EDTMP, one should also image the patient using planar static imaging techniques to ensure that uptake in the areas previously identified on the skeletal scintigraphy are present.

Patient Selection Criteria

The best candidates for samarium radiotherapy are patients that have primary bone tumors with primarily osteoproliferation and uniform radiopharmaceutical uptake of ^{99m}Tc-MDP. The cortex of the diseased bone should be intact. Cortical destruction (at least in appendicular tumors) has been shown to be a negative predictor of tumor lesion response to ¹⁵³Sm-EDTMP radiotherapy.^{17,18}

Axillary skeletal tumors, primarily skull and mandibular tumors, appear to be more responsive than appendicular bone tumors.¹⁸ Benign disfiguring tumors, such as ameloblastoma and multilobular tumor of bone (in the few cases treated to date), have been radiosensitive to ¹⁵³Sm-EDTMP treatment. Small metastatic bone lesions that are noted to have marked uptake patterns seen on ^{99m}Tc-MDP skeletal scintigraphy, appear to be radiosensitive and respond to ¹⁵³Sm-EDTMP treatment (Figure 23.2). The treatment of bone pain associated with metastatic bone lesions is the primary indication for using ¹⁵³Sm-EDTMP in human medicine. As a rule, multiple myelomas and other myelogenous tumors do not appear to be as radiosensitive or responsive to

¹⁵³Sm-EDTMP radiotherapy. Other invasive soft tissue tumors, such as squamous cell carcinomas, which have documented patterns of increased ^{99m}Tc-MDP uptake, also appear to respond to ¹⁵³Sm-EDTMP radiotherapy at the current dosing protocol.

¹⁵³Sm-EDTMP treatment can also be used as an adjunctive treatment to extend the length of response by bone tumors to external beam radiation therapy. This appears to be an effective treatment for animals with relatively early diseases based on radiographs, where amputation of the affected limb is not an option. Unresectable lesions of the axial skeleton may also benefit from a combination of ¹⁵³Sm-EDTMP and external beam radiation therapy treatments. Randomized clinical trials have not been completed to date in veterinary medicine, so the true role for ¹⁵³Sm-EDTMP radiotherapy in the treatment of bone tumors or tumors that involve bone has yet to be defined. In one case report, a dog with local relapse of an osteosarcoma after previous partial maxillectomy was given two ¹⁵³Sm-EDTMP dosages of 1.5 mCi/kg or 45 MBq/kg body weight at time 0 and 15 weeks later.²² There was no tumor recurrence noted locally or distantly at 21 months after surgery and therapy.²²

Rationale and Specific Goals for Treatment of Skeletal Tumors

One of the primary goals for treatment in humans as well in animals is for control of skeletal pain associated with the tumor lesions. In humans and dogs, the administration of ¹⁵³Sm-EDTMP has been shown to reduce tumor-associated skeletal pain, thereby making the patient more comfortable.^{7,8} However, this response again appears to be dependent upon the tumor location (appendicular versus axial) as only one of nine dogs showed any degree of appreciable pain control. The mean survival time in dogs that have been treated with ¹⁵³Sm-EDTMP radiotherapy for primary bone tumors without cortical breakthrough (T1 lesions) is 27 months.⁸

Summary

¹⁵³Sm-EDTMP is a good radiotherapy option for animals with primary benign or malignant and metastatic bone tumors of the axial and appendicular skeleton. ¹⁵³Sm can be used as a single therapy or in conjunction with external beam irradiation

