The medical use of radiopharmaceuticals up to 2025

An exploration of the future medical use of high flux reactor isotopes

A report written and translated by Technopolis Group, commissioned by the Dutch Ministry of Housing, Spatial Planning and the Environment (VROM), and supported by the Dutch Society of Nuclear Medicine (NVNG) under the lead of Dr. J.F. Verzijlbergen

This document constitutes the official position of the EANM (European Association of Nuclear Medicine) concerning the prospects of a technetium shortage, after revision by the EANM Executive Committee and the National Delegates of the EANM.

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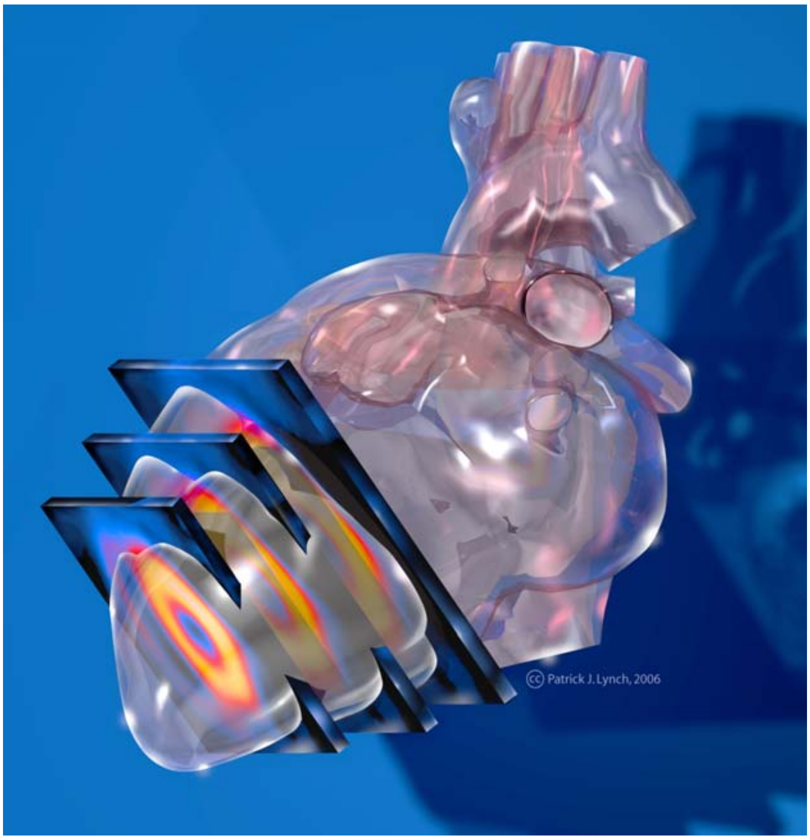

SPECT nuclear imaging of the heart, short axis views, Patrick J. Lynch

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1. Introduction

1.1 A study commissioned by the Ministry of Housing, Spatial Planning and the Environment (VROM)

In April 2008, Technopolis received a request from the VROM Ministry within the decision framework for the construction of a new High Flux Reactor (HFR). The Petten-based HFR, which will reach the end of its useful life in the not too distant future, is used for the neutron irradiation of uranium. In the process molybdenum is created, which decays into technetium. Technetium is widely used in nuclear medicine for imaging techniques.

In 2003, a report by VROM's Civil Service steering group made it clear that there is currently no alternative to the medical applications of technetium[1]. The use of HFR products for medical imaging techniques also makes a major contribution to HFR's operating results. Indispensable medical applications and the economic rationale both play a part in legitimising the construction of a new research reactor.

If an application is made for a new research reactor, the Dutch Government, including the VROM Ministry, will have to decide on its justification. In this context the VROM Ministry will have to consider not only the need for HFR products (Technetium in particular) but also what alternative technologies might have to offer in the longer term, i.e. after 2015. VROM's request therefore concerns an exploration into alternative future technologies to gain an insight into the relevance of a new research reactor. The exploration will involve not only alternative production methods but also alternative (imaging) technologies. The present report addresses only the latter question.

1.2 HFR background

Since 1962, the HFR has been in the possession of the Institute for Energy (IE) of the Joint Research Centre (JRC) of the European Commission (EC). The Nuclear Research and Consultancy Group (NRG) is the reactor's licensee. The reactor is operated and maintained by NRG personnel.

The HFR is the largest European producer of Molybdenum-99, which decays to technetium-99m, the radio-isotope used in many radiopharmaceuticals. Radiopharmaceuticals are principally used for imaging of biological bodily processes. The most frequently used imaging isotope is technetium. In technetium-based imaging, many different molecules can be labelled by means of this isotope. These molecules are administered to the patient, enabling visualisation of the radiopharmaceuticals by means of specific imaging equipment. This application is used for diagnostic purposes in various medical areas, including oncology and cardiology, as well as in bone scanning and the functional imaging of organs such as kidneys, liver, brain and lungs. The importance of technetium to the medical world is considerable: 80% to 85% of all nuclear examinations use technetium, totalling 40 million examinations a year, half of which are in North America[2] and 30% to 40% in Europe. Approximately 250,000 examinations[3] take place in the Netherlands.

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[1] Medische isotopen en de hoge flux reactor. [Letter to the Lower House of the Dutch Parliament] No. 25422-27 with appendix, March 2003.

[2] Triumf, 2008. Making Medical Isotopes.

[3] NRG: http://www.nrg-nl.com/product/fuel/isotopes/index.html, visited August 2008.

Apart from technetium, there are various other HFR products with medical applications (see Table 1). The most important of these other isotopes in terms of market size are iodine-131 and iridium-192. These are of great importance to particular groups of patients. In addition, there are other isotopes whose use is increasing, including lutetium-177 and yttrium-90. Their application is connected to new developments in the therapeutic application of radio-isotopes.

Table 1 Overview of possible HFR medical applications

HFR Product	Application
Molybdenum-99/ technetium-99m	Diagnostic imaging in oncology, cardiology and bone scanning, and the functional imaging of organs such as kidneys, liver, brain and lungs.
Iodine-131	Treatment of thyroid gland disorders and cancer.
Xenon-133	Diagnostic lung function imaging.
Strontium-89	Treatment of painful bone metastases.
Iridium-192	Cancer treatment, including cancer of the lungs, head, neck, mouth, tongue and throat, and treatment of vascular constriction.
Samarium-153	Treatment of metastatic bone pain and bone cancer.
Rhenium-186	Treatment of metastatic bone pain and arthritis.
Iodine-125	Treatment of prostate cancer and ocular cancer.
Yttrium-90	Treatment of arthritis and malignant lymphomas.
Erbium-169	Treatment of arthritis in smaller joints
Lutetium-177	Treatment of tumours.
Holmium-166	Development of treatments for liver cancer and blood cancer.

NRG, 2008: www.nrg-nl.com

1.3 Aim of the study

The investigation commissioned by the VROM Ministry entails an exploration into the possibilities of future alternative medical imaging technologies and the future medical need for radio-isotopes in general and technetium in particular. Currently, the HFR is of great importance for the production of radiopharmaceuticals and to the medical world in general, at the national as well as the European and worldwide levels. The question of what the situation will be like in the period 2015 - 2020 needs to be answered in terms of the following research questions:

1. *'What is the predicted market size of future imaging technologies for medical purposes – that is, between now and 2025 – and what will be the relative share of technetium-based imaging applications in that market?'*

2. *'What new or developing medical imaging technologies may affect or supersede technetium-based imaging technology in the period between now and 2025, in terms of both quality and quantity?'*

These questions concern not only aspects of technology or feasibility, but also non-technological aspects.

With respect to technological aspects, the time needed to develop a particular technology for medical applications is relatively long owing to stringent regulations. Moreover, if a new technology were to become available, its application would not necessarily be as wide as the current application of technetium.

With respect to non-technological aspects, factors such as cost, patient safety, limited radiation burden, logistics, infrastructure and staff technical expertise may all play a part in the choice of a particular imaging technology or modality.

1.4 Demarcation of the study

An estimated 90% of radiopharmaceuticals are used in medical imaging. Therefore we shall concentrate on medical imaging techniques. Medical imaging technologies make use of not only reactor isotopes like molybdenum-technetium but also radio-isotopes which are produced in a cyclotron (particle accelerator). In this study, the context of the different imaging techniques and the development of each of them are presented. Other applications of radiopharmaceuticals, such as in therapy, are also included in this report because of their qualitative medical importance; however, less emphasis is placed on them because of their smaller quantitative importance in comparison to medical imaging.

In this exploration into the future, the period up to 2025 was chosen. Although the lifespan of a possible new reactor would far exceed 2025, the study is restricted to this period because of growing uncertainty beyond 2025.

As already mentioned, the questions considered include technological aspects of feasibility, but also non-technical issues. Because of the very strict regulations, the period for medical application of technological development is rather long. When a new technology is available one cannot simply assume that it will be used as much as technetium is at present. Other factors which could play a major role in the choice of imaging technology or modality are costs (for treatment but also for investment in instruments), security for patients, limitation of exposure to radiation, logistics, infrastructure (e.g. suitability for a cyclotron) and the technical expertise of personnel.

The study is principally oriented towards the situation in the Netherlands, where medical imaging is well developed owing to the presence of a large Dutch producer. In other countries the relationship between the different imaging technologies could be different; therefore the presented results cannot simply be extrapolated. Nevertheless, the same questions are relevant on an international scale, given the shortfall in the production of reactor isotopes.

1.5 Report layout

The report attempts to provide the broadest based answers to questions of place and volume regarding the future use of technetium-based medical imaging. Chapter 2 first explains what methodology was adopted and why. This is followed in chapter 3 by a discussion of current medical imaging modalities and their use, providing a more detailed picture of the production of radiopharmaceuticals and market developments in this area. Chapter 4 deals with predicted future developments concerning the application of various imaging modalities and the use of technetium. Chapter 5 contains a summary of the conclusions.

2. Method of investigation

Answers to the research questions are provided by a combination of methods for the identification of future developments. The greatest possible number of experts has been involved in the entire process, enabling the creation of a sound picture of future developments in imaging technologies in general and the use of technetium in particular. Technopolis has refrained from making technological choices itself: the independence and scientific correctness of the study are guaranteed by an experts' committee.

2.1 Explorations into the future

Exploring is a way of anticipating future sector developments in a timely fashion. The purpose of an exploration is, among other things, to develop a picture of the future jointly with others inside or outside the organisation in order to gain an insight into the location of future changes. An exploration is also a process for the identification of such changes and their impact on an organisation's environment. Explorations may be quantitative as well as qualitative, and may be based on expert opinion (as, for example, in a Delphi survey). Various methodologies are available, including environmental scanning, targeted surveys, scenario analyses, roadmapping, brainstorming sessions and panels of experts. Clearly, all explorations into the future are accompanied by a measure of uncertainty; the further the view of the future, the more uncertain and varied the results.

The present exploration uses the following combination of methods to arrive at a maximally reliable result:

- an experts' committee;
- structured and exploratory interviews; and
- a Delphi study, accompanied by a survey.

The above methods are discussed in greater detail below.

2.2 Experts' committee

An experts' committee (EC) was important in safeguarding the quality of the study. The committee was composed of high-level experts, with a collective insight into the various areas relevant to medical imaging, diagnostics and research (see appendix A.1). At three stages in the investigation the EC made the following key contributions:

- identifying experts, in relation to both the interviews and the Delphi survey;
- providing an overview of the current state of the art;
- validating the results of the Delphi exploration and generating a consensus.

2.3 Exploratory interviews

One of the first exploratory steps is mapping of the environment: what are the domains and the medical indications to which radiopharmaceuticals are applied, what other imaging technologies exist and what are the purposes for which they are used, what are the prospects, and what are the present and future domain issues and uncertainties? What environmental changes affect the domains in question?

For this part of the exploration, interviews were conducted with ten experts (researchers and end users) in the area of imaging and nuclear medicine, as well as representatives from industry (see Appendix A.2). These exploratory interviews provided greater insight into the most recent technological developments, as well as the possible role of non-technological aspects in future developments.

2.4 Delphi survey

The purpose of a Delphi survey is the identification of the views held by a certain target group, and the development of a joint image of the future. The studies often involve the generation of a design orientation in relation to research which is predominantly technological in nature. Delphi surveys involve consultations with large groups of experts, who are asked for their opinions on certain problems or issues, and possible solutions. Delphi surveys are particularly useful at the goal-determining stage. They help in gaining insight into important future developments for relevant stakeholders in the target group and their expectations in relation to those developments. The disadvantage of the method lies in the fact that the anonymity of the survey increases the risk of a low response rate. Preferably, therefore, the participants are a group of committed stakeholders or experts pleased to offer their opinions.

