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*REVIEW ARTICLE*

# Nuclear Imaging Modalities and Radiopharmaceuticals in Veterinary Medicine

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***Nuclear Imaging Modalities and Radiopharmaceuticals in Veterinary Medicine***

***SUMMARY***

*Nuclear imaging modalities are based on radiopharmaceutical accumulation in organs and are imaged by a scintillation gamma camera and these radiopharmaceuticals consist of radionuclidic and pharmaceutical parts. Compared with other imaging modalities such as computed tomography (CT), nuclear imaging provides pathophysiological and morphological information. These applications as positron emission tomography (PET) and single photon emission computed tomography (SPECT) in veterinary medicine have been gaining attention for several decades, although some disadvantages, such as a lack of equipment and staff in veterinary science and high costs. This may be due to the pet industry's growth, the number of pet owners, and developed technologies. In this review, nuclear imaging techniques in veterinary medicine were examined and frequently used radiopharmaceuticals were included. Apart from preclinical studies, it has been observed how important the research in this field is relatively new, especially considering that the use of nuclear medicine applications in clinical veterinary.*

***Key Words:*** *Radiopharmaceuticals, veterinary nuclear medicine, positron emission tomography, Technetium-99m, scintigraphy, nuclear imaging modalities.*

***Veteriner Hekimliğinde Nükleer Görüntüleme Yöntemleri ve Radyofarmasötikler***

***ÖZ***

*Nükleer görüntüleme yöntemleri, organlarda radyofarmasötik birikimine ve organların bir sintilasyon gama kamerasıyla görüntülenmesine dayanmaktadır. Bu radyofarmasötikler radyonüklidik ve farmasötik parçalardan oluşur. Bilgisayarlı Tomografi (BT) gibi diğer görüntüleme yöntemleriyle karşılaştırıldığında nükleer görüntüleme patofizyolojik ve morfolojik bilgiler sağlar. Veteriner hekimliğindeki bu uygulamaların (pozitron emisyon tomografisi (PET) ve tek foton emisyon bilgisayarlı tomografisi (SPECT)) kullanımı, ekipman ve personel eksikliği, yüksek maliyetler gibi bazı dezavantajları olmasına rağmen son yıllarda giderek artmaktadır. Bunun nedeni evcil hayvan endüstrisinin büyümesi, evcil hayvan sahiplerinin sayısı ve geliştirilen teknolojiler olarak sıralanabilir. Bu derlemede, veteriner hekimliğinde nükleer görüntüleme teknikleri incelenmiş ve sıklıkla kullanılan radyofarmasötikler dahil edilmiştir. Klinik öncesi çalışmalar dışında, özellikle klinik veterinerlikte nükleer tıp uygulamalarının kullanımının, bu alandaki araştırmaların nispeten yeni olması nedeniyle ne kadar önemli olduğu görülmüştür.*

***Anahtar Kelimeler:*** *Radyofarmasötikler, veterinerlikte nükleer tıp, pozitron emisyon tomografisi, teknesyum-99m, sintigrafi, nükleer görüntüleme yöntemleri.*

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## INTRODUCTION

Nuclear imaging modalities are not commonly used in veterinary medicine due to high costs and strict regulations (Greco, Meomartino, Gnudi, Brunetti, & Di Giancamillo, 2023). However, they (PET, SPECT and their combinations with CT) show increasing usage in veterinary medicine research and clinics (Rowe et al., 2013). Nuclear medicine in veterinary science follows the development and trends in human medicine and it is rapidly developing.

Regulations and protocols in nuclear medicine in veterinary are governed by the rules of the International Atomic Energy Agency (IAEA) and should follow published protocols and regulations by national authorities as in human nuclear medicine applications (Milardovic, 2021). IAEA also published a report entitled "Radiation Protection and Safety in Veterinary Medicine," which explains general requirements and principles of nuclear imaging in veterinary medicine and radiation protection for practitioners (IAEA, 2021).

