State-of-the-Art Nuclear Medicine:

SPECT and SPECT/CT Imaging

An introduction to Mainstay Diagnostic Testing in Non-invasive Medicine

White Paper

Association of Imaging Producers & Equipment Suppliers
(European Industrial Association for Nuclear Medicine and Molecular Healthcare)

An initiative of the AIPES NewTech Working Group

Introduction

Until the end of the 1800s, Medical Imaging entailed invasive and potentially harmful diagnostic procedures. In lack of efficient diagnostic tests, diseases were frequently missed or else diagnosed long after their onset. During the last century, however, medical imaging technology has progressed rapidly, and both medicine and human life have been positively affected to an extent never seen before. As a result, life expectancy has increased continuously over the past century.

By now the overall costs for medical care in Europe constitute 10% of the gross domestic product [1], mostly consisting of diagnostic procedures. The relatively high diagnostic costs stem from the therapeutic principles of Western Medicine, since the foundation and condition for a particular therapy is the appropriate diagnosis of the disease. Today, non-invasive imaging technologies supplement and often replace standard physical examinations. Imaging technologies rely on the non-invasive acquisition, as well as on the display, of human body images. They help provide earlier and more efficient treatment for patients and thus, ideally, reduce therapy costs through an early and exact image-based diagnosis.

Modern and non-invasive image-based medicine began with the discovery of X-rays by Wilhelm Conrad Röntgen in 1895, which resulted in the birth of a new medical discipline, referred to as Radiology [3]. The development of radiological imaging has been swift, and its area of usage is growing continuously. Most significant milestones include the development of the first X-ray Computed Tomography (CT) systems during the early 1970s [4], and of Magnetic Resonance (MR), which began in the 1980s [5]. Since then, these two imaging technologies have dominated the non-invasive assessment of human anatomy. However, when diagnosing diseases or monitoring responses to therapy, anatomical imaging alone does not always provide the complete picture. Functional or metabolic changes may occur even in the absence of a corresponding anatomical alteration. This is the domain of functional and molecular imaging, Nuclear Medicine, in particular.

The main task of Nuclear Medicine is not the representation of the anatomy, as in Radiology; it is the non-invasive visualization of functional and metabolic processes. The key idea in Nuclear Medicine is for the subject to first incorporate minute amounts of a radioactively labelled biomolecule. Once the biomolecules are properly distributed inside the body, Nuclear Medicine Imaging techniques are used to visualize the metabolism of the substance by measuring the distribution of the radioactively labelled biomolecule through external detection of the emitted radiation. These techniques were initiated in the late 1940s; even before the development of CT, Single Photon Emission Tomography (SPECT) was created to produce 3D-images of metabolism [6]. With the introduction of Positron Emission

Tomography (PET) [7], the field of Nuclear Medicine benefited from another strong diagnostic method. Today, approximately 7 million Nuclear Medicine examinations are performed annually in Europe, which corresponds to 44 examinations per 1000 inhabitants and per year. Most of these examinations (>75%) are performed with SPECT or SPECT/CT systems [8].

This article aims to explain the SPECT method and its current significance within medicine, and outlines the future of this technology as well as its development potential in Europe.

The Principles of Nuclear Medicine

Like its companion, Radiology, Nuclear Medicine is a relatively young medical discipline. Henri Becquerel discovered Radioactivity in 1896, a prerequisite for Nuclear Medicine, which can be dated back to the early 1920s. At the time Georg de Hevesy, a Hungarian chemist, and Friedrich Adolf Paneth, an English chemist of Austrian origin, developed the tracer method with which chemical elements can be marked and traced, based on radioactive labels [9].

Interestingly, one of the first practical adoptions of this phenomenon had a domestic origin outside the medical field. Hevesy once added a small amount of a radioactive isotope to his meal because he suspected his landlady of using the Sunday meat pie leftovers for the following week’s dinner. Indeed, a week later he managed to measure radioactivity in the "fresh" pie. This way, he was able to blame his landlady for reusing leftovers [9], a rather unappetizing fact to support what later became the most sensitive clinical imaging modality.

Today, the procedure involving a radioactive isotope is called Tracer Method. The distribution and the path of a tiny amount of a radioactive substance in the human body are observed from the outside by mapping the radiation (FIG 1). Thus, we gather information about the metabolic functions of the body. In contrast to radiological processes, which produce images of the structure, Nuclear Medicine processes create images of the function.

Tracers - the Starting Point of Nuclear Medicine Imaging

Tracers in Nuclear Medicine are applied in minimum doses (< 10 nmol, which corresponds to the amount of 1kg sugar in Lake Constance), which have no pharmacological effect and do not influence the metabolic processes to be examined. The radioactive label of these tracer molecules used in conventional Nuclear Medicine, such as SPECT, are gamma emitters.

These emitters have only a short half-life, so that radiation exposure can usually be compared with a corresponding X-ray method.

Extensive research was conducted on the development of tracer molecules, also referred to as radiopharmaceuticals. Among the many discoveries and developments, however, the most significant events were the production of Technetium-99m (^{99m}Tc) during the 1930s and the development of methods to separate ^{99}Mo and ^{99m}Tc in an economically viable way. ^{99m}Tc has a number of advantages, such as a short half-life of 6h, low-energy gamma rays and chemical properties for straightforward tracer molecule labelling. Thus, metastable ^{99m}Tc is by far the most important tracer for scintigraphic examinations worldwide [10].

Typically, organic ligands, with a strong disposition to bind to cells in the organ to be investigated, are connected to technetium and mostly injected intravenously into the patient's blood circulation. The characteristic gamma radiation can be recorded and used for a non-invasive diagnosis, e.g. of tumours [11, 12]. Furthermore, the ^{99m}Tc-generators enable the extraction of ^{99m}Tc from a source that contains decaying ^{99}Mo. ^{99}Mo has a half-life of 66 hours and can be delivered across larger distances to hospitals and practices, where the decay product ^{99m}Tc is subsequently extracted. The supply of ^{99m}Tc in the individual departments can be met through generators that are delivered weekly. Supplying it via ^{99}Mo is very cost effective despite the production involved, e.g. ^{99m}Tc costs are a fraction of FDG or any other contrast media.