In the present case, experts from different areas shared their views on the development of future imaging technologies that might provide alternatives to technetium. Our Delphi survey used an online questionnaire (SurveyMonkey) to safeguard the survey's efficiency and effectiveness.

The Delphi survey questions were validated by the Experts' Committee and were subsequently posted on line among a group of 102 mainly Dutch experts. The experts in question were reminded twice, yielding a response rate of 45%. In total, 46 persons completed the questionnaire. Figure 1 contains an overview of the geographical distribution of respondents.

Figure 1 Geographic distribution of the respondents

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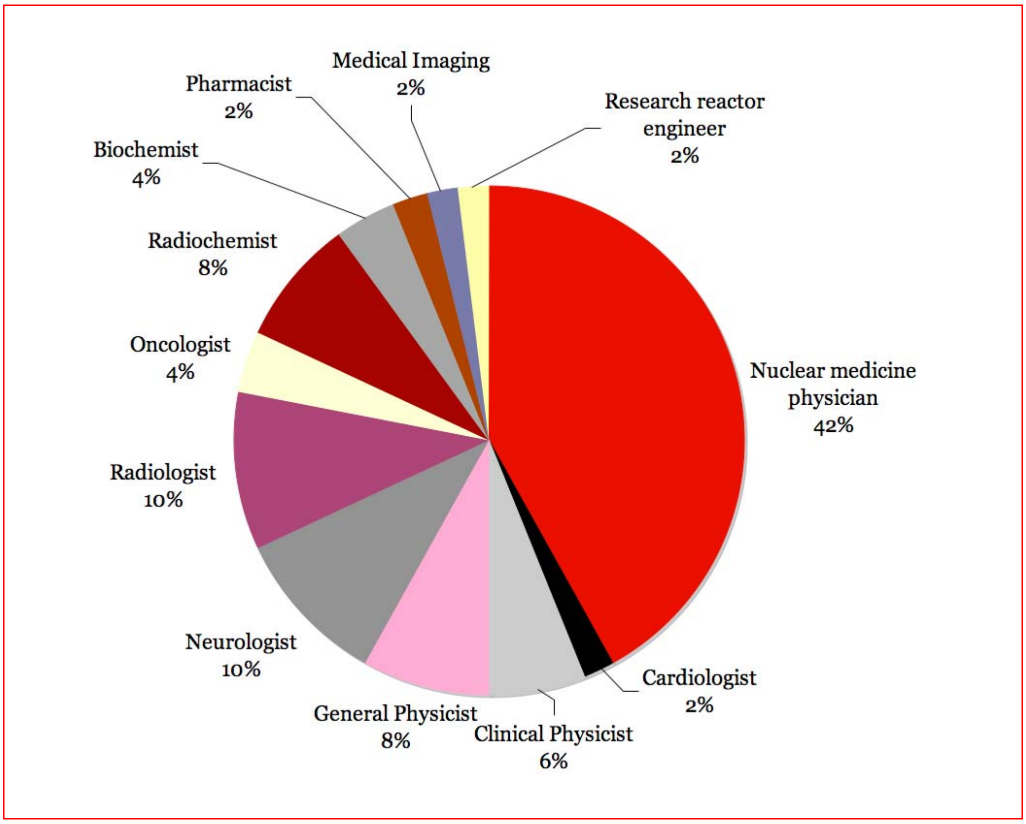
The group of respondents included a high percentage of nuclear physicians (42%). This group has the best insight into the use of reactor isotopes in clinical practice. The other respondents were radiologists, internal medicine specialists, oncologists, (clinical) physicists, (radio)chemists and pharmacists. Approximately 70% of respondents were physicians; the others had mainly technical backgrounds (see Figure 2).

Figure 2 Respondents' fields of expertise



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3. Current system

3.1 Explanation of technologies

Following the discovery of X-rays in 1895, many types of imaging technique were developed in the 20th century, to afford, as it were, a look into the human body.

It is impossible to imagine current medicine without medical imaging, a process in which computers play an indispensable part. In 2006 about 8.5 million X-ray photographs were taken; more developed techniques such as CT and nuclear imaging are frequently used, and the number of procedures is growing rapidly. In 1991, 360,000 CT examinations were conducted, but by 2006 the number had risen to 890,000. The number of nuclear examinations grew from 200,000 in 1991 to 380,000 in 2006. [4]

Medical imaging is a field that is still under strong development. Refinement of imaging techniques, increases in image resolution and specificity, increases in efficiency, more economical forms of radiation, etc. still demand a great deal of research, involving physicians, engineers, physicists, chemists, IT experts, biologists and mathematicians.

3.1.1 Current imaging technologies

- CT scans

CT is short for computed tomography. The principle is fairly simple. On one side of the patient there is an X-ray source, on the other side, an X-ray detector. The source emits a narrow bundle of rays which passes through the patient in a straight line and is cumulatively weakened by the tissues through which it passes. The strength of the remaining radiation is measured by means of a detector. Subsequently the bundle of rays and the detector are shifted over a small distance, leading to a new measurement. A large number of measurements are obtained, for each of which the exact locations of the detector and the source are known. Subsequently, a two-dimensional array is constructed by computer software. One way of back-calculating the original X-ray tissue densities is by means of a back-projection algorithm, whereby the density of a measurement is selected to examine the number and identity of the cells passed by that particular ray. The advantage of the method lies in the excellent visualisation of all types of abnormalities, including not only bones but also many other types of tissue, with a resolution capacity of one or a few millimetres. The disadvantage is, in particular, the higher radiation burden compared with conventional X-rays (1 CT scan is, roughly speaking, the equivalent of 200 X-ray photographs).

- MRI scans

MRI is short for magnetic resonance imaging. The technology makes use of the fact that protons (mainly hydrogen but also phosphorus particles) behave like tiny magnets, creating a magnetic field. The process is known as particle ‘spin’. Spin is capable of operating with or against an external magnetic field. There is a difference in energy between the two states, depending on the strength of the external magnetic field. When nuclear protons are subjected to an electromagnetic radiation pulse with

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[4] RIVM: Diagnostic: trends in number of examinations
http://www.rivm.nl/ims/objrct_document/019n1101.html

the precise amount of required energy (in MR scanners the pulses are generated in radio waves), proton spin may 'turn over'. After a short time the nucleus thus 'affected' falls back into its basic state, emitting a photon in the process. The creation of a gradient in the strength of the magnetic field, as well as interactions with the hydrogen nuclei, and measurement of the amount of different wavelength radiation that returns from the regressive spin jointly provide information about the numbers and locations of hydrogen nuclei. A three-dimensional image is formed by means of receivers and data processors. To visualise the result, the scanning application is usually presented in the form of computer simulations of body or head 'slices', which may, as required, be viewed in three (sagittal, transverse and coronal) anatomical planes, as well as from any desired angle. Modern MR scanners have a resolution capacity of approx. 0.3 mm (2005). To increase MR scanning contrast, a contrast fluid may be injected into the bloodstream. In the case of MRI, such fluids usually include gadolinium compounds, which have paramagnetic properties.

MRI thus enables the investigator to distinguish between tissues containing a great deal of hydrogen and those containing little hydrogen. Since all types of tissue have different hydrogen densities, the technique enables detailed anatomical observations; for example, distinguishing blood from fat and organ tissues. Consequently MRI scanners are particularly useful in obtaining images of soft tissues. The advantage is that no use is made of X-rays or radioactivity. The drawback is that, owing to its strong magnetic field, the technique is not suitable for patients with metallic implants (such as pacemakers).

- Echography

Echography, also called ultrasound, is a technique that applies ultrasonic sound waves, which move through the body and reflect areas at the interfaces between soft and hard tissues. The type of sound applied in medical echography is ultrasound; that is, sound of such a high frequency that it is not detectable by human hearing. The ultrasound enters the body via a transducer. The ultrasound waves reflected in the body are received by the same transducer (which transmits and receives in turn) and are converted into a (very weak) electrical AC voltage. The electrical echo signals are subsequently converted by a scanning converter into video images, which appear on a monitor. The possibilities for digital processing of the signals have expanded enormously in the last few decades.

The most widely known application of ultrasound is in pregnancy monitoring, but it can also be applied, for example, in measuring speed of blood flow. The fields of medical application include radiology, cardiology, urology, obstetrics and gynaecology in general. The disadvantage of the technique is its limited applications. It is mainly suitable for soft tissue. The advantage of the technique lies in the absence of radiation.

- Optical imaging

Optical imaging is a technique based on interference and the bending of light that is fired onto a body or tissue from a laser or infrared light source. The body is injected with proteins marked by, for example, a fluorescent marker. Optical imaging may be subdivided into diffusion and ballistic imaging systems. Since the penetrability of the body in relation to light is relatively small, optical imaging is unsuitable in certain contexts, for example organ examinations.

- Nuclear medicine

Nuclear medicine is a mainly medical diagnostic discipline for imaging metabolism and other functional processes in the human body. Prior to the imaging process a radioactively labelled tracer is administered to the patient. The strength of the technique lies in the fact that substances move to organ systems in very selective ways. Labelling these substances to radioactive tracers (particularly technetium) enables imaging of the distribution of such substances in the human body with the aid of gamma cameras or PET scanners. Three different modalities are available for this process: planar scintigraphy, SPECT (single-photon emission computed tomography) and PET (positron emission tomography).

- Planar scintigraphy is the simplest available technique, yielding a two-dimensional projection image of tracer activity distribution in the human body. The technique is based on gamma radiation that is created in the decay process of a radionuclide.
- SPECT (single-photon emission computed tomography) was developed on the basis of planar imaging, which involves gamma cameras taking series of planar shots during rotations around the patient. SPECT generates three-dimensional images of nuclear activity distribution, enabling the physician to view activity distributions in cross-sections of the human body. The technology is based on the gamma radiation created during the decay of radioactive isotopes. The gamma radiation is received by a photon detector, which consists of a scintillating crystal (e.g. sodium iodide) in which a small light flash is created in interaction with a gamma quant. The location of the light flash in the crystal is recorded by a row of horizontal and vertical photodetectors positioned along the crystal. A collimator is positioned in front of the crystal. This is a lead plate which contains a large number of narrow channels drilled to prevent entry by gamma quants that fly off at an angle, while normally letting through quants that are perpendicular to the surface of the crystal. The process results in the detection of gamma quants in the crystal that are known to be emitted by the patient’s body part in a perpendicular position underneath the detector. The depth of the body part that emits the gamma photon cannot be measured. Consequently, the result is a kind of two-dimensional photograph of the patient, depicting organs that emit radioactive rays against a less active background. Moving the detector in a circle or semicircle around the patient and combining the series of two-dimensional images thus obtained (e.g. by means of a software back-projection algorithm) enables the generation of a three-dimensional image with a resolution capacity of between 0.5 cm and 1 cm, which is relatively low compared with that of other technologies (CT, MRI and PET scanning). Currently, research is being conducted into the use of other crystals to increase resolution capacity. Isotopes that are suitable for SPECT typically have a half-life of several hours to a few days. Isotopes such as technetium-99m, with a half-life of 6 hours, are frequently used. With longer half-life values, the radiation burden for patients becomes too high, while a shorter half-life would allow neither for the required speed of connection constructions nor for sufficient storage time.
- PET (positron emission tomography) has entered clinical practice in the last few decades. Compared with SPECT, the technology offers the advantages of higher sensitivity, increased spatial resolution and the use of small biologically fundamental tracers. However, PET scanning has the disadvantage of being more expensive than SPECT scanning.

  PET is an imaging technique whereby a radioactive isotope (a PET radionuclide) is administered into the patient’s body. During decay, the isotope produces positrons (particles with the mass of electrons but with a positive charge). Electron and positron interaction causes the annihilation of both particles, releasing energy in the form of two gamma photons. The resulting gamma rays are detected by a ring of hundreds of detectors: a PET camera. When two photons are detected simultaneously by two detectors in a 180 degree position opposite to each other, the gamma rays originate from the decay of the same positron, which must have been positioned on a straight line between the detection points. The time difference between the two gamma photon detection processes enables calculation of the linear position where the annihilation took place. However, the speed of light is so high that even modern detector rings have much greater angular than distance accuracy. A large number of joint decay events observed from different angles by the ring of detectors is capable of being composed by computer software into a three-dimensional image, for example by means of a back-projection algorithm. The resolution capacity is fairly high (a few millimetres). In fact, the resolution depends on positron load up to the point of annihilation on interaction with a (free) electron.