Nuclear imaging modalities are considered safe, non-invasive and highly sensitive for early detection of diseases. However, regulations and protocols published by IAEA or other authorities should be followed for the safety of animals, owners and practitioners. Nuclear imaging modalities are mostly used for clinical purposes/diagnosis of diseases in large-sized animals, while used for disease research/preclinical purposes for small-sized animals. After a radiopharmaceutical application, animals' urine, feces, sweat and saliva become radioactive due to the excretion/elimination of radiopharmaceuticals. Small animals can be removed after the imaging process, and they are generally controlled by their owners/handlers, unlike larger animals such as horses. Bigger animals should be followed 24 hours after the imaging process (Lattimer, 2022; Milardovic, 2021). Clinically, thyroid glands, bones, kidneys and livers were the most imaged organs in veterinary medicine (Milardovic, 2021).

The most common usage of scintigraphy in veterinary is bone scintigraphy, especially for horses. Bone damage in racehorses can easily be detected with these imaging methods. Scintigraphy in veterinary medicine provides many advantages over traditional diagnostic modalities: 1. More sensitive for bone damage than radiographs; 2. Gamma cameras can be located anywhere on the horse's body; so any part of the body can be imaged; 3. Subtle lameness can be detected with gamma cameras, while only visible lameness can be detected with other traditional methods; 4. Blood flow can be traceable to the distal limb which is very helpful for some of the injuries and time lost for blood supply can be detected. Thyroid, portal, renal scintigraphies and glomerular filtration rate (GFR) determinations are the other common nuclear imaging procedures in veterinary medicine (Centre).

## PET IMAGING

PET imaging plays an important role in diagnosing, monitoring, staging and therapy planning of diseases. It provides functional information besides the structural information (Yitbarek & Dagnaw, 2022). Although PET imaging applications focused on oncology, it has also been used for nononcologic diseases such as neurology, inflammation detection, and lameness evaluation in veterinary medicine (Yitbarek & Dagnaw, 2022).

PET is based on two 511 keV photons detected by a scanner. PET radionuclides emit positrons, and this positron is annihilated with an electron after its travel. Then, two 511 keV photons with opposite directions occur. These photons are detected by two detectors, and data is collected from many angles around the body (Saha, 2018; Sharp & Welch, 2005).

The first PET/CT scanning was started to use in 2001, and the number of PET/CT centers around the world has increased rapidly since then. Some of these facilities are trying to provide these techniques to veterinary medicine as well as human medicine with little differences (Table 1) (Figure 1) (Lawrence, Rohren, & Provenzale, 2010).

**Figure 1.** A dog undergoing PET/CT scaning (Reproduced with permission from Lawrence et al.,2010) (Lawrence et al., 2010).

PET imaging modality, especially the combination of PET and CT in veterinary medicine, shows increased popularity nowadays. The increasing number of people with pets, caused development in technology leading to the increase in to applications and developments in veterinary medicine (Martinez et al., 2012).

**Table 1.** Comparison of nuclear imaging in veterinary and human medicine.

| Nuclear imaging in veterinary medicine | Nuclear imaging in human medicine |
|---|---|
| Animals are mostly required to be anesthetized. | Patients do not need to be anesthetized. |
| There is no standartized PET/CT protocols. | There are standartized PET/CT protocols. |
| High cost. | Relatively high cost. |
| Veterinary staff are exposed to radiation for longer periods. | Staff are exposed to radiation for shorter periods. |
| Used both in preclinical and clinical studies. | Used both in preclinical and clinical studies. |
| After imaging process, animals have to be hospitalized to avoid radiation exposure. | No need to be hospitalized. |
| Same rules and regulations should be followed. | |

**Radiopharmaceuticals Used for Veterinary Medicine**

***$^{18}$F-fluorodeoxyglucose (FDG)***

$^{18}$F-FDG is the common radiopharmaceutical used in human medicine to detect cells with high metabolic activity such as tumours, inflamed cells, heart and brain while used for tumour detection, cardiac and neuroimaging in veterinary medicine. It is a glucose analogue and transported into the cells via glucose transporter-1 (GLUT-1) and GLUT-6 which are transporter proteins (Lawrence et al., 2010). Adenocarcinoma, lung tumours, lymphoma, melanoma etc. can also be detected and staged in veterinary medicine by using a PET/CT agent like $^{18}$F-FDG due to their increasing glucose consumption (Greco et al., 2023).