Hence, more than 90% of Nuclear Medicine examinations worldwide are performed with ^{99m}Tc-tracers. This procedure allows the examination of bone tissue for example, or else of the thyroid, the heart, the lungs, the kidneys, the brain and those parts of the intestine that are not readily accessible by other means. TABLE 1 shows a summary of the nuclides and radiopharmaceuticals used most frequently in Nuclear Medicine Imaging today.

From Signal to Image

The tracer method can be used for localisation diagnostics, for example, to detect and localise the inflammation centre point in the skeleton. However, as it monitors the progress of the radiating substance (or tracer) from intake to elimination, it can also be used to gather information on organ functioning, for example during kidney function scintigraphy.

The starting point for Nuclear Medicine Imaging, as it is known today, is the Gamma Camera, developed by American Biophysicist Hal Oscar Anger in the 1950s [13]. This camera enables not only the detection of gamma rays, but also the visualisation of their distribution as a scintigram (from Latin *scintilla* = spark, and Greek γράφειν = to draw,

describe). A gamma camera contains a detector or scintillator, such as sodium iodide or a semi-conductor array, which converts the energy of the gamma photons emitted from the tracer, and hence the distribution of the tracer inside the human body, into an electronic pulse. The original gamma ray positions in the body can be determined using sophisticated electronics and image reconstruction methods (FIG 2, FIG 4).

SPECT

Already in the 1960s, David Kuhl and his team extended the 2D gamma camera technology to three dimensions. Contrary to conventional planar imaging, Single Photon Emission Computed Tomography (SPECT) acquires multiple images from various angles around the patient. This is achieved through gradual or continuous rotation of the detectors around the patient [14-16] (FIG 2, FIG 3, and FIG 4).

SPECT presents a number of advantages over planar scintigraphic imaging, such as:

- Better localisation of lesions deep inside the human body,
- Much improved spatial resolution: detectable lesions <1cm,
- More precise topographical mapping of organs and physical structures, and
- Easier comparison with other sectional imaging techniques (e.g., CT, MRI).

SPECT examination sensitivity is higher than with 2D technology, thus improving the validity of the examination. This is similar to moving from simple X-ray imaging to CT imaging. FIG 4 shows a patient with suspected bone metastases whose planar image is within normal limits, while SPECT enables to clearly visualise an isolated metastasis in the body of a vertebra.
SPECT became commercially available in the early 1970s, and by the end of that decade the methodology had started to be used routinely in Nuclear Medicine. Today nearly all gamma cameras are SPECT-capable, with the exception of a few dedicated thyroid cameras.

SPECT/CT

A major Nuclear Medicine Imaging limitation is the restricted anatomical information that many examinations offer. The more specific a tracer, the less anatomical background information is reflected in the tracer distribution since the tracer accumulates almost exclusively in the target region. However, anatomical co-localization is essential, especially in Oncology, since knowledge of the exact location and extent of the disease is crucial to select

an appropriate therapy [16, 17]. To bypass this limitation, it has been proposed to physically combine SPECT and CT within a single gantry. The resulting dual-modality SPECT/CT systems intrinsically match the outstanding specificity and sensitivity of Nuclear Medicine SPECT Imaging with the anatomical precision of X-ray CT. This combination also provides an option to elegantly solve another, physical key problem of SPECT Imaging: attenuation correction.

Following the pioneering efforts of the late Bruce Hasegawa in the 1990s, who assembled a SPECT system back-to-back with a clinical CT [19], the first commercially available SPECT/CT was the Hawkeye in 1999 (GE Healthcare, Haifa, Israel) [18]. This device combined a low power output X-ray tube with a SPECT camera. In the following year, the first SPECT/CT system with multidetector CT was introduced, in order to support the full diagnostic effectiveness of a multi-slice CT in the context of a dual-modality SPECT/CT examination [20]. Across all SPECT/CT Imaging technologies, the main SPECT/CT benefits are increased sensitivity and specificity compared with single modalities, since the amount of unclear findings can be significantly lowered. For this reason, the number of combined SPECT/CT devices has continuously increased in Europe during the past years (FIG 5).

Clinical Use of SPECT and SPECT/CT

The clinical use of SPECT is manifold. In clinical practice the examination process focuses on the skeletal system, as well as the thyroid, myocardium, kidneys, lungs, brain and tumours (FIG 6). Numerous original papers and reviews clearly attest to the clinical value of SPECT and SPECT/CT for the most diverse range of conditions [see 14-17, 21-37].

Here, we will highlight the potential of SPECT, by means of selected examples for bone scintigraphy, myocardial scintigraphy, brain scintigraphy and sentinel node scintigraphy.

Bone Scintigraphy

For over 30 years, planar bone scintigraphy has been used as a sensitive method for detecting and characterizing focal bone pathologies. Bone scintigraphy sensitivity is increased through the introduction of the tomographic SPECT acquisition mode [14, 38]. Nonetheless, functional bone imaging lacks specificity [39]. For that reason Radiography, CT and MRI are frequently performed after bone scintigraphy to further characterize lesions that are evident on bone scans. Integrated SPECT/CT offers a direct correlation of focal bone

pathology with anatomic structures and therefore minimizes the number of equivocal findings.

Diagnosing Bone Metastases: The main bone scanning indications are screening for bone metastases and evaluating the treatment response (FIG 4). Although most bone metastases appear as hot spots, some appear as cold lesions. Benign lesions, such as hemangioma, may also appear as cold, rendering the differential diagnosis problematic. The differentiation between benign and malignant lesions can usually be achieved following CT co-registration, which is intrinsic to SPECT/CT [40-43].

Benign Bone Lesions: Bone scintigraphy also plays a significant role in this area, in particular for the diagnosis of arthritis, of occult fractures, for planning a Nuclear Medicine Joint Therapy (radio synovectomy) and for orthopaedic diseases. Applying the method here also revealed that, compared with bone scintigraphy and SPECT, the use of SPECT/CT increases diagnostic accuracy in the evaluation [44], e.g. of orthopaedic disorders affecting the extremities [45] or post-traumatic lesions (FIG 7).

