

Notes by the OPECST

Number 1 - December 2007

Nuclear medicine

Presentation

Nuclear medicine uses the properties of some artificial radioactive isotopes, combined or not with a carrier molecule, to diagnose, follow-up and manage a large and varied number of pathologies, as well as to treat some of these pathologies by metabolic radiotherapy.

The radioactive molecule is called the marker; the molecule to which it may be combined is called the carrier; together they form the radiopharmaceutical or radiotracer. The latter behaves like a micro-emitter of gamma radiations detectable using devices like gamma cameras.

Administered to the patient, radiopharmaceuticals concentrate selectively in some organs or lesions where the metabolism and/or normal or pathological functioning can then be assessed. Depending on the type of radiation emitted by the isotope it will be possible either to visualise these tissues (gamma radiation), or destroy them (alpha or beta-minus radiation).

With positron emission tomography (PET), nuclear medicine has improved the efficacy of its metabolic, molecular and functional investigations. By combining in the same piece of equipment a scanner also called a tomodesitometer (TDM) and a PET device, the PET—TDM now offers both molecular and functional imaging and also precise morphological and anatomical imaging, which constitutes considerable progress.

Recent technological developments and new radiopharmaceuticals are strengthening even more the role of nuclear medicine in managing cancers and also in cardiology and neurology.

For instance, unlike other medical imaging techniques (magnetic resonance imaging, X-ray

imaging and echography) where metabolic studies are still largely a matter for research, nuclear medicine is naturally adapted to it and forms, to date, the only molecular imaging technique used on a daily basis clinically.

Radiopharmaceuticals

Radiopharmaceuticals must comply with the following properties:

- Be specific to an organ, a function or a pathology;
- Have a short half-life (from a few hours to a few days) and an energy (50 to 600 keV) adapted to detection;
- Be able to be used at very low concentrations, so as not to modify the metabolism of the organ studied.

The most frequently used radioactive isotopes are: technetium-99m, thallium-201, xenon-133, iodine-123 and -131, krypton-81 and, more recently, a beta emitter, fluorine-18.

Technetium is by far the most used, as it presents several advantages:

- The gamma photons it emits have optimal energy for maximum sensitivity in usual detection systems;
- Its physical half-life is 6 hours, meaning it is quite short and limits the subject's irradiation;
- This element can be produced extremely simply by a nuclear medicine service as it is available in the form of a small generator;
- It can be combined with many molecules of biological interest;

Notes by the OPECS7 - Notes by the OPECS7 - Notes by the OPECS7

• It is relatively inexpensive compared with other isotopes.

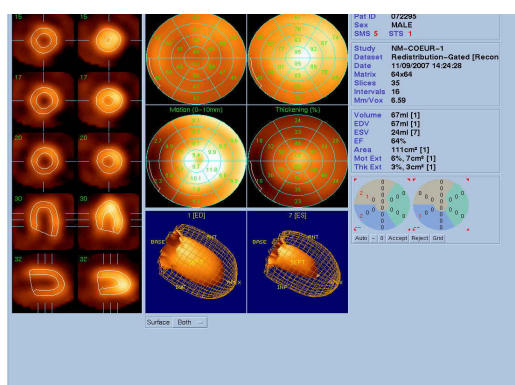
Radiopharmaceuticals are considered as drugs and are therefore subject to the same administrative constraints. Furthermore, their

radioactive nature subjects their use to the various regulations on patient radiation protection, exposure of nuclear medicine personnel, the close family circle, and, more generally, the environment.

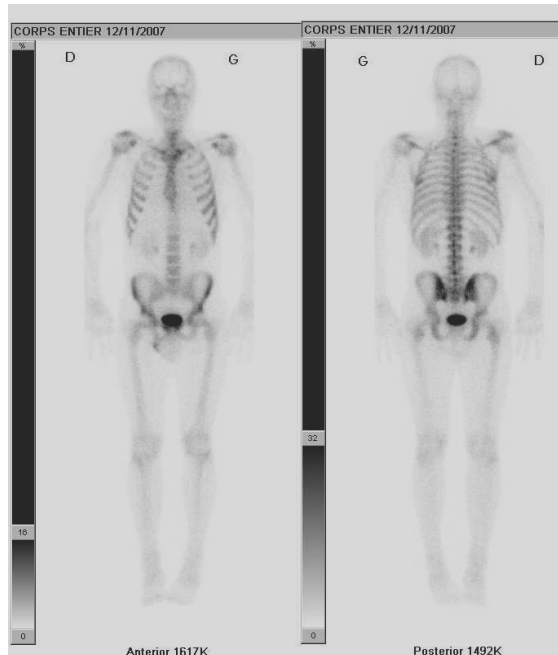
Examples of the use of radioisotopes

There are dozens of radiopharmaceuticals with specific physico-chemical and biological properties; a radiopharmaceutical is therefore chosen in terms of the organ to be explored and the pathology. For instance:

- Scintigraphic images of the thyroid are made after administering iodine-123;
- Xenon, by its gaseous nature and solubility, is suitable for pulmonary ventilation studies;
- In cardiology, thallium-201, which has chemical and biochemical properties close to that of potassium, is therefore a marker of potassium exchanges and, by the same token, a coronary flow marker;
- Fluorine-18 marked fluorodeoxyglucose is widely used for PET imaging in cancerology;
- Technetium-99m marked red blood cells allow the heart chambers to be visualised;
- Technetium-99m marked HMPAO (hexamethylpropylene amine oxime) is taken up almost proportionally to cerebral blood flow and therefore allows areas of abnormal perfusion to be seen;
- Technetium-99m marked diphosphonates are used for bone scintigraphy. In this application, diphosphonates are taken up in the hydroxyapatite crystals depending on bone metabolism.