The standardized uptake value (SUV) is the measurement value of radiopharmaceutical uptake in tissues/organs and shows tracer activity. It is a common parameter and helpful guide in clinical decisions (Rohren, Turkington, & Coleman, 2004). SUVs of osteosarcoma, lymphoma, blastomycosis, pulmonary carcinoma and soft tissue carcinoma in healthy dogs have been calculated in several studies. Also, SUVs of parenchymal organs were found similar in healthy humans and dogs by LeBlanc and co-workers (LeBanc, Jakoby, Townsend, & Daniel, 2008). However, some differences were determined in the SUV of healthy cats from healthy dogs and humans. Lower average hepatic and renal uptake was found compared with dogs and humans. Also, higher cardiac uptake was observed in cats rather than dogs and humans after 12-18 hours of fasting (LeBlanc et al., 2009).

***$^{18}$F-Sodium Fluoride (NaF)***

Orthopedic imaging is getting increased usage in veterinary nuclear medicine. $^{18}$F-NaF provides bone remodeling, bone tumours detection in veterinary medicine and horse lameness imaging (Yitbarek & Dagnaw, 2022). $^{18}$F-NaF was a common skeletal imaging agent in the 60's. However, it is considered as an alternative radiopharmaceutical to Technetium-99m ($^{99m}$Tc)- methylene diphosphonate (MDP) when high spatial resolution and higher sensitivity are required due to the cost and availability. Currently, it has become popular in bone imaging again because of the developments in technology with PET/CT (Li, Schiepers, Lake, Dadparvar, & Berenji, 2012; Valdés-Martínez et al., 2012). Moreover, $^{18}$F-NaF provides higher and faster bone uptake with a rapid clearance which causes a high bone/background ratio (Lawrence et al., 2010).

***$^{18}$F-3'-Deoxy-3'-Fluorothymidine ($^{18}$F-FLT)***

$^{18}$F-FLT is a thymidine analog, and plays a role in DNA synthesis as a thymidine substrate. $^{18}$F-FLT is trapped in cells due to phosphorylation by thymidine kinase 1; thus PET images are obtained. The early preclinical studies, for veterinary usage of $^{18}$F-FLT, showed promising results in the characterization of neoplastic diseases and the evaluation of therapeutic responses in dogs (Rowe et al., 2013; Shields et al., 2002). Besides, $^{18}$F-FLT is also very useful for neoplastic lesion detection, and therapy monitoring in dogs with lymphoma, sarcoma and carcinoma. Based on this information, $^{18}$F-FLT was also investigated by Rowe and co-workers in healthy cats to provide information for potential clinical applications in a cat species (Rowe et al., 2013). $^{18}$F-FLT is a promising agent for also dogs with lymphoma for monitoring the therapy protocol (Figure 2) (Lawrence et al., 2009).