Since most radionuclides applied in PET scanning have a very short half-life, they must be produced shortly prior to application. PET radionuclides are produced in cyclotrons or nuclear reactors. For PET applications, cyclotron-produced radionuclides are normally used, which, as non-radioactive atoms, are included in natural chemical synthesis reactions. For example, glucose uptake by the body can be visualised in this way, while use can also be made of radioactive hydrogen (H) or carbon (C).

PET applications depend on the nature of the substance selected. The choice is determined by the process or tissue to be imaged. For example, PET is applied in examinations of cardiovascular disease [to determine blood flow and the viability of the heart muscle by means of ^{13}N-NH3 (ammonia) and ^{18}F-fluorodeoxyglucose (FDG)] and brain diseases (e.g. Alzheimer's, Parkinson's disease and other dyskinesias). Compared with SPECT, PET offers higher sensitivity and resolution, while positrons are normally more suitable for the visualisation of fundamental body processes. The PET technique is limited mainly by the following three factors, which make it laborious and costly:

- the applied radionuclides have very short half-lives, and values of fewer than two hours or even some minutes are fairly common, requiring the presence of a nearby cyclotron for nuclide preparation;
- within the available timeframe, the nuclide must be incorporated into the substance that is to be used;
- a substance capable of showing the sought abnormality must be available to medical science.

Table 2 gives a survey of the different imaging modalities, the resolution that can be achieved and the advantages and disadvantages.

Table 2 Overview of some of the characteristics of various imaging techniques

Imaging	**Resolution**	**Based on**	**Advantage**	**Disadvantage(s)**
CT	0.3 mm	X-rays	Visualisation of defects in bones and organs	Exposure to radiation
MRI	0.3 mm	Magnetism	Imaging of soft tissues	Cost and magnetic interference (e.g. with pace makers)
SPECT	7 mm	Gamma radiation	Imaging of metabolism and functional processes	Low spatial resolution, exposure to radiation
PET	4 mm	Gamma radiation	Imaging of metabolism and functional processes	Cost, availability and exposure to radiation
Ultrasound	1 mm	Sound	Safe imaging of soft tissues	Limited applicability
Optical	0.01 mm	Light	Measurement of activity over the course of time	Limited penetration depth

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3.1.2 *Medical indications for current modalities*

The choice of one of the different imaging technologies depends in the first instance on the medical indication that requires diagnosis. In some cases such indications can be shown by means of a single technology. However, given uncertainty about a particular condition, several available techniques may be used to confirm a diagnosis. For that reason the overview of indications below shows a certain amount of overlap. For example, a neurologist might use various imaging technologies to show an abnormality; the choice of modality usually depends on the neurologist's expertise, as well as the expertise of the available hospital staff and the presence or absence of specific modalities. A contributory fact is the division between nuclear medicine and radiology into two separate medical disciplines which are respectively responsible for SPECT/PET and CT, MR and conventional X-ray examination and echography. In some hospitals these departments operate as separate units while in other hospitals they are integrated. In some hospitals one discipline may be stronger than the other, and this situation may also change when new staff are appointed. In short, the list of indications below must be considered in the light of these observations.

- CT indications (non-exhaustive)

Oncological indications of various sorts, both for staging and for follow-up, abnormal urinary tracts, complex skeletal disorders, bone tumours, monitoring liver shunts, neck abnormalities and suspect abdominal swellings.

- MRI indications (non-exhaustive)

Brain diagnostics for disorders such as tumours (brain, hypophysis), ischaemia (deficient supply of oxygen to the cardiac muscle), arteriography (blood vessels), demyelinisation (of the nerve cells), trauma, dementia, infections, slipped discs, spinal marrow abnormalities and bone infections, myocardial infarcts, cardiomyopathy (disorders of the cardiac muscle), disorders of the cardiac valves, disorders of the kidneys and adrenal glands, pelvic abnormalities (prostate and womb), swellings and tumours in soft tissues, disorders of soft joint tissues and ocular nerve blocking.

- SPECT indications (non-exhaustive)

Localisation and estimation of size and extent of specific tumours, skeletal abnormalities, inflammations or infections, blood flow to the cardiac muscle, cardiac function and brain abnormalities, including Parkinson's disease.

- PET indications (non-exhaustive)

Particularly valuable within the framework of staging and follow-up of lung cancer (NSCLC) and malignant lymphatic disorders, intestinal carcinomas, head and neck tumours, unexplained pulmonary affections, melanomas, oesophageal carcinomas, ovarian tumours, thyroid tumours, cardiology (vitality of cardiac muscle tissue) and neurology (dementia).

3.2 Production of radiopharmaceuticals

3.2.1 *The current situation*

Distributed all over the world, there are one hundred reactors that produce isotopes for purposes other than power generation. However, the majority are not suitable and are not used for medical applications. Supplies of molybdenum/technetium for the entire medical market are dominated by only a few reactors. Table 3 presents an overview of the reactors that produce molybdenum for medical use. The table contains two estimates, one provided by NRG in 2002 and one made for Nuclear Engineering International (NEI) in 2008.

Table 3 Overview of the worldwide production capacity of molybdenum-99

NRG, 2002		NEI, 2008	
Reactor	*Share*	*Reactor*	*Share*
NRU (Ca)	45%	NRU (Ca)	38%
HFR (EU/NL)	27%	HFR (NL)	26%
Safari-1 (SA)	9%	Safari-1 (SA)	16%
BR2 (Be)	8%	BR-2 (Be)	16%
HIFAR (Aus)	2%	Rest of the world	4%
OSIRIS (F)	2%		
FRJ2 (D)[5]	2%		
Others	5%		

NRG, 2002 & L. Kid, Nuclear Engineering International, 2008

In the European context the HFR is an essential reactor, given that it meets approximately two-thirds of the European demand and more than one-quarter of the worldwide demand for technetium (see Table 3; the rows marked in grey indicate the European share). The HFR is a large producer because it meets two key conditions. An effective system for the provision of reactor isotopes for medical application requires a high number of operational hours and a sound infrastructure. Operational hours are important since a fairly constant supply of isotopes is required, in part owing to molybdenum decay. Furthermore, the infrastructure surrounding the reactor must be highly developed, enabling the speedy processing of isotopes (according to Good Laboratory Practice guidelines) and subsequent transportation to hospitals. Molybdenum has a half-life of 66 hours, requiring isotopes to be delivered to hospitals within a few days. On both points the HFR scores highly as one of the most favourably situated reactors in the world. It is operational highly frequently, and the Netherlands has a strong infrastructure and is densely populated, enabling all hospitals to be reached in good time. From an international perspective the situation of the Netherlands in general and the location of the HFR in particular (in the neighbourhood of Amsterdam Airport Schiphol) is an important aspect in the prominent position of the HFR in the European market.

Apart from the importance of HFR's production share in absolute terms, one of the other aspects of the placement of several reactors on European territory is the desire to be self-supporting in radiopharmaceuticals. Dependence on non-EU countries is often regarded as undesirable, since these are often countries that are politically or diplomatically unstable and where favourable working conditions or safety are not guaranteed. As there are only a few suitable reactors outside Europe, European willingness to be dependent on the countries involved is a political question.

[5] The research reactor Juelich has been closed in the meantime

For the Netherlands as well as the rest of Europe, the HFR is currently of great importance in maintaining the production capacity of medical isotopes and safeguarding the availability of sufficient reactor isotopes for medical imaging[6].

3.2.2 The future

The use of technetium has increased by 50% in the last ten years, and is expected to continue to rise in the next few years[7]. NRG expects a moderate increase in European sales during the coming years. It also expects an increase in the use of technetium outside Europe, in particular outside the conventional markets. Increased prosperity in developing countries will lead to greater demand for nuclear imaging, and thus to higher pressure on the world market for technetium. Although NRG expects the relevant countries to become self-supporting in the long term, they also predict extra large purchases during transitional stages (between increased use and production setup).

In this light there is a risk of a shortage of medical isotope-producing reactors in the long term. This situation is exacerbated by (increasingly frequent) reactor maintenance activities. The current four major reactors, collectively responsible for 96% of molybdenum production, are already obsolescent, having been commissioned in the 1950s and 1960s[8]. In all probability these reactors will reach the end of their useful life before long. Safety considerations require regular maintenance, and these reactors will eventually be closed down.

Furthermore, no great increase is anticipated in suitable new reactors. No new reactors are expected or planned in North America either in Canada or in the United States, although there are some reactors in the United States that could be converted to produce small quantities of technetium[9]. In France the construction of the Jules Horowitz reactor has commenced. Commissioning is planned for 2014. The reactor will produce sufficient technetium for approximately one-quarter of current technetium use. However, this will not be sufficient to meet the increasing demand, especially when viewed in combination with the current reactors' regular production failures. For further information on the production of radiopharmaceuticals, please refer to the report of the Reactor Instituut Delft, which has been undertaken on behalf of VROM at the same time as this study, or to international studies[10, 11,12].

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6 Rapportage over de gevolgen van de (langere) sluiting van de hoge flux reactor in Petten voor de voorziening van radio-isotopen voor medische toepassingen**.** [Report on the consequences of (longer-term) closure of the Petten high flux reactor for the provision of medical reactor isotopes]. Inspectie voor de Gezondheidszorg, 2002. [Healthcare Inspectorate]

7 L. Kid, 2008. Cures for Patients. Nuclear Engineering International.

8 NRU: http://www.nrureactor.ca/html/index.html

Safari-1: http://www.igorr.com/home/liblocal/docs/Proceeding/Meeting%208/ouo_06.pdf

BR2: http://www.sckcen.be/SCKCEN_Information_Package_2007/CDROM_files/NL/Info_NL/pdfs/2_Installaties_De_BR2_Reactor.pdf

9 Advanced Molecular Imaging and Therapy, 2008. Preliminary Draft Report of the SNM Isotope Availability Task Group

10 Advanced Molecular Imaging and Therapy, 2008. Preliminary Draft Report of the SNM Isotope Availability Task Group

11 Triumf, 2008. Making Medical Isotopes

12 L. Kid, 2008. Cures for Patients. Nuclear Engineering International.

3.3 Respondents' use of radiopharmaceuticals

Section 3.1.2 indicates which modalities are suitable for which medical applications. However, it does not make clear what are the key modalities for certain disorders. The questionnaire asked respondents which type of imaging technology they used for certain disorders. Respondents were asked to distribute 100% over the modalities for use within the following categories: cardiology, oncology, neurology, bone scanning and other organ imaging.

The modalities that use reactor isotopes are planar nuclear imaging, SPECT and multi-modal[13] imaging technologies which combine SPECT with another modality. Estimates of the relevant reactor isotopes for each disorder domain require summing of the relative contributions of planar and SPECT modalities.

The data presented in the sections below require the comment that the picture sketched need not be entirely representative of the use of reactor isotopes in the whole of Dutch medical practice. Our group of respondents was composed of leading physicians and researchers from university or other major hospitals. In general, these respondents have more modalities available than an average regional hospital. They are more often able to use PET scanners and scanner operating personnel than the average Dutch hospital. Furthermore, the respondents' hospitals have more expertise at their disposal in relation to imaging technologies, which is bound to affect the choice of certain modalities. The experts' committee has estimated that conventional technologies would be more prominently represented if a picture of total use in the Netherlands were to be provided. This would be true, in particular, of echography, CT, MRI, planar imaging and SPECT. However, the present group was selected with a view to providing a comprehensive overview and experience of imaging techniques in clinical practice and research.