Myocardial Scintigraphy

Myocardial perfusion SPECT illustrates the function of the heart muscle (the myocardium) and is mostly performed in patients with known or suspected coronary artery disease (CAD). The examination displays the blood flow of the myocardium under stress conditions (e.g. after riding a bike or taking medication) and at rest.

The most common indications for myocardial scintigraphy are:

- Suspicion of a CAD with medium clinical probability
- Issues of hemodynamic relevance of stenosis with known CAD (identifying location and severity of an existing coronary stenosis)
- Assessment of viable myocardium in CAD patients to assess the potential benefit of revascularization
- Risk stratification and evaluation of patients who are at risk of having a myocardial or coronary incident.
- Post-intervention revascularization (coronary artery bypass graft, angioplasty) and myocardial evaluation.

Myocardial perfusion SPECTs (FIG 8) are powerful predictors of future clinical events and are considered to be the most comprehensive tests, providing information about the severity

of coronary stenosis, the areas with ischemia, the severity of ischemia, the total mass of viable myocardium and the pump function of the heart, along with objective parameters such as end systolic volume, end diastolic volume, stroke volume and ejection fraction. SPECT myocardial scintigraphy has by far the most extensive clinical and scientific evidence in medical literature, among all stress imaging methods (stress echocardiography, cardiac MRI, cardiac CT). The absence of a positive finding on cardiac SPECT corresponds to an excellent prognosis for the patient over the next 12 months, a very low probability (<1%) of a sudden cardiac death or a non-fatal myocardial infarction (negative predictive value 99%). A normal finding after a myocardial scintigraphy usually does not require any additional coronary angiography, at least during the following 12 months. The use of myocardial SPECT imaging as a "gate keeper" to determining the indication for a coronary angiography is cost efficient, according to investigations in Europe and the US [46].

Brain SPECT

There are numerous ways to examine the brain with SPECT technology. Depending on the chosen tracer, Nuclear Medicine examinations can diagnose dementia, cerebrovascular diseases, epilepsy, Parkinson's Disease and cerebral death. As an example, FIG 8 shows two patients who were examined with DatSCAN™ (Ioflupan) for suspected Parkinson's Disease. Through the dopamine transporter ligand, the presynaptic dopamine transporter of the dopaminergic system (striatum) can be visualised and quantified, i.e. the higher the amount of nerve cells available, the larger the amount of the tracer building up. While the dopamine releasing nerve cells are dying in Parkinson's Disease, this is not the case in other diseases such as essential tremor, providing a differentiation between the diseases. With a normal DatSCAN™ result, a Parkinson’s Syndrome can be excluded with a certainty of 97% [47] (FIG 9).

Therapy Planning

SPECT examinations are often the starting point for further therapy planning, such as surgery. FIG 10 and 11 show exemplary pre-surgical SPECTs of patients with hyperpara-thyroidism [17] and breast cancer [33].

Beyond planning "conventional" therapies, SPECT is also crucial for Nuclear Medicine therapies. In 1926, the eminent radiobiologists Regaud and Lacassagne predicted that “the

ideal agent for cancer therapy would consist of heavy elements capable of emitting radiations of molecular dimensions, which could be administered to the organism and selectively fixed in the protoplasm of cells one seeks to destroy” [48]. This prescient statement is still a workable definition of targeted molecular radionuclide therapy.

In contrast to the diagnostic use, which requires tracers with low radiation exposure, the starting point for a therapeutic use is different. Here, damage to the diseased tissue is required in order to achieve a therapeutic effect. For example, beta emitters are standard radioisotopes used for internal radiation treatment in Nuclear Medicine. The beta particles, which are released during the radioactive decay, transfer nearly all their energy to the irradiated tissue, within a millimetre range. For this reason they allow for an effective treatment of the disease "on site", which usually causes very few adverse events.

In addition to the radioiodine therapy mentioned above, Nuclear Medicine therapies include numerous other well-established treatments. These can be used against inflammable joint disease, metastasised tumours with prominent pain symptoms, tumours of the adrenal medulla, leukaemia, lymphomas, neuro-endocrine tumours, metastases of the liver that cannot be removed surgically and a number of other diseases. Some of these treatments can be performed as outpatient procedures, while others treatments require hospitalization. Nuclear Medicine therapies are generally safe, effective and related to only minimal adverse events.

Overall, the significance of the therapies has been growing continuously over the past years, resulting in a 13% increase between 2006 and 2010 in Europe [8].

The basis for these treatments often is a SPECT examination to help determine whether therapy is possible and - increasingly so - what dose should be administered to an individual patient in a planned treatment. The idea is to conduct SPECT examinations that simulate both the progress of the therapy and the absorption of the therapeutic substance to enable a calculation of the therapy activity (called dosimetry) [49]. Furthermore, SPECT enables disease monitoring during and after therapy as well as treatment efficacy, for instance in patients with thyroid carcinoma [50, 51]. The underlying concept of an individualized radionuclide therapy based on pre-therapeutic planning will be increasingly significant in the future, as will be the SPECT and SPECT/CT systems [52, 53].

The Future of SPECT

In the future, SPECT and SPECT/CT will play an increasingly vital role for the diagnosis and therapy planning of numerous diseases. SPECT/CT clearly improved the clinical potency of SPECT, and will continue to do so. The development, investigation and clinical introduction of new tracers for Cardiology, Oncology and Neurology applications [55, 56] will further foster the use of SPECT and SPECT/CT.

In addition, it must not be underestimated that SPECT and SPECT/CT cameras are available in most European hospitals, and that outpatient diagnostic centres are also equipped with numerous cameras. Finally, treatment costs are relatively low in comparison to other imaging processes.

In conclusion, the European Health System is broadly prepared for the imminent shift of medicine “toward molecular diagnoses and treatments” – and SPECT/CT will be an important part of this future.

Are you interested in further information about Nuclear Medicine?