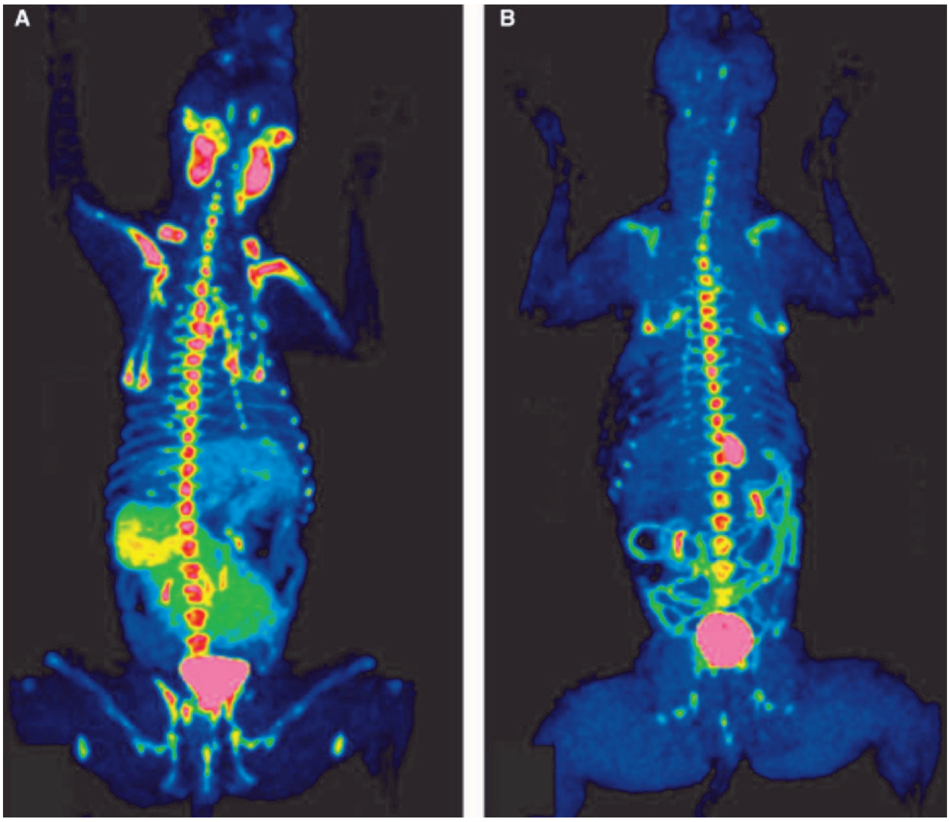


**Figure 2.** $^{18}$F-FLT PET/CT images of a Golden Retriever with Non-Hodgkin's Lymphoma; (A) before therapy (B) after 3 weeks of chemotherapy (Reused with permission from Lawrence et al.,2009) (Lawrence et al., 2009).

$^{18}$F-FLT also showed higher specificity in cancer types -metastatic to lymph nodes- or caused by an inflammatory response- compared with $^{18}$F-FDG (LeBlanc & Peremans, 2014).

***Copper-64 ($^{64}$Cu)-diacetyl-bis-N4-methylthiosemicarbazone (ATSM)***

It is the other PET radiopharmaceutical used for hypoxia and an effective marker to depict hypoxic tissue (Black, McJames, Rust, & Kadrmas, 2008). It shows high trapping in hypoxic tissues while rapid clearance in normal tissues (Hansen et al., 2012; Hetrick, Kraft, & Johnson, 2015).

## NUCLEAR SCINTIGRAPHY and SPECT IMAGING

The planar imaging system is a two-dimensional imaging modality that consists of a collimator filter, scintillator crystal and photomultiplier tubes, and a 2D gamma camera (Mattoon & Bryan, 2013). Even though planar imaging modalities have been used for years in veterinary medicine. Scintigraphy is the most sensitive imaging technique for detecting rib fractures in horses (Spriet & Vandenberghe, 2024).

SPECT is a three-dimensional imaging modality that is acquired with a gamma camera and reconstruction of a three-dimensional image volume. Multiple cameras rotate around the patients and provide information about the uptake of radiopharmaceuticals. The most common SPECT radionuclide is $^{99m}$Tc in both human and veterinary medicine (Sarcan & ÖZer, 2023). SPECT imaging is only used for lameness diagnosis in horses and several diseases of small animals (Figure 3) (Yitbarek & Dagnaw, 2022). However, SPECT has an increasing interest in veterinary clinical settings (Yitbarek & Dagnaw, 2022).

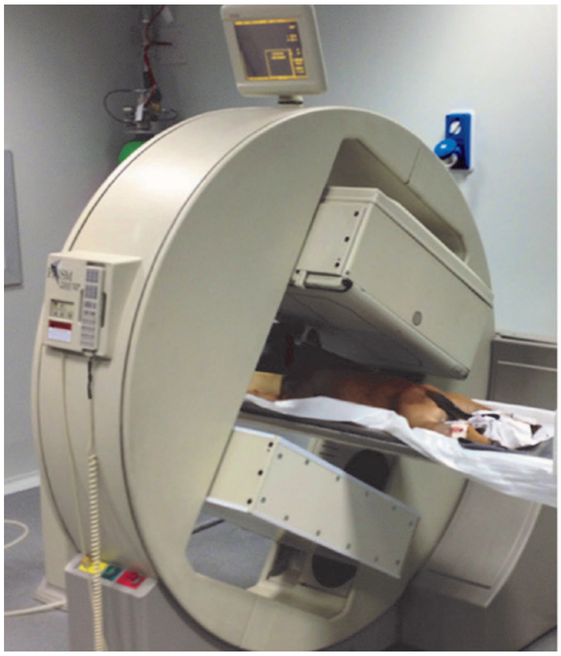

**Figure 3.** A dog underwent SPECT scan [Reused from Greco et al. 2023 under CC-BY-NC-ND] (Greco et al., 2023).

***Renal Imaging***

The earlier SPECT application in veterinary medicine is renal morphologic imaging. $^{99m}$Tc radiolabelled diethylenetriaminepentaacetic acid (DTPA), glucoheptonate (GH), dimercaptosuccinic acid (DMSA), and mercaptoacetyltriglycine (MAG3) are used for renal morphologic imaging (Balogh et al., 1999). These agents provide dynamic images to assess renal flow, the function of renal parenchyma and real-time GFR (Milardovic, 2021). GFR determination with imaging procedure, is one of the best ways to estimate renal function and early kidney diseases in dogs and cats. Renal scintigraphy also provides individual and total kidney function in dogs and cats, which makes it more advantageous than other imaging modalities (Peterson).