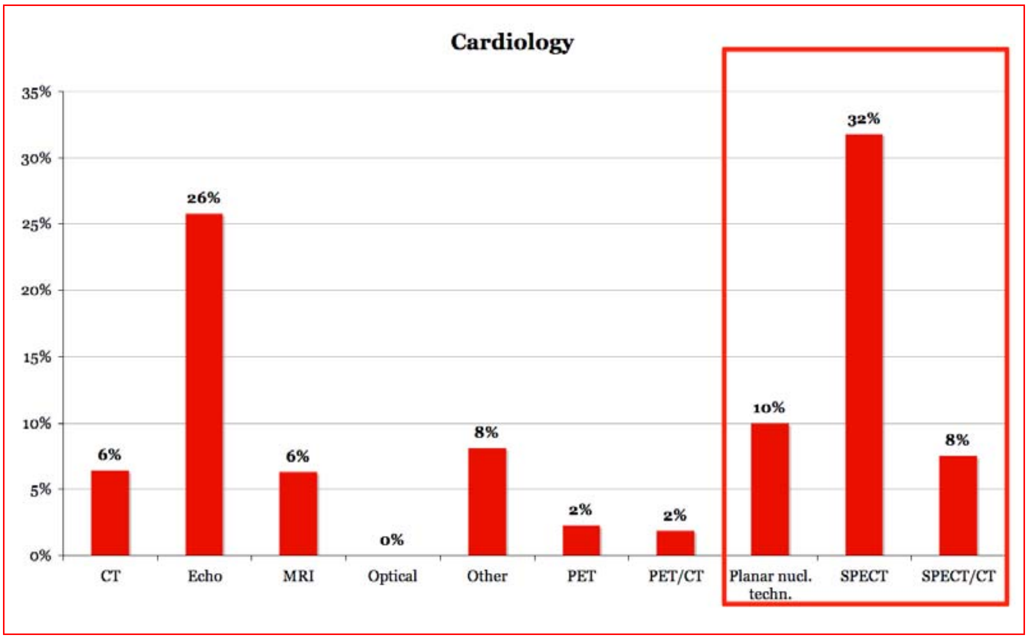
[13] Multi-modal scanners are imaging devices which combine different modalities in a single piece of equipment.

3.3.1 Cardiology

Figure 3 shows the survey results regarding the preferential use of imaging in cardiology. The dominant modalities in this domain are SPECT and echography. According to the experts' committee, this matches the most common medical practice for highly prevalent cardiac complaints and cardiac infarcts or ischaemia. To a lesser extent, planar nuclear imaging is also relevant in cardiology, as are MRI and CT, which are mainly used in heart failure diagnostics. PET modalities are not yet common in cardiology.

In total, respondents reported use of modalities that are dependent on reactor isotopes in 50% of cases. These were distributed as follows: planar nuclear imaging, 10%; SPECT, 32%; and SPECT/CT, 8%.

Figure 3 Relative use of modalities in cardiology. Imaging techniques that require reactor isotopes are shown in the red box.



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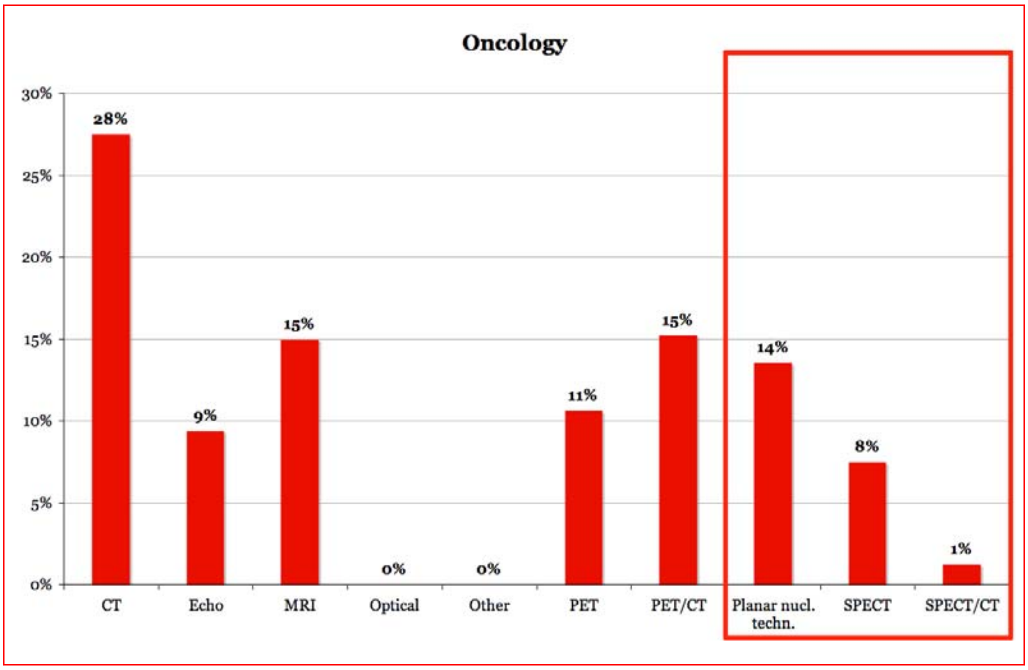
3.3.2 Oncology

Figure 4 shows the relative preferential use of modalities in oncology. The overwhelmingly dominant modality is CT scanning. Also relevant are MRI, PET, PET/CT and planar nuclear imaging. CT is still the preferred choice as the first diagnostic step in cases of suspected cancer and in treatment follow-up. In further examinations, nuclear medical imaging is used to determine tumour activity. This is possible with SPECT, but the present group of respondents often opt for a PET modality at this stage. Planar nuclear imaging is the preferred choice in determining bone metastases.

Our respondents reported use of modalities that depend on reactor isotopes in approximately 23% of cases; planar nuclear technology was used in 14%, SPECT in 8% and SPECT/CT in 1%.

Figure 4 Relative use of modalities in oncology. Imaging techniques that require reactor isotopes are shown in the red box.



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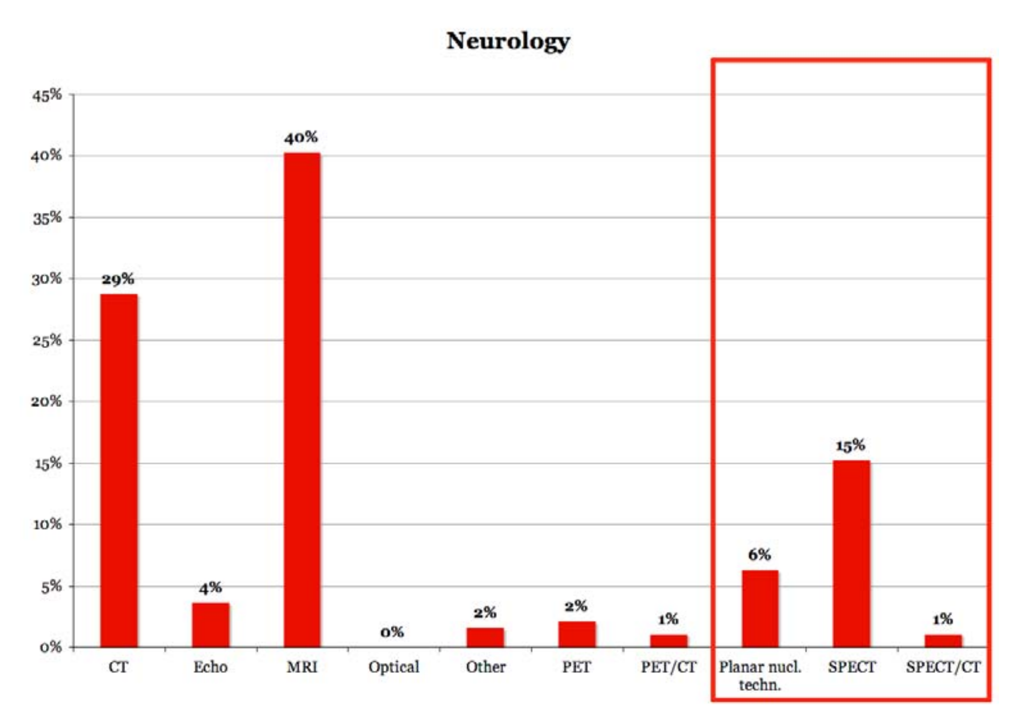
3.3.3 Neurology

Figure 5 shows the relative preferential use of modalities in neurology. MRI is the dominant modality, followed by CT. Of the other modalities, only SPECT is applied moderately often. This picture corresponds with the normal first choice in brain diagnostic indications. The important role of MRI reflects its value in imaging of the brain, as a soft tissue. The contribution of SPECT is explained by its use in diagnostics for Parkinson's disease and associated disorders, and by its use in dementia.

Respondents reported application of reactor isotopes in 22% of cases by means of the following modalities, with the following distribution: SPECT, 15%; planar nuclear imaging, 6%; and SPECT, 1%.

Figure 5 Relative use of modalities in neurology. Imaging techniques that require reactor isotopes are shown in the red box.



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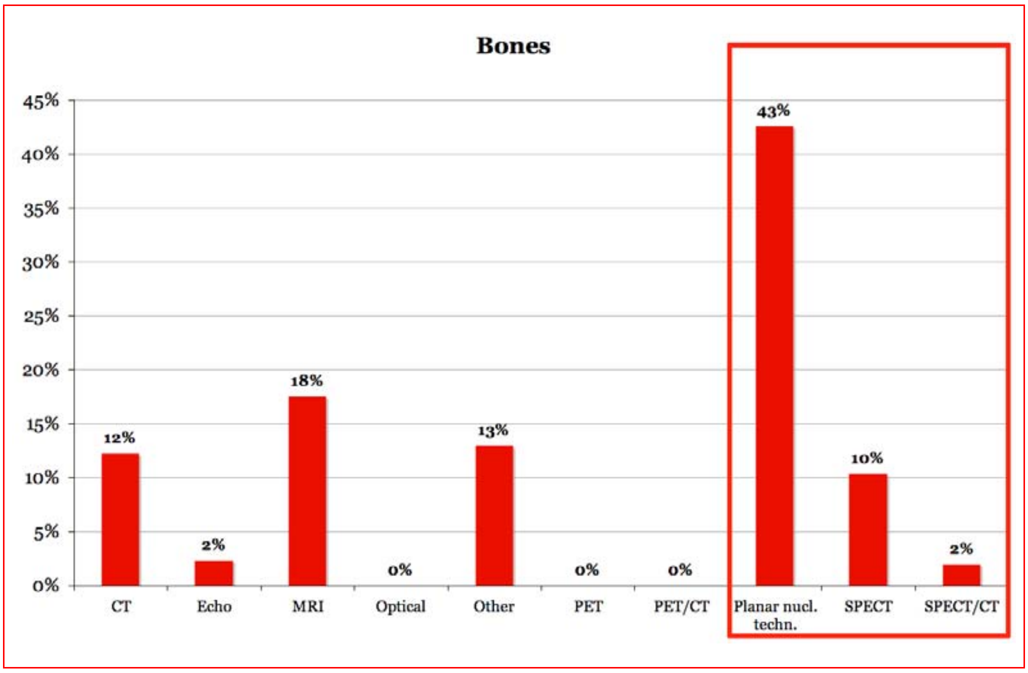
3.3.4 Bone scanning

Planar nuclear technology is the dominant modality in bone scanning, and respondents reported its use in 43% of cases (see Fig. 6). Other relevant modalities are MRI, CT and SPECT. SPECT is used mainly in determining the exact localisation of bone metastases and in orthopaedics and sports medicine. The results may overlap with the result for planar imaging in the oncology domain, thus leading to an overestimation of the total share of planar nuclear imaging. MRI is used in diagnostics for joints.

Respondents reported use of reactor isotopes in 55% of cases, particularly in planar nuclear applications but also in SPECT (10%) and SPECT/CT (2%).

Figure 6 Relative use of modalities in bone scanning. Imaging techniques that require reactor isotopes are shown in the red box.