Figures

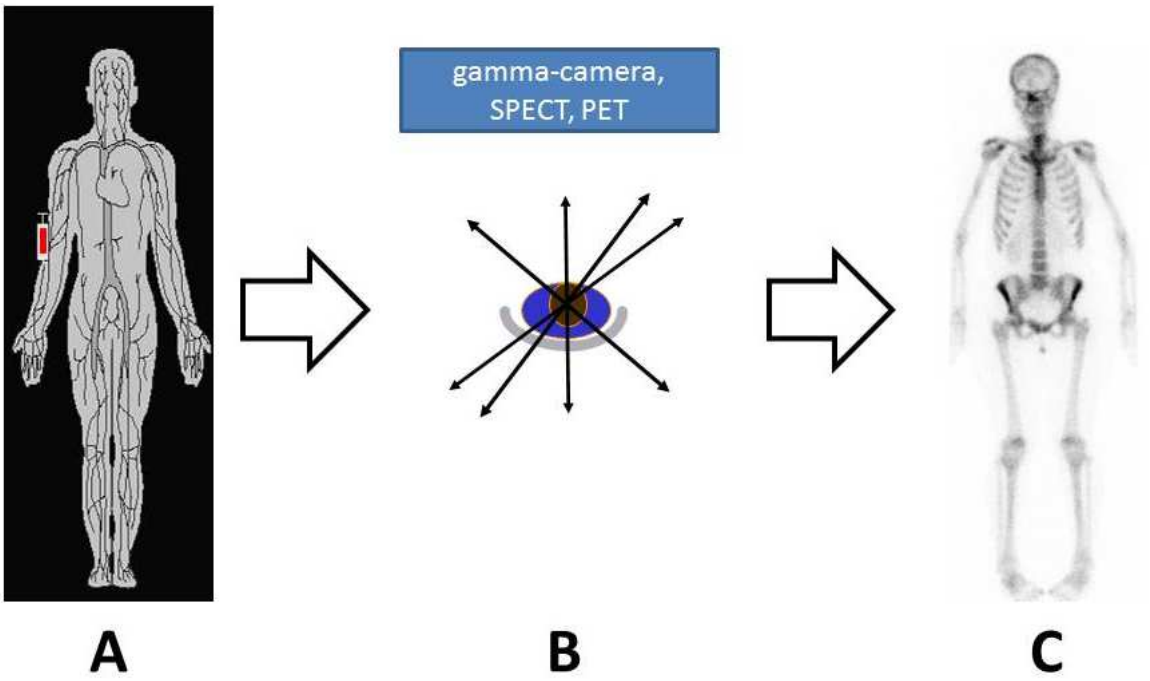

FIG 1: Principle of Nuclear Medicine Imaging: a radioactively labelled tracer is typically injected into the patient (A). The emitted radiation can be detected from the outside (B) and the measured signals are used to reconstruct images of the tracer distribution (C).

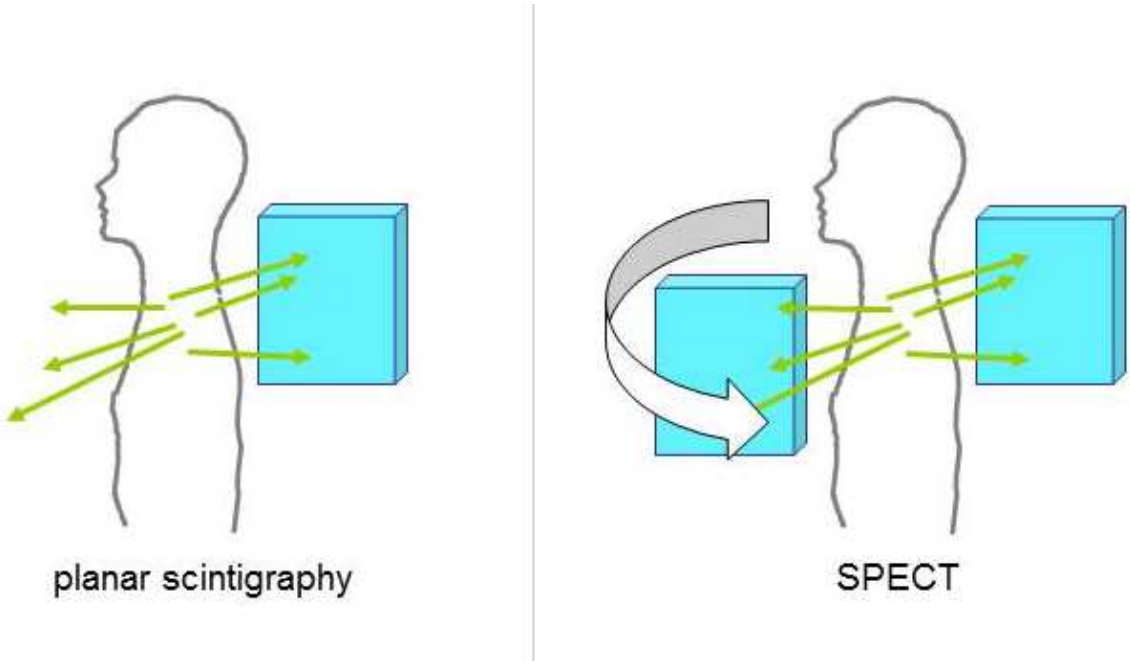

FIG 2: Principle of Planar Scintigraphy versus SPECT. The SPECT camera rotates around the patient, thus, enabling a tomographic image reconstruction of the tracer distribution.

FIG 3: Patient undergoing a SPECT/CT examination of the heart.