$^{99m}$Tc-DTPA is used in various animal species; however, GFR measurement could be changed according to the animal species; because plasma protein binding affects the GFR measurements. If the $^{99m}$Tc-DTPA binds the plasma proteins, GFR could be reduced and falsely measured (Tyson & Daniel, 2014). Among these renal imaging SPECT agents, $^{99m}$Tc-DMSA was detected earlier for renal tubular damage caused by gentamicin in dogs, compared with $^{99m}$Tc-DTPA and $^{99m}$Tc-MAG3 (Lora-Michiels, Anzola, Amaya, & Solano, 2001).

***Liver Imaging***

Portal scintigraphy is another modality frequently used in veterinary medicine, especially in diagnosing portosystemic shunt (Figure 4) (Morandi, 2014). It has also been used for liver function quantification and biliary tract assessment in dogs and cats.

Studies proved that hepatobiliary scintigraphy showed high sensitivity (83%) and specificity (94%) for extrahepatic biliary obstruction in veterinary practice (Kozat & Sepehrizadeh, 2017). Portal circulation is blood flow from blood vessels to the stomach, intestines and ends with the liver and heart. Portosystemic shunt is the abnormal portal circulation and commonly seen in dogs, cats, pigs, foals and calves. $^{99m}$Tc-sulfur-colloid is one of the first radiopharmaceuticals used for a portosystemic shunt in dogs in the early 80s. $^{99m}$Tc-pertechnetate, $^{99m}$Tc-iminodiacetic acid (IDA) derivatives, $^{99m}$Tc-mebrofenin and $^{99m}$Tc-disofenin have been investigated as portal scintigraphy agents. In comparison of two, $^{99m}$Tc-mebrofenin provides better morphologic images than $^{99m}$Tc-disofenin (Morandi, 2014).

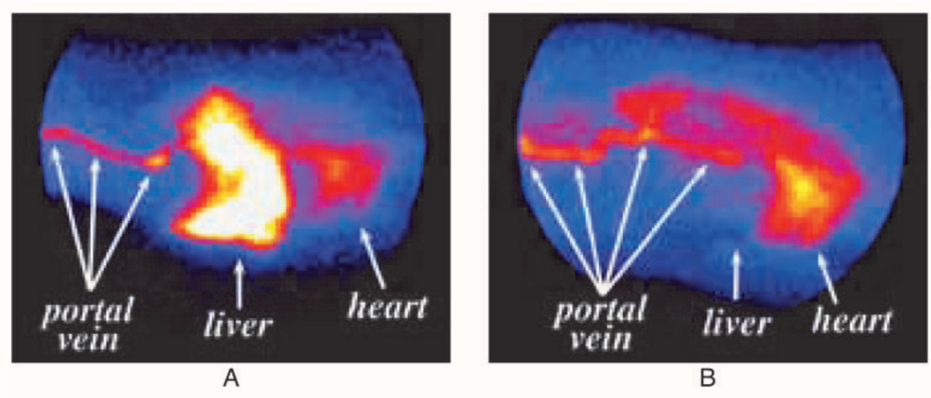


**Figure 4.** Portal scintigraphy of (A) a healthy dog (B) a dog with a portosystemic shunt [Reused from the document on website] (Peterson).

***Lung Imaging***

Lung tumours and lymph node metastasis are hardly prognosed and defined in dogs. Intrathoracic biopsy of lymph nodes is recommended; however, there is no specific guide for it. For this purpose, $^{99m}$Tc-sulfur colloid has been investigated as a SPECT agent for mapping thoracic lymphadenectomy in dogs (Tuohy & Worley, 2014).