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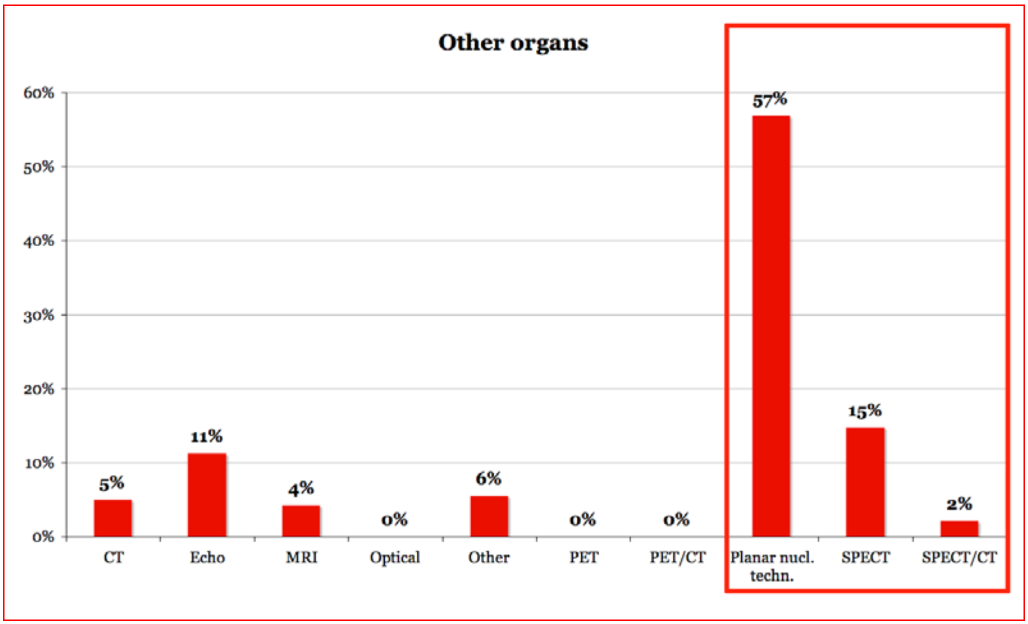
3.3.5 Other organ scanning

Planar nuclear technology is also predominant in other types of organ scanning, being applied in 57% of cases (see Fig. 7). It is used mainly for determination of the functional aspects of organs such as the kidneys and liver. Other important modalities are echography and SPECT. There may be a certain amount of overlap with SPECT results in the cardiology domain, probably leading to an overestimation of SPECT's total share.

Reactor isotopes also play an important role in examinations of the other organs. Respondents reported use of modalities requiring reactor isotopes in 74% of cases.

Figure 7 Relative use of modalities for other organs. Imaging techniques that require reactor isotopes are shown in the red box.



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3.3.6 Use for therapeutic purposes

It is estimated that more than 90% of medical reactor isotopes are used for imaging purposes. The remainder are used, in particular, for therapeutic purposes (see Table 4). Although in quantitative terms this particular domain is relatively unimportant, it is of vital importance to quality of life for a smaller group of patients. For example, there is no alternative to the iodine-131 treatment of thyroid cancer. Reactor isotopes are also of great importance in palliative therapy (which focusses on the treatment of symptoms), where they are used for pain control in bone metastases, with morphine as the only alternative.

Table 4 Reactor isotopes for therapeutic use

Isotope
Iodine-131
Strontium-89
Iridium-192
Samarium-153
Rhenium-186
Iodine-125
Yttrium-90
Lutetium-177
Holmium-166

NRG, 2002; Technopolis Group

3.3.7 Summary of findings

Reactor isotopes play a major part in current medical imaging for our respondents in cardiology (50%), bone scanning (55%) and other organ scanning (74%). There is a less prominent role for reactor isotopes in oncology (23%) and neurology (22%). As mentioned earlier, these results are not representative for the average Dutch situation, but they do provide a picture of the state of affairs in university and other major hospitals (collectively referred to as STZ hospitals [cooperating major clinical training hospitals]). This is where the majority of patients are treated. In the general Dutch situation, conventional technologies (including CT and planar nuclear imaging) are bound to have a greater share. The results in this study represent the situation in practice in the hospitals which lead the way.[14]

Although the therapeutic use of reactor isotopes is minor relative to their total use, qualitatively speaking they play a key part in this specific category.

The experts' committee endorses the above picture regarding the use of reactor isotopes. In oncology, CT is currently the dominant modality, while the use of PET is growing. MRI is frequently used in neurology, while SPECT is used in determining the

[14] A complete picture of the use of different modalities now (and in the past) can only be achieved by requesting the numbers of images taken in the departments of radiology and nuclear medicine of all Dutch hospitals, split by modality.

functionality of tissues, although in that area, too, the application of PET is growing. CT and MRI are generally used in every radiology department, while planar techniques and to a lesser extent SPECT are dominant in nuclear medicine. Reactor isotopes are consequently of great importance for medical imaging at present, particularly in the areas mentioned. Furthermore, they play an even more important role in all the hospitals without PET scanners. Currently, a great deal of research is being conducted into PET applications in a limited number of medical centres (including VUMC, UMCG, ErasmusMC, UMC St Radboud in Nijmegen and St Antonius in Nieuwegein). PET use is frequent in 10 hospitals. In addition, another 35 hospitals operate combined PET/CT scanners, enabling access to the technology in principle.

The distribution of the use of various modalities for certain disorders shows that several modalities may be used for the same disorder. As mentioned in section 3.1.2, the selection of a certain modality within an imaging domain may be based on medical considerations, or on the preference or expertise of the physician or imaging assistant. In section 4.1.2 we shall discuss determinants of the choice of certain modalities in greater detail.

4. Explorations into the future use of radiopharmaceuticals in medical practice

Radiopharmaceuticals play an important role in medical practice, in particular in diagnostic imaging. This chapter will deal in greater detail with the experts' future expectations in this area. The focus will be on whether and to what extent reactor isotopes will remain important in the future; in other words, will the modalities that currently use reactor isotopes (SPECT, planar imaging and multi-modality techniques) still be used in 2015 and 2025?

4.1 Modalities

4.1.1 Trends

On the basis of the interviews, some important trends were identified that are capable of causing shifts among the imaging modalities, potentially leading to substitution of one modality by another:

- **Improvements in current modalities.** Current modalities are still being incrementally improved by further developments, including technological improvements, such as increases in sensitivity and resolution, further software development for associated data processing and combinations of parameters. This will eventually increase scanning quality and lead to improved diagnostics, or the wider usability of particular scanners. PET is a good example of a technology that is still fully in development. Experts are still expecting great progress in this area, for example as a result of the discovery and testing of, or experiments with, new tracers, enabling the wider use of PET scanners. However, 'older' modalities such as SPECT also continue to evolve. Currently new crystals are being tested and applied, enabling higher SPECT resolutions. While some experts expect that SPECT will eventually match PET resolution capacities, others disagree.

  Our interviews show that PET is one of the fastest growing modalities. Some of the interviewees in this study, as well as a Canadian experts' panel[15], expect PET to grow more quickly than SPECT. However, it is a moot point as to whether this will lead to major shifts from investigations currently conducted by means of planar nuclear techniques and SPECT towards PET. Much of the development will be focussed, in particular, on extending the possibilities for medical science, leading to improvements in the diagnostics of specific cases and thus to the use of PET as an add-on. The interviewees also pointed out that so far no modality has disappeared from the total range.

- **Combinations of modalities**. One of the most important developments running parallel to modality improvements is the combination of modalities. Currently PET/CT scanners are among the most frequently selling multi-modal scanners. Other combinations are still under development, including SPECT/CT, PET/MR and SPECT/MR scanners. The PET-MRI combination, in particular, is a physics-intensive modality. The greatest advantage of multi-modal scanners lies in the possibility of gaining information about metabolism and spatial information (location) by means of a single piece of equipment. In contrast, in measuring metabolism by means of a SPECT scanner, localisation of metabolic processes is less clear. Such information is better established by

[15] See Triumf, 2008.

means of CT scanning applications. A combination of the two modalities achieves the best of both worlds.

Combinations of modalities require further technological development, particularly in the area of equipment integration. They also require strong software development in relation to multi-modal scanners, since two sets of data must be combined.

- **Development of new tracers**. The tracing and representation of certain processes (e.g. metabolism) or substances (e.g. certain proteins) requires tracers which attach themselves to the right place in the body and which can subsequently be represented by means of a modality. New tracers act as modality-enabling agents, increasing the modal possibilities. Currently many tracers are being developed, in particular for PET, but expectations are also high for other modalities. Nanotechnologies and bionanotechnologies hold promise for the development of new tracers and markers, including optical, MR or other modalities. Although new tracers might lead to shifts between modalities, it is not entirely clear yet which modalities will be stimulated in the process. In the recently established Center for Translational Molecular Medicine (CTMM), research into biomarkers and imaging technologies is combined.
- **Development of new treatments**. Although reactor isotopes are mainly used for imaging purposes, they are undoubtedly of qualitative therapeutic importance. Reactor isotopes already play an important role in the treatment of thyroid and prostate cancer (by means of iodine-131 and iridium-192 respectively), as well as in the palliative treatment of bone metastasis, and they appear to be fast gaining in importance. For example, some years ago lutetium-octreotate was first used as a radiopharmaceutical in the treatment of neuroendocrine tumours, which occur mainly in the stomach, intestines and pancreas, spreading harmful substances. The beauty of these applications lies in the fact that the administered substances move selectively towards the cells to be treated, in contrast to external radiotherapy which also exposes the surrounding tissue to radiation. On average, lutetium treatment yields an increased life expectancy of 4 years, with a relatively good quality of life[16].
- **Development of new equipment and modalities**. Although there is currently no prospect of a totally new modality, an exploration into the future needs to include such a scenario of ‘unforeseen circumstances’. In this survey we examined the length of time required for a new laboratory product to be developed for preferential clinical use (see Fig. 8). According to the respondents, the average duration from the first research stage to clinical proof is eight years. From that point onwards, preferential use takes at least another ten years. Therefore, if certain options have been overlooked in these explorations into the future because they have only very recently come under development, their preferential use will take another eighteen years. Although expert estimates differ quite considerably, the above averages were confirmed in our interviews with the experts from industry and medicine, as well as by the experts’ committee.

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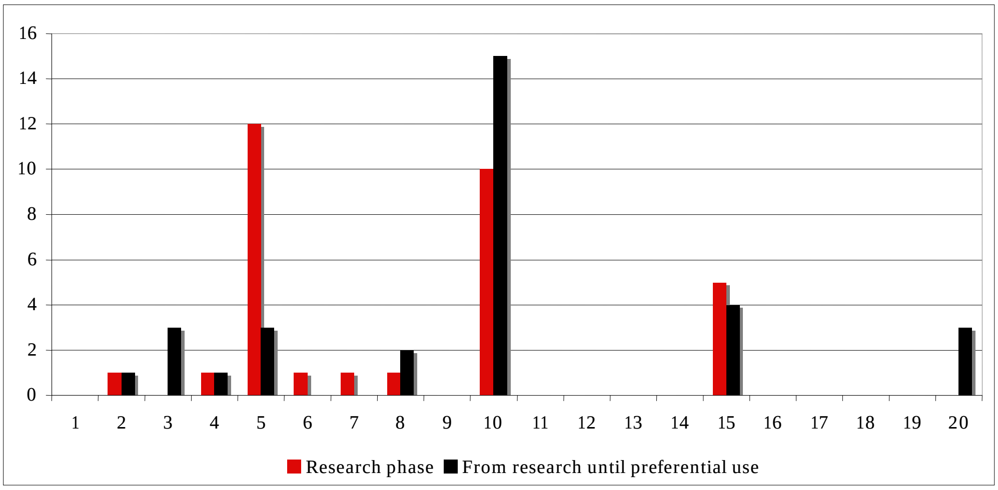
[16] http://www.nrg-nl.com/general/nieuws_nl/cms/2008/200801161635.html

Figure 8 Experts' estimates of the length of the innovation process in years from initiation of research to clinical proof, including clinical trials (red), and of the length of time, in years, from clinical evidence to preferential use (black). Average values: research phase: 8 years; implementation: 10 years



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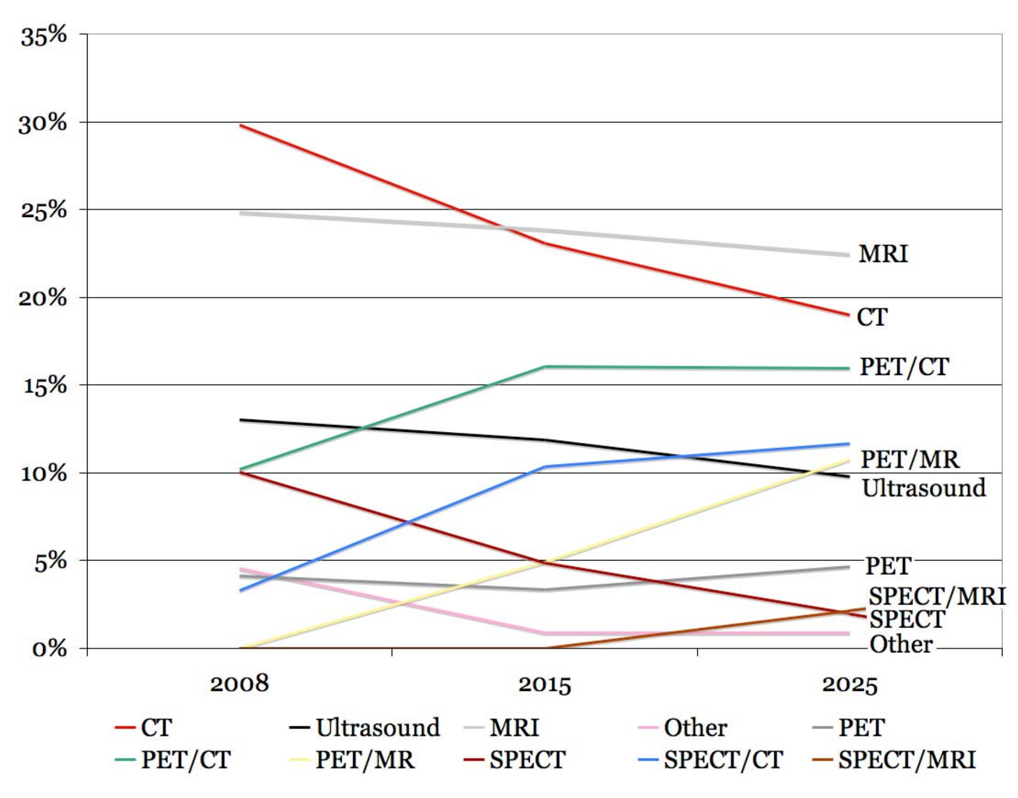
4.1.2 Expectations of use

In our survey we asked respondents about their expectations regarding the use of the various modalities in clinical practice. By means of interviews we identified all the possible modalities that might play a more prominent role in the future. Respondents were asked to distribute 100% over all the modalities for each of the years 2008, 2015 and 2025. Figure 9 shows the results. Note that the figures express the share of one modality relative to the other modalities, rather than absolute numbers.