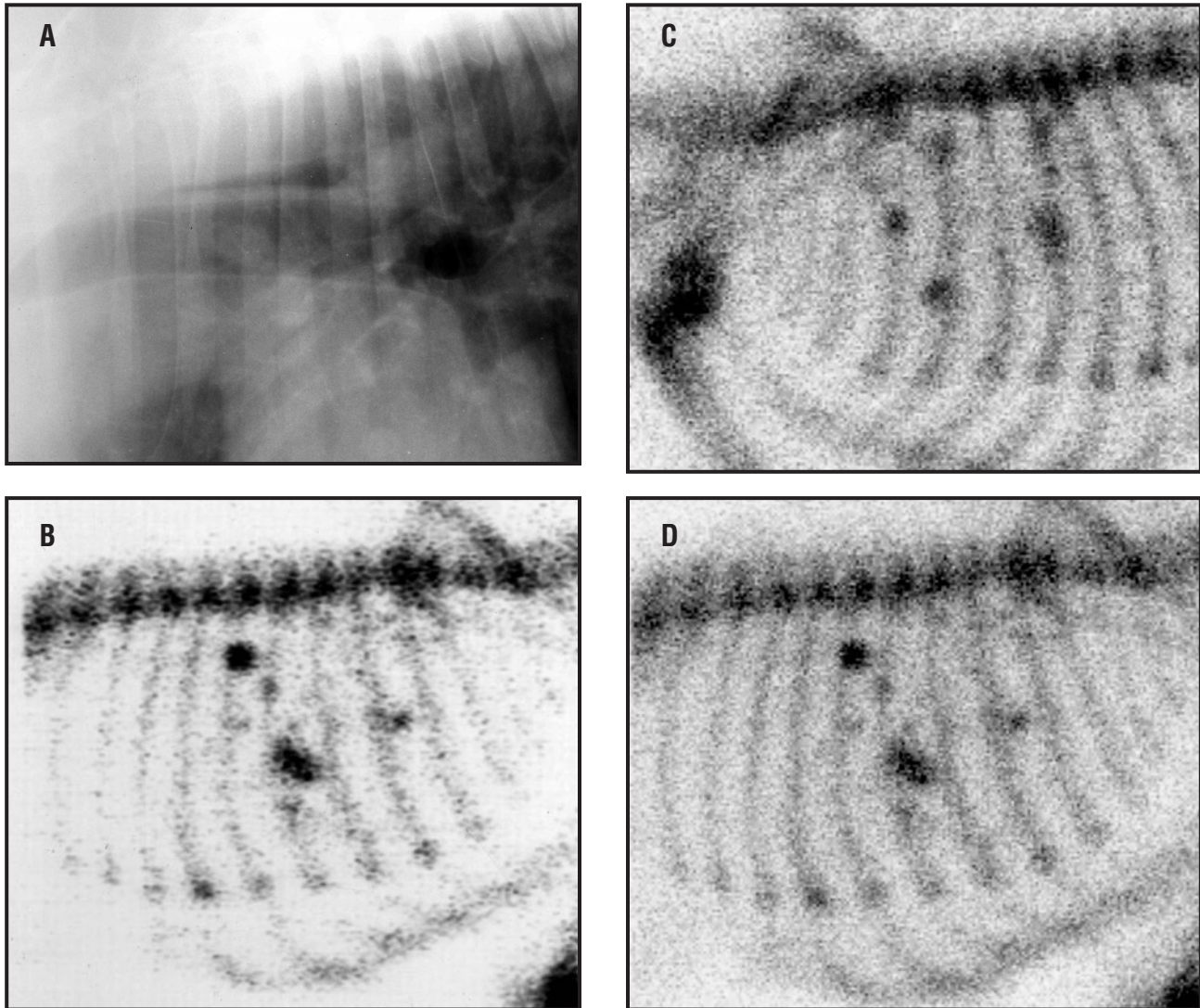


Figure 23.2: A dog with pulmonary metastatic osteosarcoma

A, Left lateral thoracic radiograph. **B**, right Lateral bone scan image obtained 2 hours after intravenous injection of ^{99m}Tc -MDP. There is radiopharmaceutical uptake within the pulmonary metastatic nodules. Left and right lateral images (**C** and **D**, respectively) document radiopharmaceutical accumulation within the same lung lesions 2 days after injection of ^{153}Sm -EDTMP.



Figure 23.3: “Superscan” of a dog with diffuse bone metastases from a primary osteosarcoma

On this left lateral, whole body image, there is disseminated, abnormal axial and appendicular skeletal uptake of the ^{153}Sm -EDTMP with no soft tissue radioactivity. Also, no radioactivity is seen within the kidneys or urinary bladder. This image was obtained two days after injection of ^{153}Sm -EDTMP.

or chemotherapy. It appears to be useful to those patients for which amputation, and limb-sparing or other surgical options are not viable options. It is best used in cases of osteoproliferative lesions with minimal osteolysis that have a homogeneous pattern of ^{99m}Tc -MDP uptake. The primary disadvantages include: length of hospitalization, radiation safety, myelosuppression, and cost (\$3500 per dose). Future investigations using combinations of ^{153}Sm -EDTMP and external beam radiation therapy or multiple dose treatments need to be evaluated.

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