***Thyroid Imaging***

Thyroid scintigraphy is frequently performed in veterinary nuclear medicine because thyroid diseases are common in dogs and cats and are also reported in other animal species (Daniel & Neelis, 2014; Kintzer & Peterson, 1994). Immune-mediated thyroiditis and idiopathic atrophy are commonly seen in dogs, while adenomatous hyperplasia and hyperthyroidism are common in cats (Rand, Behrend, Gunn-Moore, & Campbell-Ward, 2013).

Hyperthyroidism is one of the most common endocrine disorders in aging cats, and generally, thyroid adenoma and/or adenomatous hyperplasia are seen (Figure 5). Thyroid scintigraphy is mostly performed in cats and it is considered as a gold standard for the diagnosis of hyperthyroidism (Lim, Lee, Cho, & Nam, 2021). $^{99m}$Tc-pertechnetate is the first choice in veterinary nuclear imaging for diagnosing thyroid diseases rather than radioiodine due to availability and low cost (LeBlanc & Peremans, 2014). However, $^{123}$I provides a higher target/background ratio compared with $^{99m}$Tc-pertechnetate. Thyroid images are taken after 20 minutes of radiopharmaceutical administration, and because of the short scanning process (approx. 3 minutes) sedation is not required (Peterson).

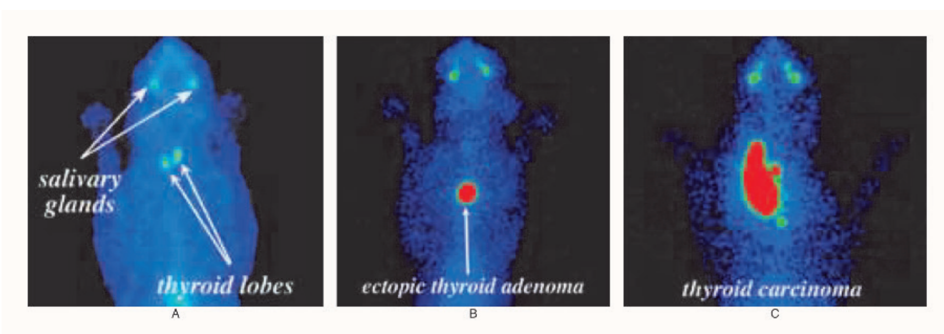


**Figure 5.** Thyroid scintigraphy of (A) healthy cat (B) hyperthyroid cat with thyroid adenoma (C) hyperthyroid cat with thyroid carcinoma [Reused from the document on the website] (Peterson).

Most thyroid tumours in dogs do not cause hyperthyroidism, so, quantitative imaging is required for hyperthyroidism in dogs.

Thyroid scintigraphy is considered the best imaging technique for dogs compared to other techniques and shows the size of the primary tumour and metastases location in %65 of dogs (Peterson). Moreover, it provides much information about thyroid gland functions, detection, and localization of thyroid tissues (Huaijantung, 2015).

***Skeletal Imaging***

Bone scintigraphy is a common procedure for infection, tumour and arthritis diagnosis in veterinary medicine (Huaijantung, 2015). It also shows high sensitivity for the diagnosis of bone injury due to the ability of osteoblastic activity detection (Trope, Anderson, & Whitton, 2011).

$^{99m}$Tc-MDP (Geissbuhler, Busato, & Ueltschi, 1998) and $^{99m}$Tc-hydroxymethylene diphosphonate (HDP) (Levine, Ross, Ross, Richardson, & Martin, 2007) are common agents for scintigraphy of horses (especially racehorses) (Figure 6A) and dogs (Figure 6B) and provide accurate images of the upper limb, pelvis and vertebral column in stress fractures and bone injuries (Cook & Cook, 2009). Besides bone injury, bone infection may also be detected in the early stages by using bone scintigraphy.

Bone scintigraphy is performed in 3 phases:

Phase I (Vascular Phase): arteries and veins are seen right after the administration of radiopharmaceuticals;

Phase II (Soft Tissue Phase): also known as the soft tissue phase, is the biodistribution of radiopharmaceuticals in the extracellular space of tissues;

Phase III (Bone phase): the detection phase of bone abnormalities/damages.

Three-phase scintigraphy may provide more information about the muscle in addition to the bone. Bone scintigraphy is also a very useful procedure for primary and metastatic bone tumours due to the osteoblastic activity of bone (Drost, Cummings, Mathew, Panciera, & Ko, 2003; Trope et al., 2011).