Figure 9 Experts' estimation of the relative use of modalities in 2008, 2015 and 2025.



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Our respondents' expectations regarding modality use were as follows:

- a relative decrease in 'regular' CT (the decrease being fairly steep, in excess of 10% in 17 years);
- a slight decrease in the share of 'regular' MRI;
- a slight decrease in the share of ultrasound;
- a fairly substantial decrease in the share of 'regular' SPECT (about 7%);
- a relatively substantial decrease in the share of 'other modalities', i.e. the ones that receive estimates of a few percentage points (planar and optical in particular);
- a fairly substantial increase in the PET/CT share (about 7%);
- a fairly substantial increase in the SPECT/CT share (about 7%);
- a sharp increase in PET/MRI (non-existent as yet);
- after 2015: the advent and rise of SPECT/MRI.

In order to isolate trends for the modalities that use reactor isotopes, the multi-modality percentage points and (some) basic modalities are summed in Fig. 9. The PET/CT share is summed both for PET and CT and the SPECT/MRI share for SPECT and MRI. Thus a picture of the total use of the basic modalities is created, although the total number of scanning applications exceeds 100%.

Figure 10 Experts' estimation of the use of modalities in 2008, 2015 and 2025, categorised into base modalities

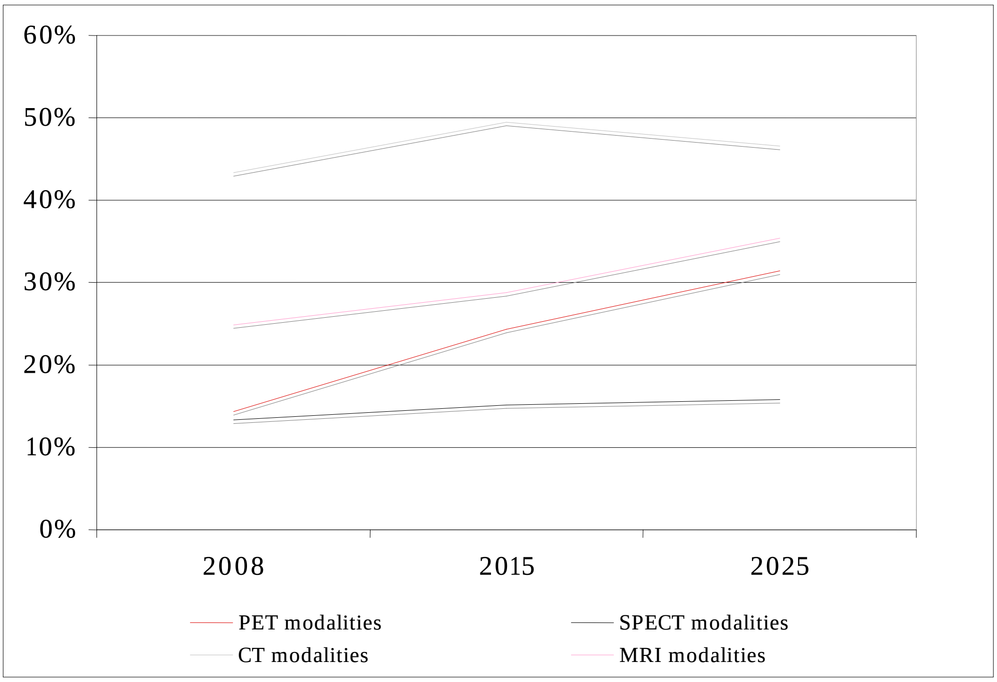

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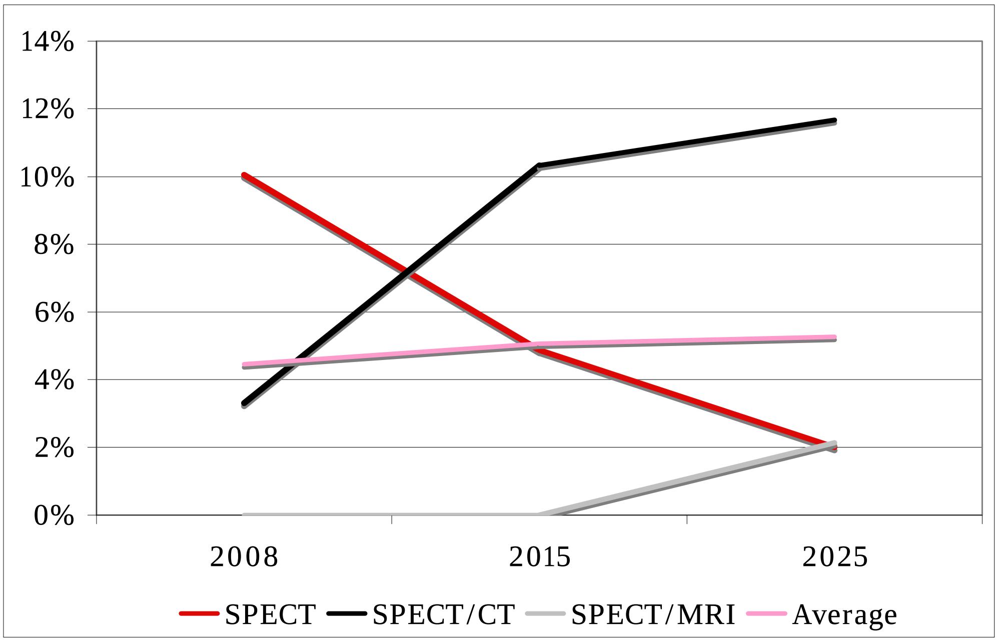
Figure 10 shows that respondents expect a strong increase in the combined use of PET and in the use of MRI. The decrease in PET and MRI is substituted by the use of multi-modality techniques. The combined use of CT is predicted to rise substantially, followed by a slight decrease attributable to greater use of MRI multi-modality techniques. SPECT is expected to stay approximately the same. The considerable decrease in the SPECT share (see Fig. 9) will be substituted by the use of multi-modality techniques: initially by SPECT/CT in particular, followed after 2015 by SPECT/MRI. Figure 11 represents an itemised picture for SPECT.

Figure 11 Breakdown of the share of SPECT modalities



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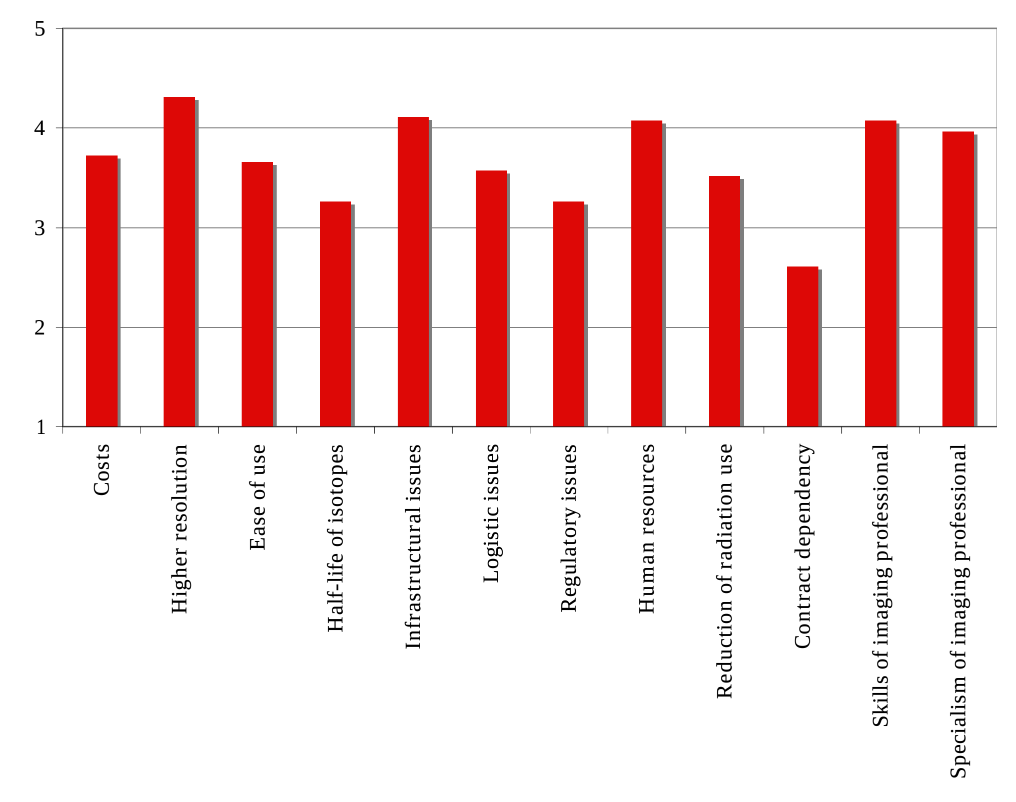
4.1.3 Dynamics of innovation

The implementation of innovative technologies is driven by both technological and non-technological factors. In the present case, technological factors concern, among other things, the resolution. Non-technological factors, on the other hand, concern problems of logistics and infrastructure relating to the use of isotopes. In the case of reactor isotopes, such problems involve the purification and reprocessing of isotopes according to good laboratory practice, and transportation to hospitals. For PET radionuclides the problems involve infrastructure relating to cyclotron production, transportation to hospitals and the availability of adequately trained personnel capable of dealing with the nuclides. In the medical domain and in hospitals, various human factors play an important role, such as the skills and specialisms of imaging assistants and convenience of use, costs, contracts and effectiveness[17].

To determine which technological or non-technological factors are decisive in the choice of particular clinical modalities, respondents were asked to indicate the relative importance or lack of importance of different factors. Figure 12 shows that the respondents considered nearly all the factors to be important to a greater or lesser extent.

[17] PET Gepast gebruik(t), ZonMW Doelmatigheidsonderzoek; January 2007

Figure 12 Factors that determine the choice of a certain modality (1= very unimportant, 2= unimportant, 3=neutral, 4=important, 5= very important)



Source: survey Technopolis Group. n=21

Only dependence on contracts was judged to be relatively unimportant. Of the four factors that scored averages exceeding 4 (important), only **higher resolution** is a technological driver. Two factors concern human aspects: **professional imaging skills** and **human resources**. The latter factor mainly concerns the highly trained personnel required for PET modalities. Finally, **infrastructure problems** were considered important, and may include technetium supply problems and difficulties in the infrastructural organisation of hospital cyclotrons. Summarising, we may conclude not only that one technological driver is higher resolution, but also that human factors largely determine a technology's success. In the present case this implies that the speed of wider PET application depends particularly on adequately trained personnel and infrastructure. The factor 'costs' was not exactly defined; it can apply to the costs of a single action or to the costs of investment for a hospital to introduce a certain technology.