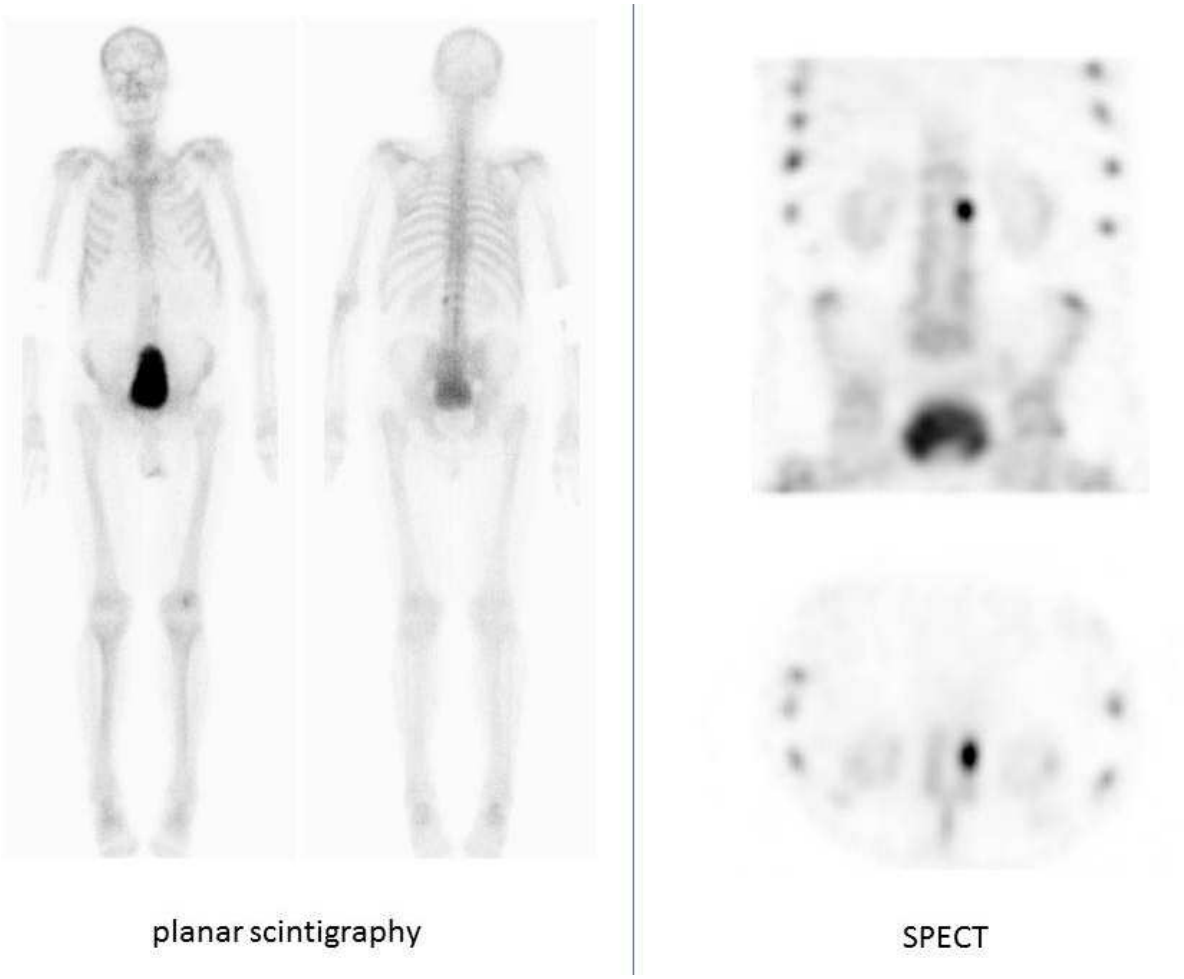

FIG 4: Bone Scintigraphy using ^{99m}Tc-labelled diphosphonate of a patient with an increase in tumour markers after prostate carcinoma treatment. The planar scintigraphies (left) show no osseous metastasis while in SPECT (right) an isolated metastasis in the body of a vertebra is clearly visible.

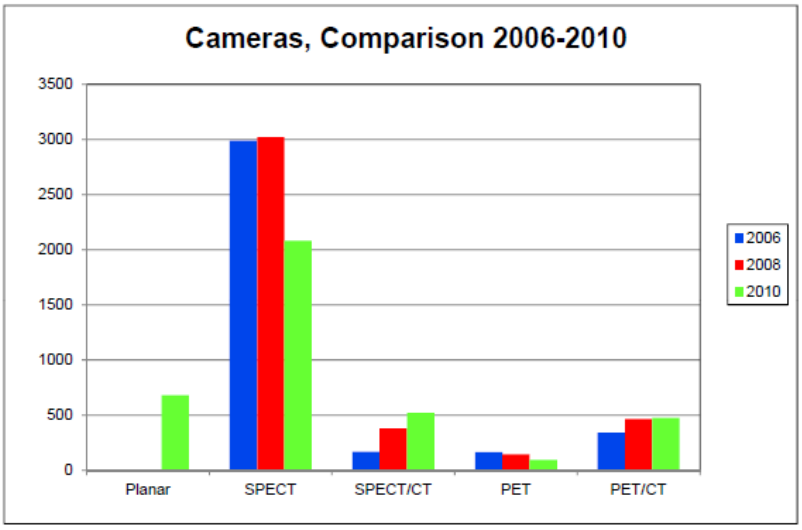

FIG 5: Distribution of Nuclear Medicine Devices in Europe [according to 8]

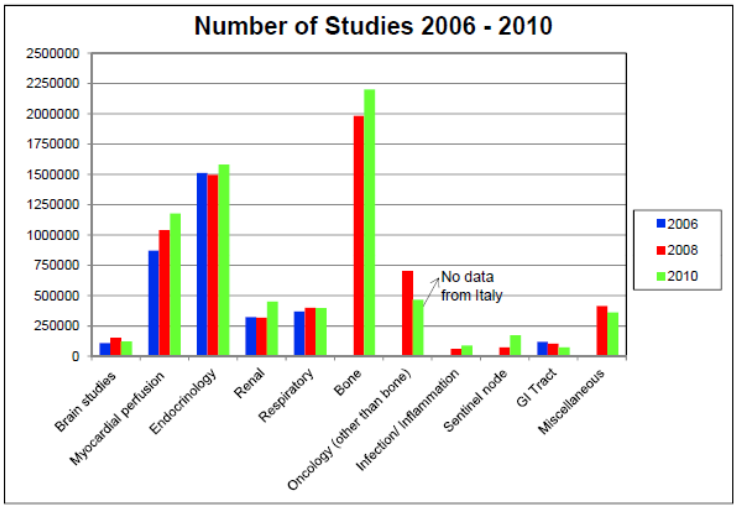

FIG 6: Number of annual Nuclear Medicine Examinations in Europe [according to 8]

