NEDERLANDSE VERENIGING VOOR NUCLEAIRE GENEESKUNDE

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Summary

The medical use of radiopharmaceuticals up to 2025

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

SUMMARY VROM* (Ministry of Housing, Spatial Planning and the Environment) REPORT

The medical use of radioisotopes up to 2025
An exploration of the future

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Introduction
In April 2008 Technopolis received a request from the VROM Ministry as part of the decision-making process regarding the construction of a new research reactor. The High Flux Reactor (HFR) in Petten is expected to reach the end of its lifespan around 2016. At the HFR in Petten, among other activities, uranium is irradiated with neutrons. The molybdenum that is generated in this process decays into technetium. VROM's focus is an exploration of alternative production methods as well as an exploration of alternative (imaging) technologies. This report only addresses the last question. Alternative production methods are – also under commission of VROM – studied by the Reactor Institute in Delft.

Background HFR

The HFR has been owned by the Institute for Energy (IE) of the Joint Research Center (JRC) of the European Commission (EC) since 1962. The Nuclear Research and Consultancy Group (NRG) hold the license for the reactor. The reactor is utilized and maintained by NRG staff. The HFR is the largest European manufacturer of radioisotopes. The vast majority of the radioisotopes are used for imaging biological processes in the body. The isotope most often used for medical imaging is technetium. The importance of technetium to the medical world is considerable: Technetium is used for 80-85% of all nuclear examinations; 40 million procedures are carried out each year, of which half in North America and 30-40% in Europe. In the Netherlands approximately 250,000 procedures take place each year (1).

Research results

The majority of the respondents comes from university and STZ hospitals (cooperating major top clinical training hospitals) and consists for the most part of nuclear physicians (42%). The other respondents are radiologists, internal medicine experts, cardiologists, oncologists, neurologists, (clinical) physicists, (radio-) chemists and pharmacists. Around 70% of the respondents are physicians; the others have mainly technical background.

Production of radiopharmaceuticals

Worldwide, there are approximately 100 research reactors that produce isotopes; most of them, however, are not suitable or not used for medical applications. The molybdenum/technetium supply for the total medical market is dominated by a handfull of reactors. Table 1 presents two estimates; one by NRG from 2002 and one from 2008, made for Nuclear Engineering International.

In the European context the HFR is an essential reactor as it provides in around two thirds of the European demand and more than a quarter of the global demand for technetium (see table 1).

Table 1 Overview of the worldwide production capacity of molybdenum-99, the European share is marked in grey.

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)[(2)]	2%		
Others	5%		

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

The HFR is a large manufacturer due to the fact that the reactor fulfills two important conditions. The HFR has a relatively high amount of operational hours, and the infrastructure in the Netherlands is well developed; all hospitals can be reached quickly. From an international perspective the location of the Netherlands in general, and that of the HFR in particular (i.e. the vicinity of Schiphol airport in the Netherlands), is an important aspect in the prominent position of the HFR on the European market.

At the moment, the importance of the HFR for the Netherlands and the rest of Europe lies in maintaining the current capacity for the production of isotopes with medical applications in order to safeguard the availability of sufficient reactor isotopes for medical imaging (3).

The future

In the last ten years, the use of technetium has increased by 50% and it is expected that this increase will continue in the years to come (4). For the coming years NRG expects a slight increase in the European distribution. Outside of Europe, NRG also expects an increase in the use of technetium, especially outside the United States. The increasing prosperity in the developing countries will lead to a higher demand for nuclear imaging and therefore to more pressure on the global market for technetium. Even though NRG expects the concerned countries to become self-sufficient in time, they anticipate an extra large purchase during the transitional phase (between increasing use and production set up).
In the long term there is a risk of shortage of reactors that produce medical isotopes. This

already shows now, when (more and more often) maintenance is carried out on the existing reactors. The current 'top 4' of reactors that are responsible for 96% of the molybdenum production are old reactors. These were put into use in the 50's or 60's of the last century (5). The lifespan of these reactors is expected to come to an end in the near future. For safety reasons reactors regularly require temporary maintenance and eventually these reactors will be closed down.

Moreover, the increase of new suitable reactors is not large. In North America no construction of new reactors has been planned. In the U.S., exploratory research is being carried out into the possibility to convert existing reactors so that they can produce small quantities of technetium (6). In France the construction of the Jules Horowitz reactor has started; this reactor is planned to be put into use in 2014. The reactor can produce around a quarter of the current European consumption of technetium, but will not produce enough to make up for the closing-down of the current reactors. For more information on the production of radiopharmaceuticals we refer to the research report of the Reactor Institute in Delft, that was carried out under the commission of VROM at the same time as this study, or international publications (4) (6) (7).