4.1.4 Summary of findings

On the basis of the identified trends (4.1.1) and modality proportions (4.1.2) it may be concluded that the experts expect a marked increase in the choice of PET modalities, in particular. Both industrial and end user interviewees indicated that this area currently shows the strongest development. Multi-modal developments appear to boost the advance of PET.

The share of SPECT modalities is expected to remain roughly the same. SPECT scanning applications will decrease in the coming years, whereas the share of multi-modality techniques combining SPECT with other modalities will increase. Industrial interviewees indicated that a great deal of work is being done on the development of

SPECT/CT. The survey shows that clinical practitioners expect this type of scanner to take up a substantial share.

As regards mixed modalities, it appears that reactor isotopes will continue to fulfil an important function. The fact that the share of SPECT scanning is expected to remain the same leads to the conclusion that the relative demand for reactor isotopes (in proportion to the total number of scans) will also remain about the same.

The implementation of a technology is determined by both technological and non-technological factors. In the choice of a certain clinical modality, higher resolution has been identified as a technology driver, while human factors are important determinants of technological success. In the present case this implies that the speed of wider PET application will depend on adequately trained personnel and infrastructure.

Section 4.2 will discuss the experts' expectations concerning the clinical use of technetium in greater detail.

4.2 Future use of technetium

4.2.1 The total number of scanning applications

The total number of scanning applications in medicine is expected to increase in the coming years. Increases in prosperity will lead to higher standards of living, improvements in medical science and increases in life expectancy. The number of medical activities will increase in proportion to increases in life expectancy and an ageing population. Furthermore, higher prosperity will lead to increases in the use of medical technologies. Combined with rising population figures, this will lead to an overall rise in the number of imaging activities.

This trend has already begun, but ageing populations and population growth will cause continued growth in the total number of scanning applications. This picture is supported by the experts' estimates. The experts were practically unanimous in their expectation of a (sharp) increase in the total number of scanning applications over time. Figure 13 shows the experts' expectations for the total number of scanning applications for the periods 2008-2010, 2010-2015 and 2015-2025. Figure 14 shows the same results represented as weighted response averages. Practically all experts reported that they expect an increase in the total number of future scanning applications. On average the experts expect an increase, while 60% of respondents expect a sharp increase for the period between 2015 and 2025.

Figure 13 Experts' expectations of the total number of scans for medical use

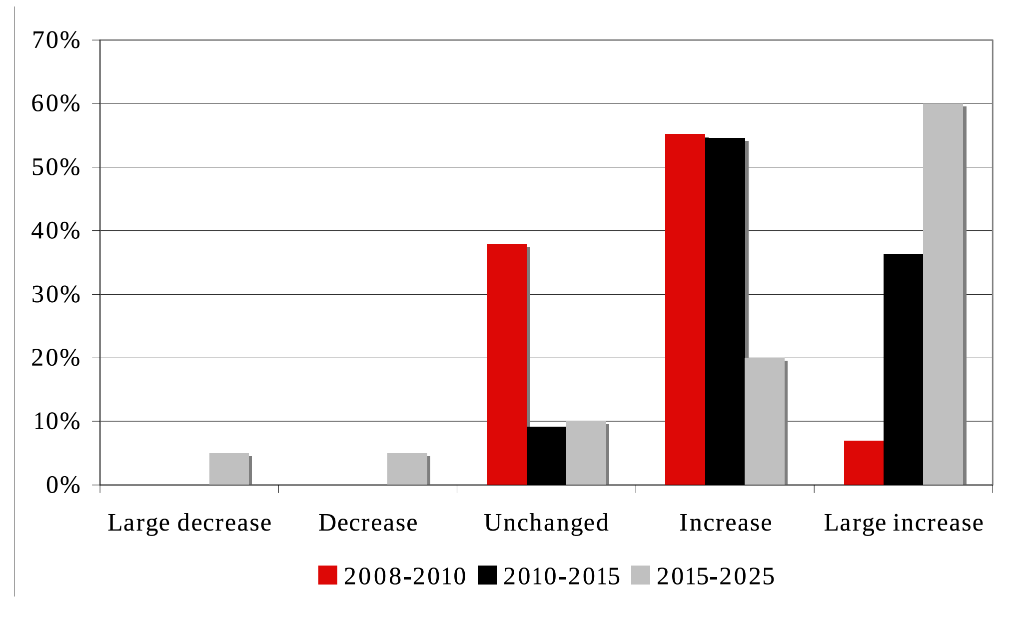


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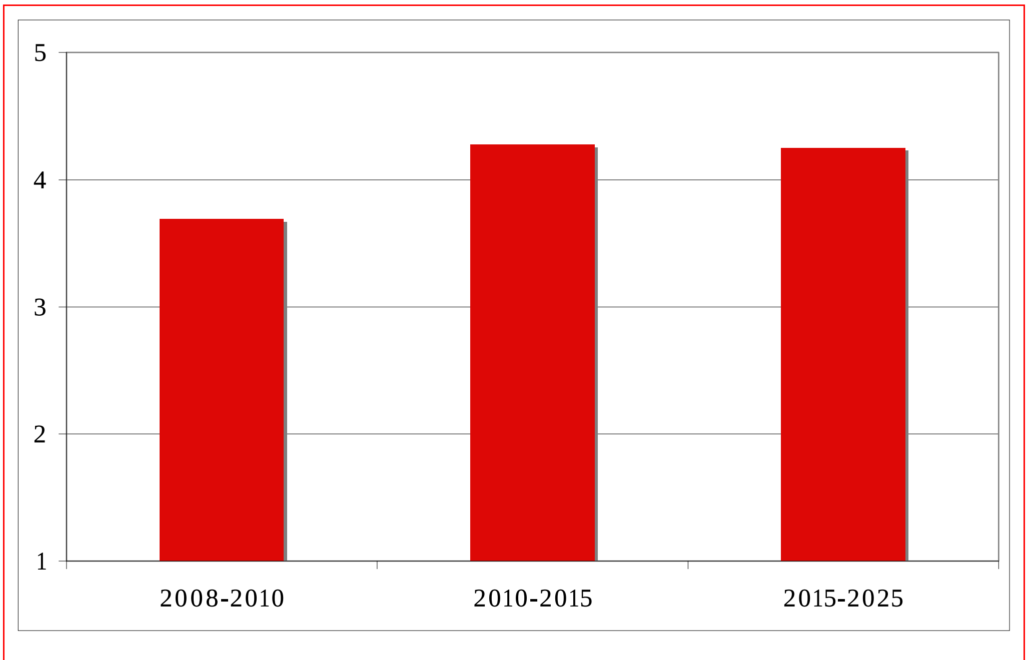
Figure 14 Weighted average of the experts' expectations of the total number of scans in 2008-2010, 2010-2015 and 2015-2025. 1= large decline, 2= decline, 3= unchanged, 4= increase, 5= large increase



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4.2.2 The probability of technetium-based scanning being replaced by other technologies.

The survey also inquired into the probability of technetium being substantially replaced by non-technetium modalities. Figure 15 represents expected probabilities of technetium replacement for the period up to 2010 (marked red), between 2010 and

2015 (marked black) and between 2015 and 2025 (marked grey). Figure 16 shows the weighted response averages.

Figure 15 Experts' estimates of the probability of substitution of technetium

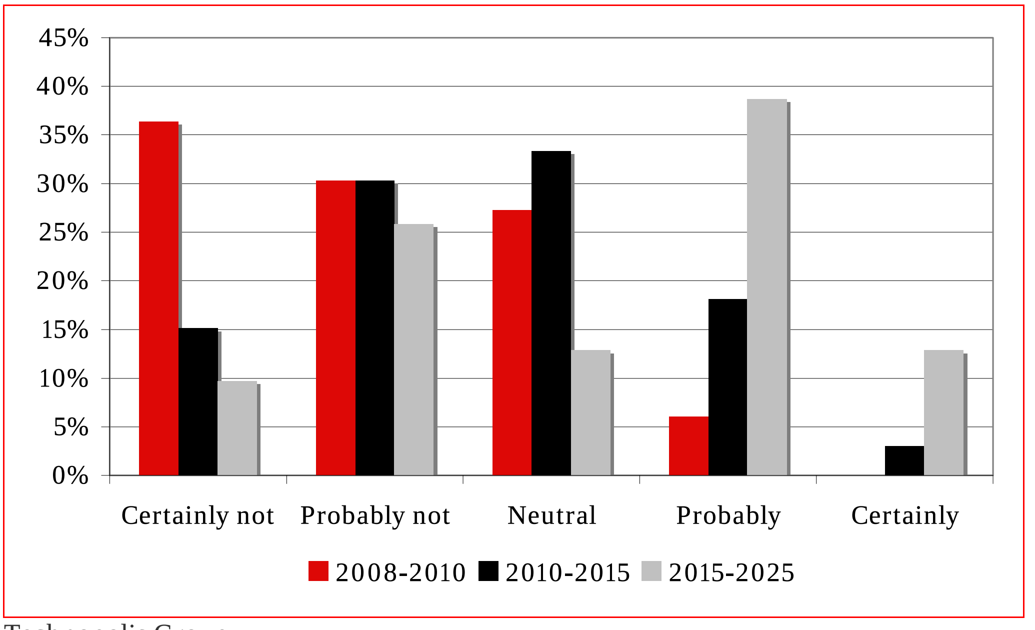

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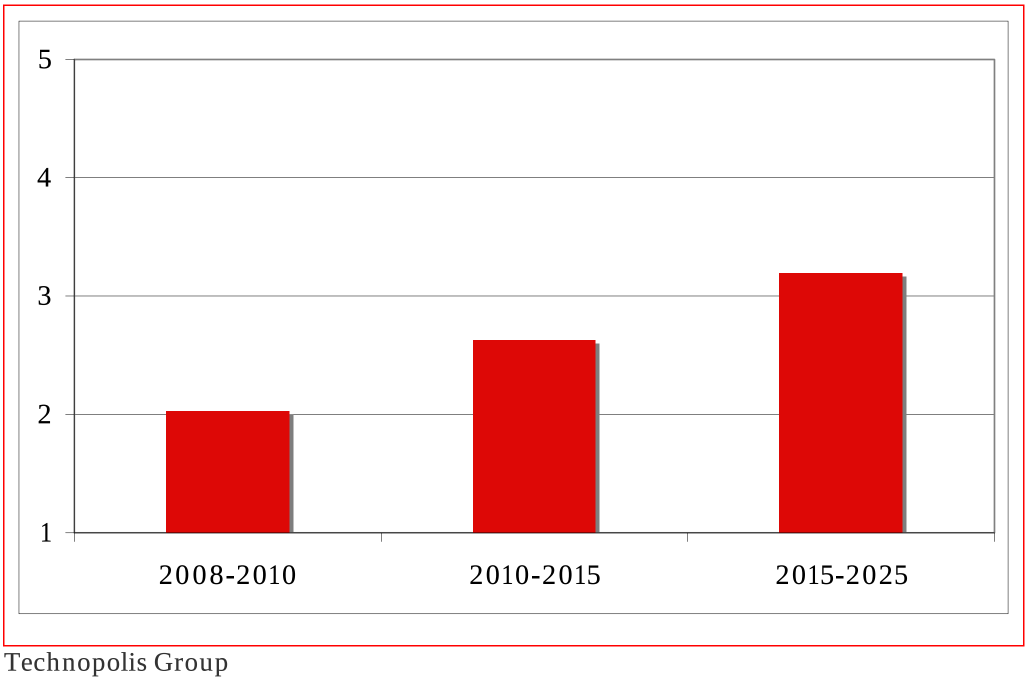
Figure 16 Weighted average of the experts' estimates of the probability of substitution of technetium. (1= certainly not, 2= probably not, 3= neutral, 4= probably, 5=certainly)



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Sixty-five percent of the respondents reported that they do not consider it probable that technetium will be partly replaced in the period up to 2010, and 30% still do not consider it probable for the period between 2010 and 2015, although this percentage was equalled by the number of neutral responses. Looking further into the future, the respondents expect an increasing chance of technetium replacement. On the one hand, this response can be explained in terms of increasing uncertainty, in the sense that predictions about the future always carry a certain measure of uncertainty. This is shown by the increasingly diverging responses when considering later periods: the spread for the period 2015 - 2025 was markedly greater than for the earlier periods (see Fig. 15). However, the weighted replacement average moved up from 'probably not' in the period 2008 - 2010 to 'neutral' for the period 2010 - 2015, with a slight tendency towards 'probable' for the period 2015 – 2025. The average value rose from 2.0 in 2008-2010 to 3.2 in 2015-2020 (see Fig. 16). Interviews made it clear that the shift can be explained mainly by the assessment that other modalities will have higher functionality during this period (also see Fig. 10). Nuclear physicians expect major developments for PET in particular. Experts from other areas of medical imaging expect breakthroughs in the areas of MRI and CT. There is no consensus on these matters. In general, the experts do not have an overall picture of future developments. However, the average assessment shows that the use of technetium will decrease slightly over time.