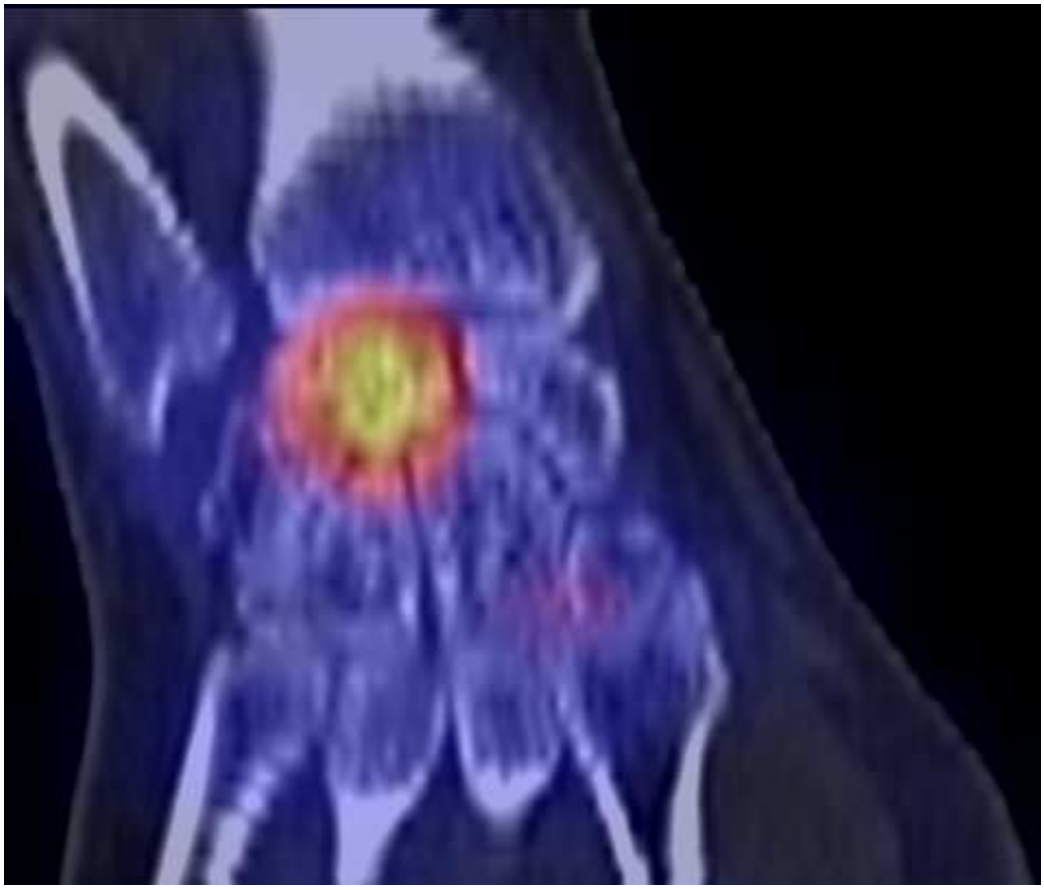

FIG 7: SPECT/CT of the wrist that shows a fracture of a small carpal bone. Previous X-ray and CT did not show any fracture while follow-up SPECT picked up post-traumatic changes without accurately localising their origin. Only SPECT/CT did provide all the required information for accurate surgery planning, which helped prevent permanent mobility restriction in the wrist.