Myocardial perfusion imaging with evaluation of the left ventricular function



Normal bone scintigraphy image

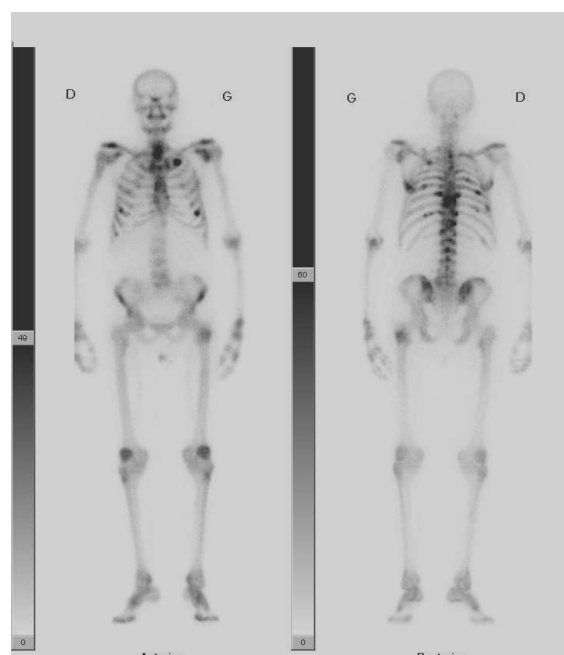


Image of bone metastases

Fields of application

Two fields of application can be distinguished for nuclear medicine: diagnostic and therapeutic.

↳ Diagnostic

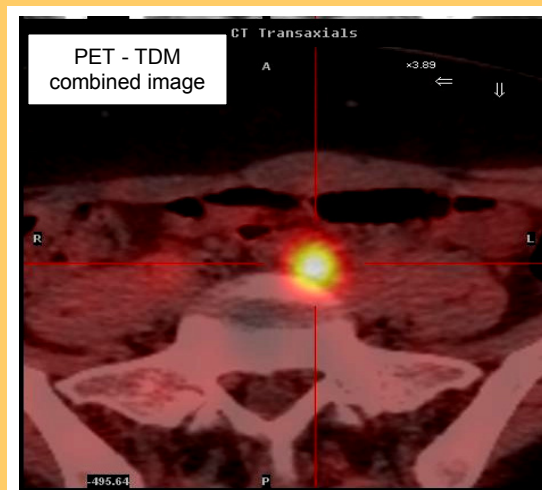
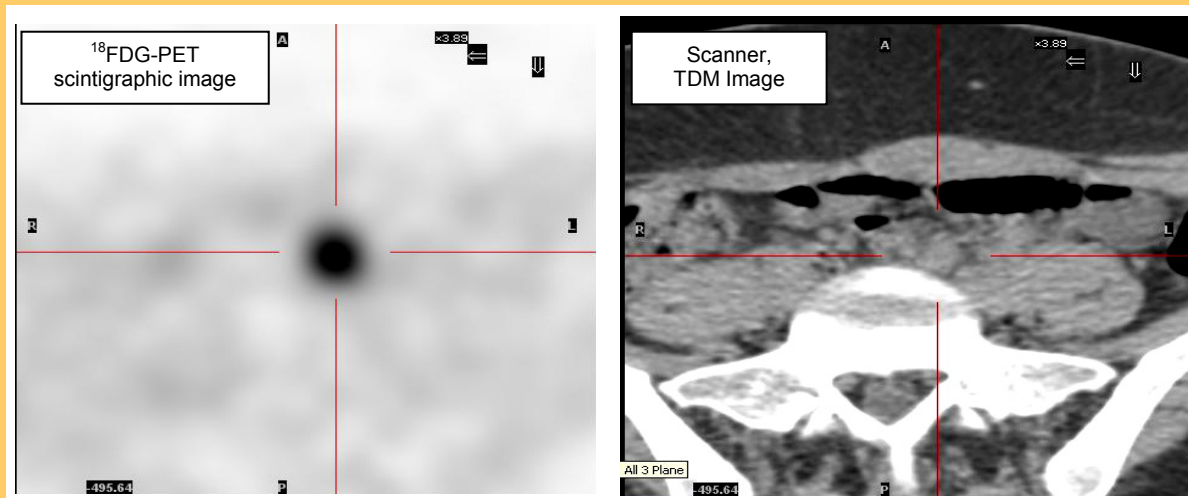
Scintigraphic imaging: the diagnosis is established by interpreting images called scintigraphies. They consist in visualising a function and/or the metabolism of an organ or a tumour, by localising the spatial and temporal distribution of a radioactive tracer using a scintillation camera (or a gamma camera). Briefly, a radiopharmaceutical is administered to the subject (intravenously, arterially, orally, or by inhalation). It then spreads through the

tissues with a preference for a target organ or a lesion. The concentration of the radiopharmaceutical in the target organ or lesion depends on the metabolic activity of these targets. The photons emitted by the isotope are captured by a gamma camera depending on their energy and the images are formed on the basis of this information.