4.2.3 Future use of technetium

The probability of substitution was investigated in greater detail in the survey by means of a quantitative assessment of the future use of technetium. The questionnaire asked the experts to estimate the total use of technetium in the future compared with 2008. Figure 17 shows the distribution of the experts' assessments in percentage points. Figure 18 (next page) shows the weighted response averages.

Figure 17 Experts' estimates of the use of technetium in 2010, 2015 and 2025, as a percentage of the current use (2008).

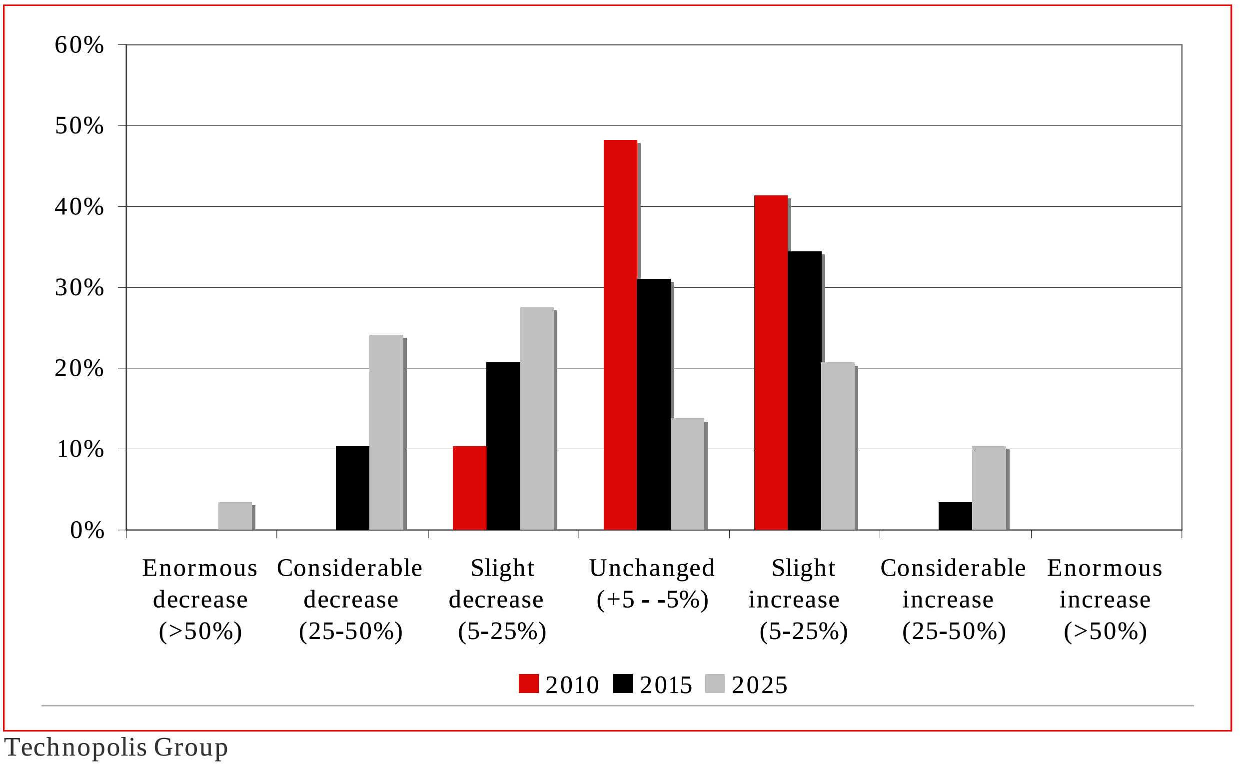

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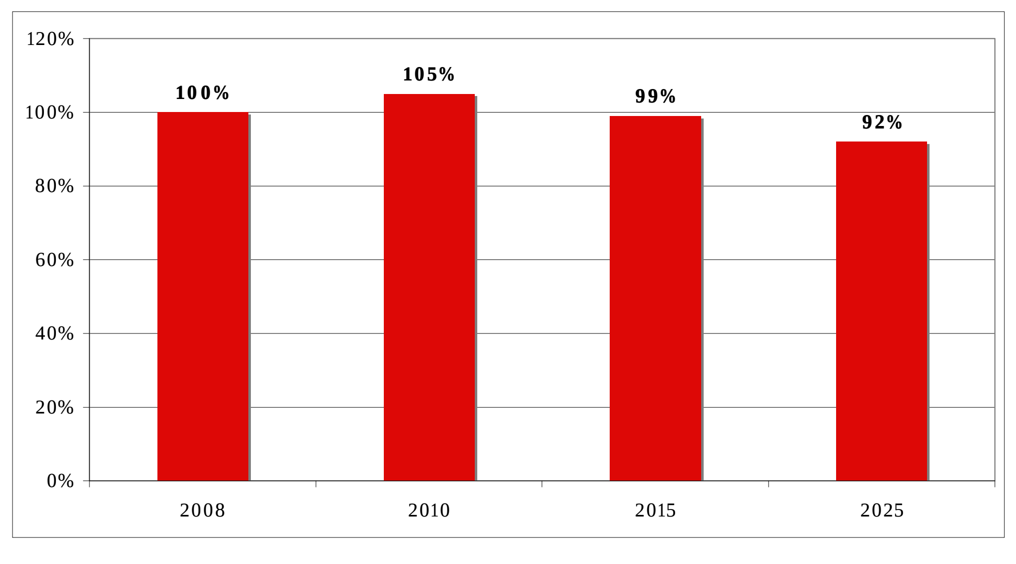
Figure 18 Weighted average of the experts' estimates of the use of technetium use in 2010, 2015 and 2025 (reference year: 2008).



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In the short term (2008-2010, marked red), nearly 90% of respondents reported that they expect the use of technetium to increase or remain as at present. This amounts to an average of 105% of current use. The subsequent period, 2010-2015 (marked black), shows an increase in the number of respondents expecting the use of technetium to decrease, but average use is expected to remain the same as at present. For the period 2015-2025 (marked grey), the response spread was wide, as was the case for the previous question. However, the weighted average indicates a slight decrease in the total use of technetium, down to 92% of the current level.

Responses to this question matched the expectations regarding technetium substitution.

4.2.4 Summary of findings

Experts are unanimous in expecting a sharp to very sharp increase in the total number of diagnostic imaging scanning applications in the future. This outcome is connected to the expected increase in the ageing of the population and population increases in general.

As regards expectations of the replacement of technetium-based imaging modalities, major changes (substitution) are not expected. Experts are divided in their opinions of the period after 2015; however, the average does shift from 'probably not' to more or less neutral, with a slight tendency towards 'probably' for 2025.

The total use of technetium shows the same trend: the use of technetium will certainly not decrease in the next few years; indeed, a slight increase is expected. For the period 2015-2025 the experts expect a very slight decrease in the use of technetium (<10%), although among our respondents the response spread was wide.

4.3 Therapeutic use

As regards the therapeutic use of reactor isotopes, the survey results are unequivocal (see Table 5). The current use of iodine and iridium is not expected to increase a great deal (represented by 0). However, the experts do expect an increase in the use of lutetium-177 and yttrium-90, which will start now and continue far into the future after 2015 (represented by +). The use of holmium-166 and samarium-153 will also increase, although not before 2010. In this respect the experts' opinions match the results obtained in the interviews and from the literature, which without exception point to the development of radiopharmaceuticals for therapeutic purposes.

Table 5 Experts' expectations regarding the application of therapy with reactor isotopes. (-- = large decrease, - = decrease, o = unchanged, + = increase, ++ = large increase)

	2008-2010	2010-2015	2015-2025
Iodine-131	O	O	O
Strontium-89	O	O	O
Iridium-192	O	O	O
Samarium-153	O	+	O
Rhenium-186	O	O	O
Iodine-125	O	O	O
Yttrium-90	+	+	+
Lutetium-177	+	+	+
Holmium-166	O	+	O

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5. Conclusion

This study was commissioned by the Ministry of VROM. It set out to answer the following research questions:

'*What is the predicted market size of future imaging technologies for medical purposes – that is, between now and 2025 – and what will be the relative share of technetium-based imaging applications in that market?*'

'*What new or developing medical imaging technologies may affect or supersede technetium-based imaging technology in the period between now and 2025, in terms of both quality and quantity?*'

The following conclusions may be drawn on the basis of interviews, the results of an online Delphi survey and validation by an experts' committee:

- Currently a range of imaging modalities (CT, MRI, SPECT and PET) is available, each of which has a specific application in the medical domain. Technetium is used for SPECT and planar technology, which are preferentially used for bone scanning (including bone metastases in oncology) and for organ scanning (including the measurement of blood flow and heart muscle function in cardiology).
- Multi-modality imaging which combines nuclear and radiological techniques in a single device is on the rise. As regards the future, shifts are predicted in the use of modalities, with the expectation of a decrease in single modalities in favour of multi-modality imaging.
- Currently there is no new technology in the picture that might affect the use of technetium. Even if it exists, the experts would expect it to take minimally 18 years before such a technology could be preferentially used in clinical practice. Also it can be expected that 'old' technologies will not disappear.
- Although high imaging modality resolution is a key technology driver, human factors are important in determining the success of a technology.

Expectations

- The experts expect a sharp increase in PET modalities, particularly in combination with CT or MRI. Partly because of superior resolution, current applications of PET will be extended, without affecting the total share of SPECT modalities. The speed of PET developments will partly depend on the development of new radiopharmaceuticals, infrastructure requirements and expertise.
- The relative share of SPECT modalities will probably remain the same, while single SPECT will in the long term be replaced by SPECT/CT, followed by SPECT/MRI (not yet available).
- The experts are convinced that the total number of scanning applications will rise (sharply) in the future. That rise has already started in the past few years.
- The experts consider it unlikely that technetium-based imaging will be replaced by other technologies in the medium term (up to 2015), although such imaging may show a slight decrease in the period 2015-2025. This is also shown by the expectations regarding the total use of technetium, which is expected to remain the same for the time being but to decrease (<10%) in the period 2015-2025. Furthermore, some experts emphasize that up to now no imaging technology has been replaced; even conventional X-ray imaging is still used, and the complete range of modalities has only been expanded gradually over the course of time.

In short, all the data show that the demand for radiopharmaceuticals which are produced in an HFR will still play an important role until 2025. The experts expect that the fast development of PET will continue and that this will result in a relative decrease in the use of reactor isotopes. However, due to low costs and the relative simplicity of SPECT and planar nuclear imaging, these techniques will persist and will be equally used.

Appendix A

Persons consulted

A.1. Experts' Committee

Expert	Institute
Professor H.J.M. Rooijmans Emeritus Professor of Psychiatry, former Chairman of *Raad voor gezondheidsonderzoek (RGO)* [Medical Research Council]	-
Professor M. Viergever Professor of Medical Imaging	Image Sciences Institute (ISI), UMC Utrecht
Professor A.A. Lammertsma Professor of Clinical Physics	Nuclear Medicine & PET Research, VUMC Amsterdam
Dr J.F. Verzijlbergen Chairman of *Nederlandse Vereniging Nucleaire Geneeskunde* [Dutch Association of Nuclear Medicine]	Nuclear Medicine Department, St Antonius Hospital, Nieuwegein

A.2. Interviews

Name		Institute
H.J.M.	Rooijmans	Former chairman of the *Raad van Gezondheidsonderzoek* [Medical Research Council]
M.	Viergever	UMC
A.A.	Lammertsma	VUMC
H.	Hofstraat	Philips
F.	Gerritsen	Philips and TU Eindhoven
P.	Luijten	CTMM, UU, Philips
R. A.	Dierckx	RUG
A.M.	Verbruggen	KU Leuven
Bob	Van der Schaaf	NRG
A.	Paans	UMCG

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