Use of radiopharmaceuticals by respondents

In a questionnaire the respondents were asked for which disorders they use a specific imaging technique. The modalities that use reactor isotopes are planar imaging, SPECT and multi-modal (8) imaging techniques that combine SPECT with another modality.

Findings

Reactor isotopes play a major part in the current medical imaging practice of the respondents:
In cardiology this is 50% (32% SPECT), for bone scans 55% (43% planar imaging, 10% SPECT, 2% SPECT/CT) and for the other organs 74% (of which planar imaging 57%, SPECT 15%).
In oncology the share of reactor isotopes is 23%; of which planar nuclear imaging 14%, SPECT 8%, SPECT/CT 1%.
In oncology the CT at 28% is still the first choice when it concerns a first diagnosis and MRI is used in 15% of the cases. In neurology too there is a less prominent role for reactor isotopes, namely 22%, of which SPECT 15%. Here MRI is the dominant modality (40%) and to a slightly lesser degree CT (29%).
These results might not be representative of the average Dutch situation, but they provide an image of the practice at the university and STZ-hospitals. In the general Dutch situations the proportions will probably be a bit different. The results in this study represent the situation in practice in the hospitals which lead the way (9). Even though therapy only accounts for a small share (10%) in the total use of reactor isotopes for medical applications, it plays an important role in terms of quality.

Explorations into the future use of radiopharmaceuticals in medical practice

Trends

On the basis of the interviews, some important trends were identified that are capable of causing shifts among to the range of modalities.
For substitution effects the following trends are important: Improvement of current modalities

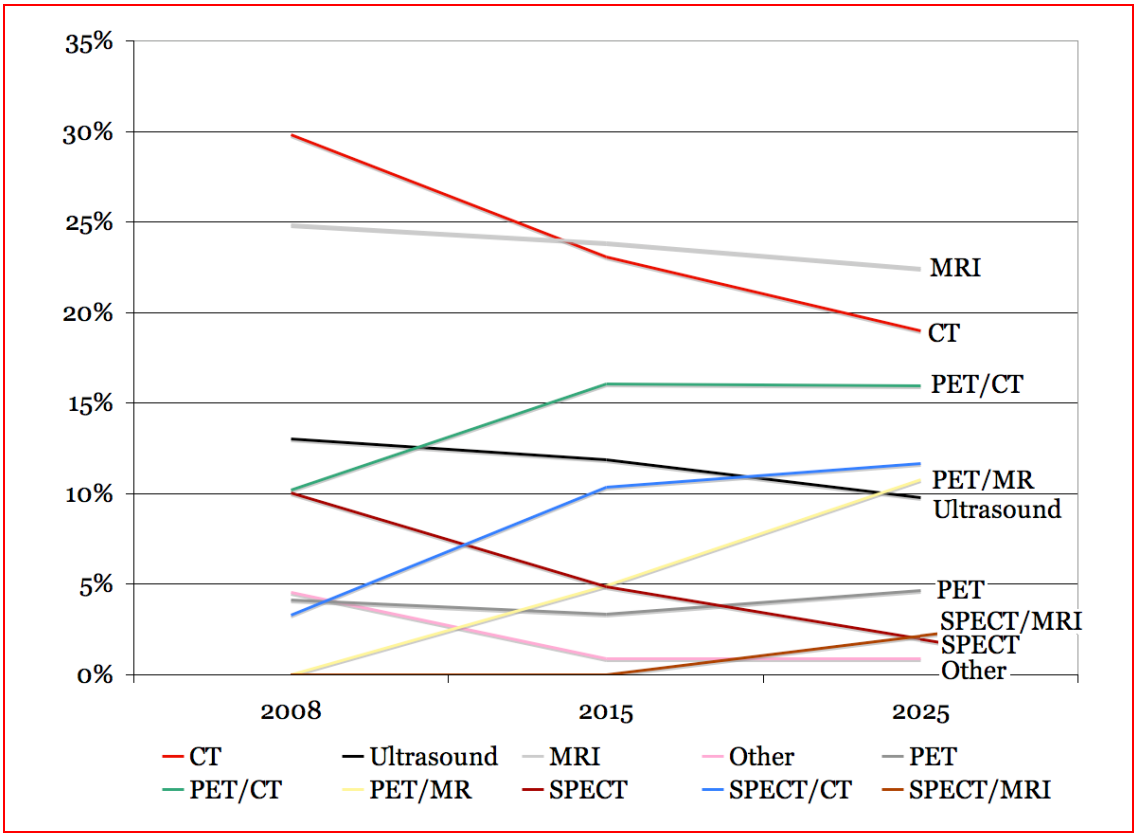
(PET is one of the fastest growing). And also: combinations of modalities, development of new tracers, development of new therapies and development of new equipment/modalities.
The length of the innovation trajectory from first research phase to clinical proof (incl. clinical trials) and from clinical proof to preferential use takes on average 18 years: 8 years for the research phase, 10 years to preferential use.