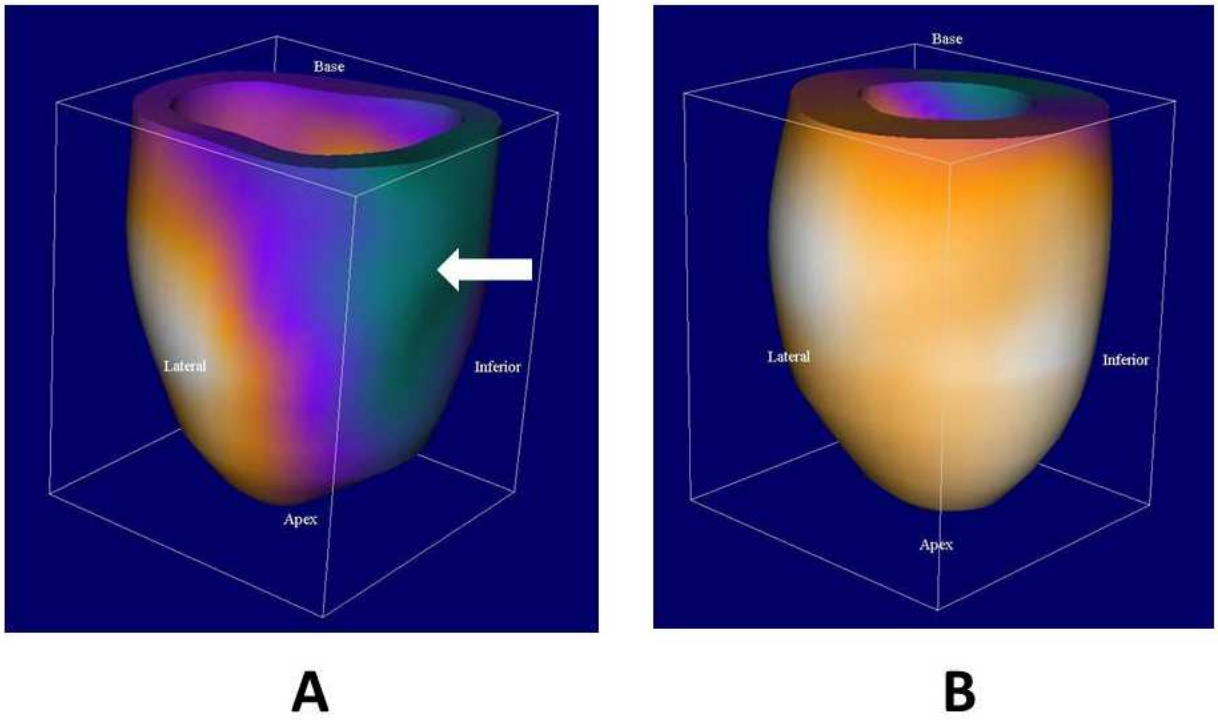

FIG 8: Myocardial Scintigraphy in a patient with a history of thoracic pain and dyspnea. Under stress, SPECT shows an area with inadequate blood flow (A). Under resting conditions, SPECT shows normal blood circulation (B). This patient suffers from stress-induced reversible ischemia caused by a coronary 1-vessel disease. A myocardium infarction is imminent, the vessel needs to be dilated or bypass surgery needs to be performed.

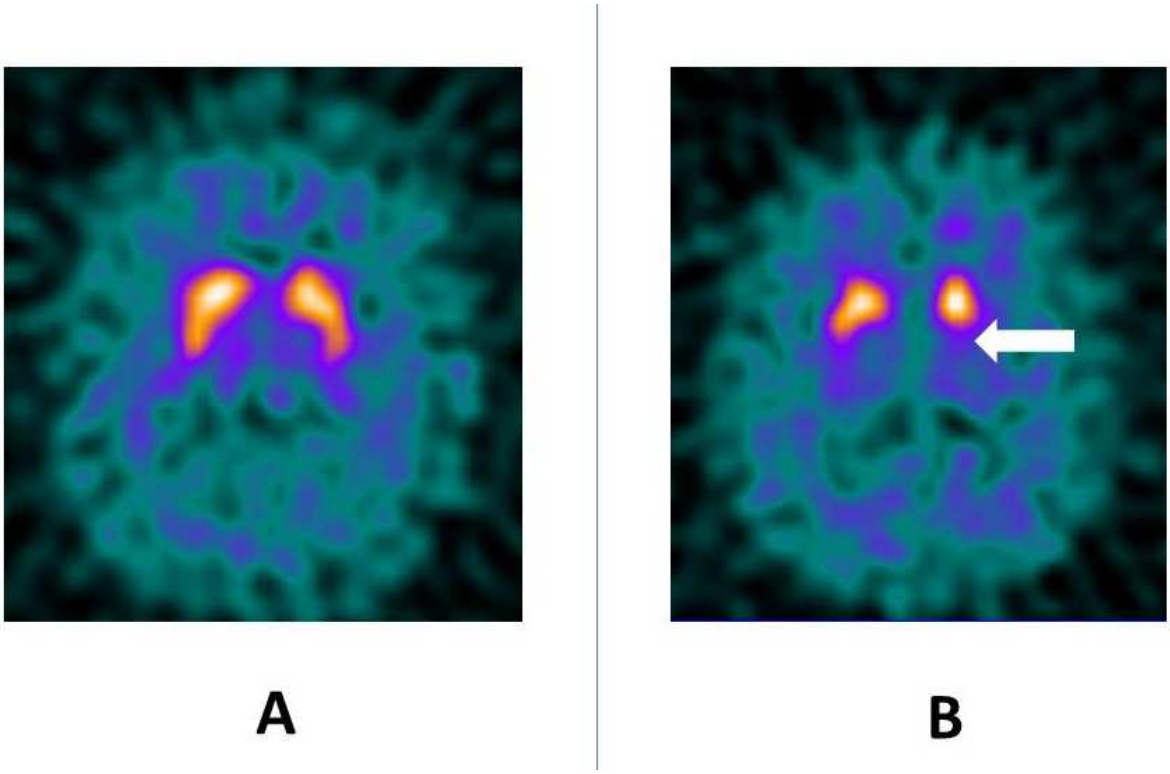

FIG 9: SPECT Imaging in Parkinson´s Disease: While the image on the left shows a normal distribution of the tracer DatScan and Parkinson's Disease can be excluded, the image on the right displays the lacking accumulation within the caudate nucleus on the left (arrow) which is typical of Parkinson's Disease.