Positron Emission Tomography (60 devices installed in France as of 31 July 2007 out of the 85 scheduled) **is the latest scintigraphic imaging technique.** The radiopharmaceutical currently used is a glucose analogue, ^{18}F FDG (fluorine-18 marked fluorodeoxyglucose). This radiotracer reflects cell glucose consumption, which is highly increased in the cells of many cancers.

The following images present the various techniques pinpointing the only metastasis of a digestive cancer undetected by conventional imaging:

- The first image is obtained with positron emission tomography;
- The second, using a scanner;
- The third, the clearest, thanks to PET-TDM, a device combining in the same piece of equipment the advantages of positron emission tomography and those of the scanner.



This technique has already gained a preponderant place in the management of many cancers: initial diagnosis, staging, choice of the best treatment, evaluation of treatment response, prognosis...

Another diagnostic possibility is to count biological samplings (blood, faeces, urines...) after administering radiotracers. For instance the following can be carried out:

- Using the dilution principle to measure total blood, globular and plasma volumes;
- Seeking and quantifying digestive bleedings;
- Estimating renal plasma flow.

↳Therapeutic

Unlike radiotherapy, which uses radioactive sources always separate from tissues (internal sealed sources of curietherapy or external radiotherapy sources), nuclear medicine uses radioactive substances in direct contact with tissues (unsealed sources).

In the framework of therapeutic applications, internal radiotherapy, long limited to differentiated thyroid cancer (iodine-131), has spread to other types of cancer. This progress is linked to the development of new carriers, new tumoural targeting methods and new radioactive isotopes, especially alpha-particle emitters.

Therefore, the fields of application of nuclear medicine are very wide and varied.

For example:

- **Endocrinology:** diagnostic and therapeutic management of thyroid pathology in particular, but also of endocrine tumours;
- **Cardiology:** coronary pathology but also rhythmic pathology and cardiac insufficiency;
- **Nephrology:** especially in children;
- **Pneumology:** pulmonary embolism...;
- **Osteoarticular pathology:** in rheumatology, palliative management of some types of bone metastasis...;
- **Neurology:** help in diagnosing dementia, epilepsy...;
- **Seeking sources of infection:** (for instance after implanting an orthopedic prosthesis...);
- **Cancerology:** initial diagnostic contribution, staging, therapeutic evaluation, prognosis; seeking relapses in cancers of the lung, stomach, colon, higher aerodigestive tracts, breast, kidney; lymphomas; osteoarticular tumours...

Some of these applications are also used in children and even in newborns.

Expected developments of nuclear medicine

PET-TDM is a highly prized instrument in the better management of cancerology patients, but leads to a relatively high additional cost. Many technical improvements, among which the development of new fluorine-18 ligands (e.g.: f-18 marked choline for the precise detection of metastases in prostate cancer), are being developed. For instance, a new technique called 'Immuno-PET' is under clinical evaluation: antibodies would be reinjected several times into the same patient after having been combined with positron-emitting radioactive atoms and would become detectable by PET imaging.

Many other fluoroinated tracers that may have major therapeutic repercussions are under clinical evaluation and are aimed at studying various tumoural functions (tumoural proliferation, hypoxia, chemotherapy-induced apoptosis, etc.).

Other positron emitters will become available in the future, like copper-64 (12-hour half-life), iodine-124 (4.1 days half-life) and yttrium-86 (15 hours half-life) in indications that cannot be developed with fluorine-18 owing to its half-life that is too short (110 minutes).

The development of new radiopharmaceutical molecules has no theoretical limit owing to the great number of molecules in the organism and in biological engineering which synthesises new molecules.

Nuclear medicine has a promising future. However, the economic and regulatory constraints to which radiopharmaceuticals are subject are curbing their take-off.

In effect, even if their development costs are lower than those of drugs, they remain high whereas it is a matter of small markets with low profitability. In addition, it should be noted that the time period between the beginning of the development of a radiopharmaceutical and its marketing is around 8 to 10 years.

Since Act no. 92-1279 of 11 December 1992, radiopharmaceuticals used in nuclear medicine have the status of drugs. In this respect, they are subject to the same regulatory framework, especially concerning the market authorisation process. As the toxicity of radiopharmaceuticals administered at very low doses has not been demonstrated, the question of a relaxation of these regulations is sometimes broached so as to give patients earlier access to the latest advances in nuclear medicine.