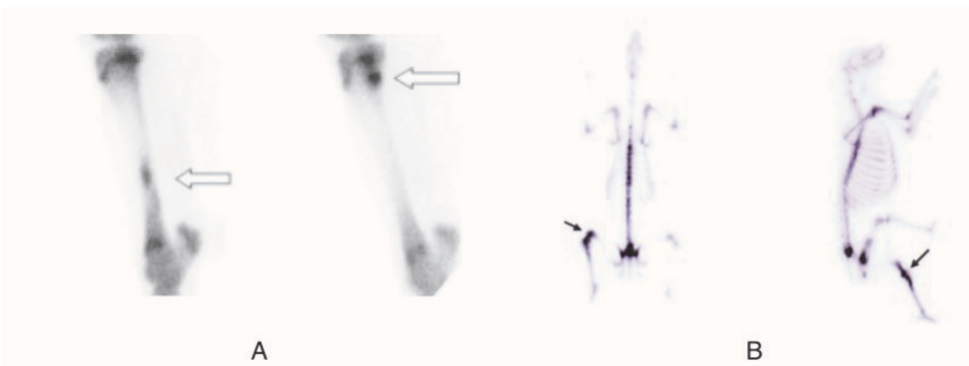


**Figure 6.** Bone scintigraphy (A) of a racehorse (spot views, hot spots: tibial stress fracture), (B) of a dog (total body, primary osteosarcoma in left knee) [Adapted from Milardovic, 2021 under CC BY 4.0] (Milardovic, 2021).

For the first time in literature, $^{99m}$Tc-MDP was studied to detect early bone lesions and their time frame of onset of the infection in *Hepatozoon Americanum* infected dogs. Bone scintigraphy was found to be a viable option for detecting *H. Americanum* bone lesions by researchers due to the characteristics of *H. Americanum* bone lesions with polyostotic, high-intensity lesions(Drost et al., 2003).

***Brain Imaging***

$^{99m}$Tc-hexamethylpropylenamine oxime (HMPAO) and $^{99m}$Tc-ethyl cysteinatedimer (ECD) are the brain perfusion imaging agents that can be used in dogs' brain imaging. When the regional cerebral blood flow of $^{99m}$Tc-ECD and $^{99m}$Tc-HMPAO was compared, the tracers' regional distributions were found to be different which means direct comparison of these tracers is not possible in dogs like humans. Besides, $^{99m}$Tc-ECD uptake and washout rate were found to be more rapid than $^{99m}$Tc-HMPAO in dogs and provided better quality images (Waelbers, Peremans, Vermeire, Piron, & Polis, 2012). In addition, $^{99m}$Tc-DTPA, $^{99m}$Tc-GH and $^{99m}$Tc-pertechnetate are common agents for brain imaging in veterinary medicine due to their lower price (Balogh et al., 1999)

## CONCLUSION

Nuclear medicine, one of the most frequently used and crucial imaging methods in human medicine, is becoming more widely used in veterinary medicine. It has been used limitedly in veterinary medicine because of high cost, lack of equipment and lack of trained personnel. However, due to developing technologies, growing pet industry, and increasing pet owner numbers, nuclear imaging methods have become widespread in veterinary medicine. In particular, high sensitivity, high resolution, and the availability of static imaging (a snapshot of the radiopharmaceutical distribution within a part of the body) as well as dynamic imaging (the imaging which administration of radiopharmaceuticals to patient over a specific period during nuclear imaging test) opportunities provide a significant advantage in this regard.

Although preclinical studies are frequently performed, the clinical usage of PET, SPECT in veterinary medicine is still limited. Although the high cost of new radiopharmaceuticals usage in nuclear imaging in veterinary, “old” radiopharmaceuticals ($^{99m}$Tc-pertechnetate, $^{99m}$Tc-ECD, $^{99m}$Tc-HDP, $^{99m}$Tc-MDP, $^{99m}$Tc-GH) are widely used. It is expected that these techniques will be used more frequently as the prices of radiopharmaceuticals and the costs of nuclear imaging methods decrease with developing technologies and opportunities. It is essential to conduct more studies in this field and to evaluate the results obtained by applying radiopharmaceuticals used in humans to veterinary medicine.

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## AUTHOR CONTRIBUTION RATE STATEMENT

Conception (AYÖ), Literature research and writing (ETS), Reviewing the text (AYÖ, ETS), Supervision (AYÖ).

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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