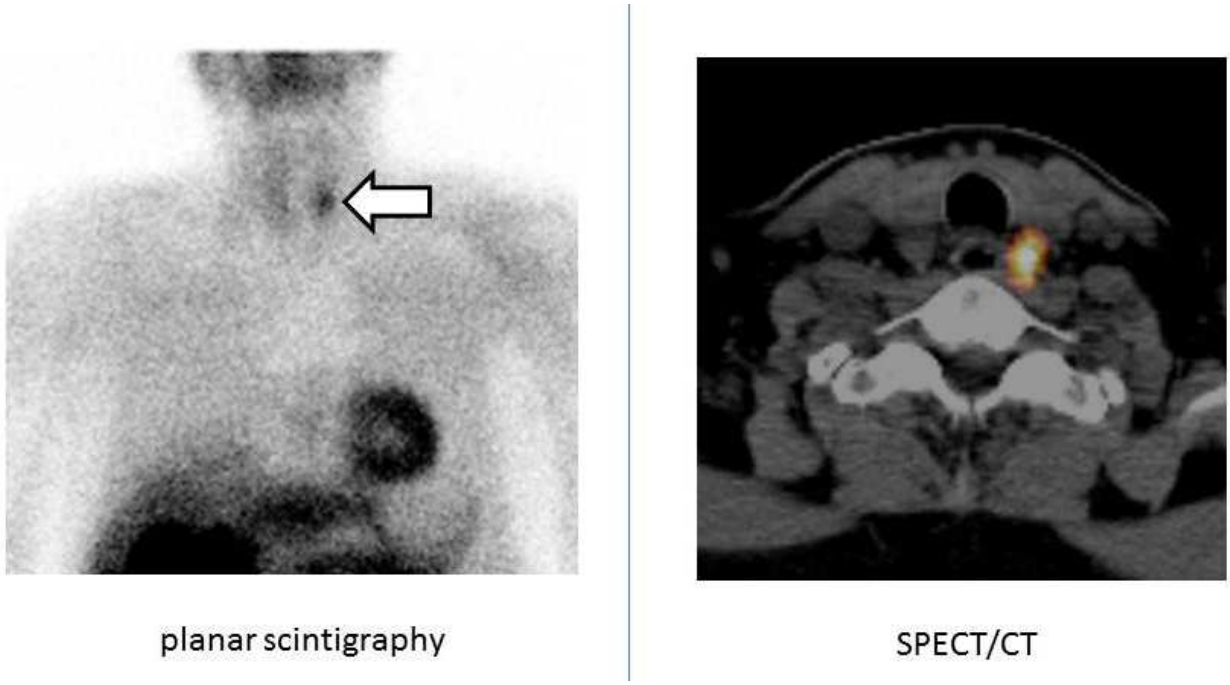

FIG 10: The Planar Scintigraphy Image of the parathyroid gland shows an adenoma (the source of hyperparathyroidism) in the parathyroid gland that could not be detected with CT Imaging. SPECT/CT shows the precise location of the lesion (right). Subsequently, surgery was planned.

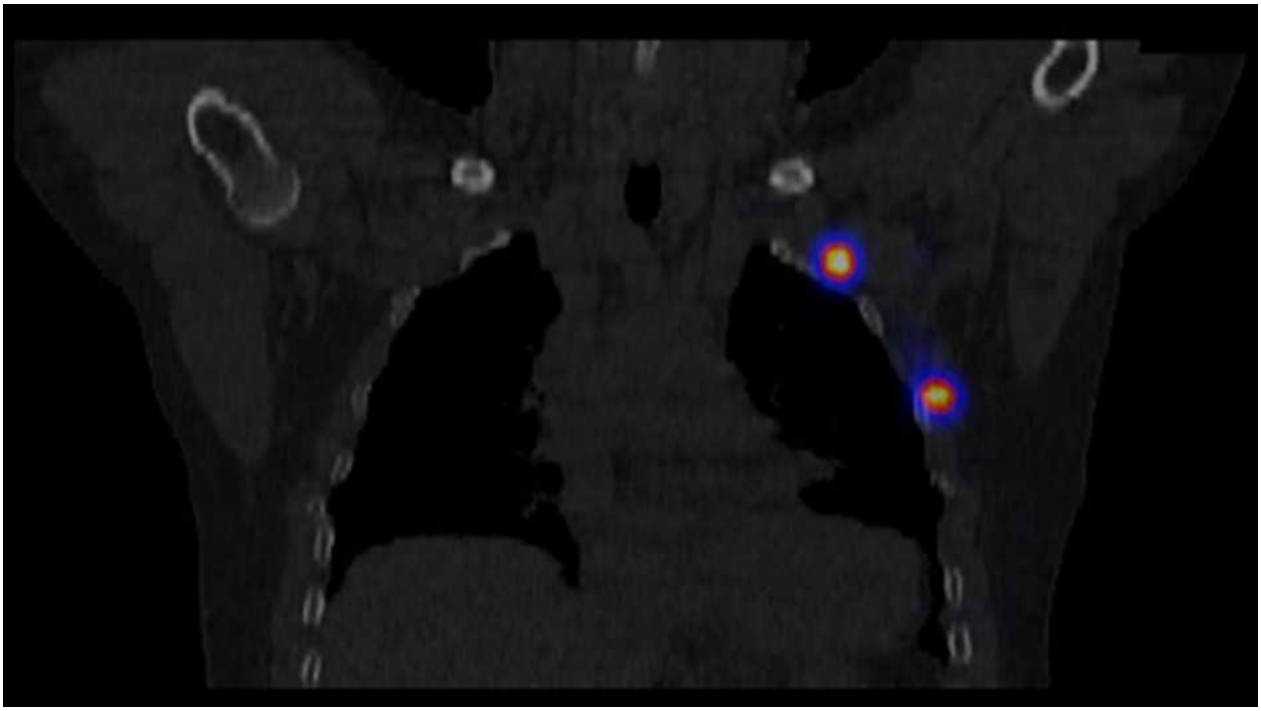

FIG 11: SPECT/CT of a female patient with breast carcinoma who had received an injection of a tracer in her affected breast before surgery to show the lymph drainage. It displays the sentinel nodes - the first lymph nodes that would be affected during a malignant tumour spread. These nodes are detected intra-surgically with a highly sensitive gamma detector, and are removed. This procedure ensures maximum security for the patient and helps spare her the unnecessary operation of the entire axilla (and its long-term effects) if the sentinel node is not affected by the cancer.

Table

Radionuclides	Half-lives	Radiopharmaceutical	Uses
^{99}**Mo** (Molybdenum-99)	2.8 days	-	Parent radioisotopes for the production of ^{99m}Tc
^{99m}**Tc** (Technetium-99m)	6 hours	Diphosphate	Bone
		DMSA	Renal cortical
		DTPA	Renal dynamics
		ECD	Brain perfusion
		HMPAO	Brain perfusion
		Labelled red cells	GI blood loss
		MAA	Lung perfusion
		Pertechnetate	Thyroid, salivary glands
		Sestamibi	Myocardial perfusion, parathyroid
		Sulfur colloid	Lymphscintigraphy, red bone marrow, gastric emptying
		Tetrofosmin	Myocardial perfusion, parathyroid
^{111}**In** (Indium-111)	2,8 days	DTPA	CSF flow, gastric emptying
		Oxin labelled white cells	Infection
		Pentetrotide	Somatostatin receptor tumours
^{123}**I** (Iodine-123)	13 hours	Sodium	Thyroid
		MIBG	Pheochromocytoma, arenal medullary, neural crest tumours
^{131}**I** (Iodine-131)	8 days	Sodium	Treatment of thyrotoxicosis and thyroid cancer
^{201}**Tl** (Thallium-201)	3 days	Chloride	Myocardial perfusion

TABLE 1: Most commonly used single photon emitting radioisotopes used in Diagnostic SPECT Imaging

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