Expectations of use

In the questionnaire we asked about the expectation of the respondents concerning the use of the different modalities in the clinical practice and which share they expect a specific modality to have in the number of scans in their clinical practice in 2008, 2015 and 2025.

Figure 1 shows the results.

Figure 1 Relative use of modalities in 2008, 2015 and 2025 (n=23)



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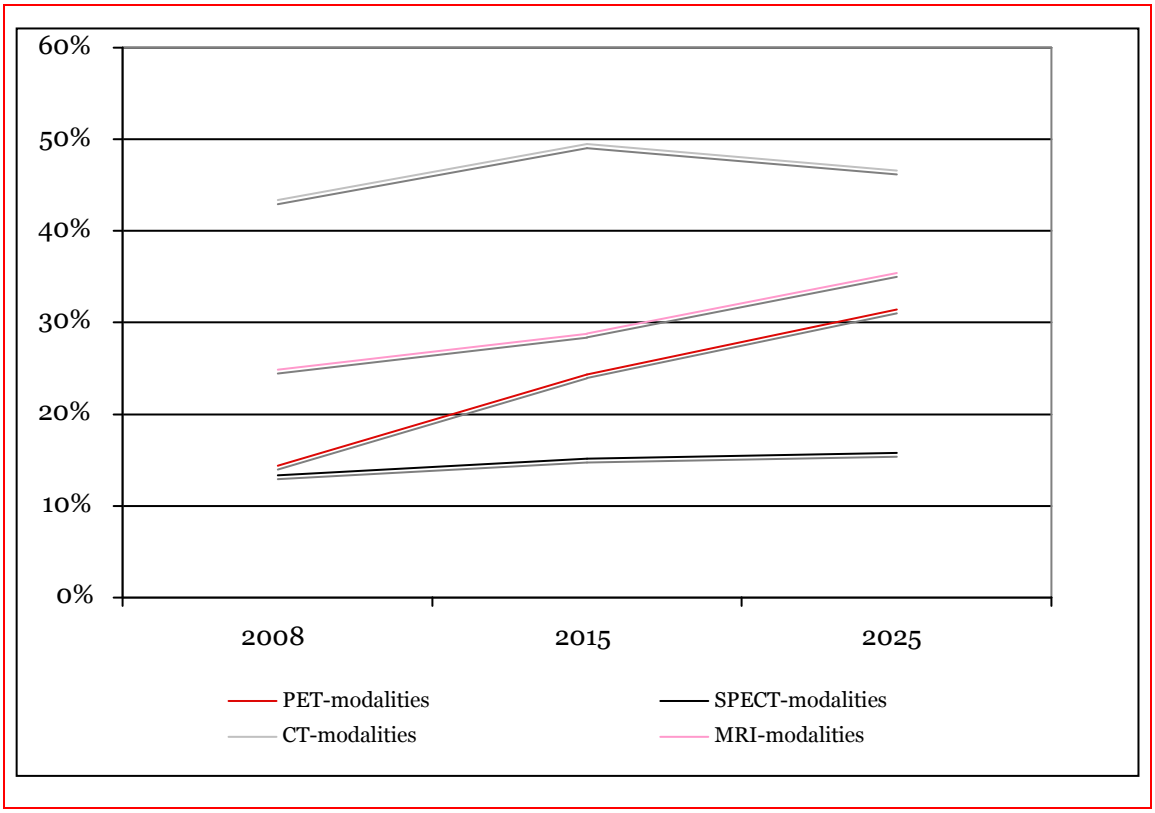
In order to highlight the trends of the modalities that use reactor isotopes, the percentages of the multi-modalities have been added to the basic modalities in figure 2. The share of PET/CT has been added to PET as well as CT and the share of SPECT/MRI to SPECT as well as MRI. This creates an image of the total use of the basic modalities; however, this puts the total number of scans over one hundred percent.
From this future expectation the following conclusions can be drawn about the proportions of the modalities.
Our respondents expect:

- A relative decrease in CT in their procedures, which is reasonably strong (more than 10% during the period of 2008-2025).
- A slight decrease in the share of single MRI's (less than 3%).

- A slight decrease in the share of ultrasound (about 4%).
- An equal number of PET procedures.
- A significant decrease of SPECT (approximately 7%)
- A substantial decrease of the other modalities (in particular planar). These are the modalities that were only estimated at a few percentages (about 4%).
- A substantial increase of PET/CT share (about 7%).
- A substantial increase of SPECT/CT share (about 7%).
- Strong emergence of PET/MRI (more than 10%).
- After 2015: advent and rise of SPECT/MRI (about 2.5% from 2015-2025).

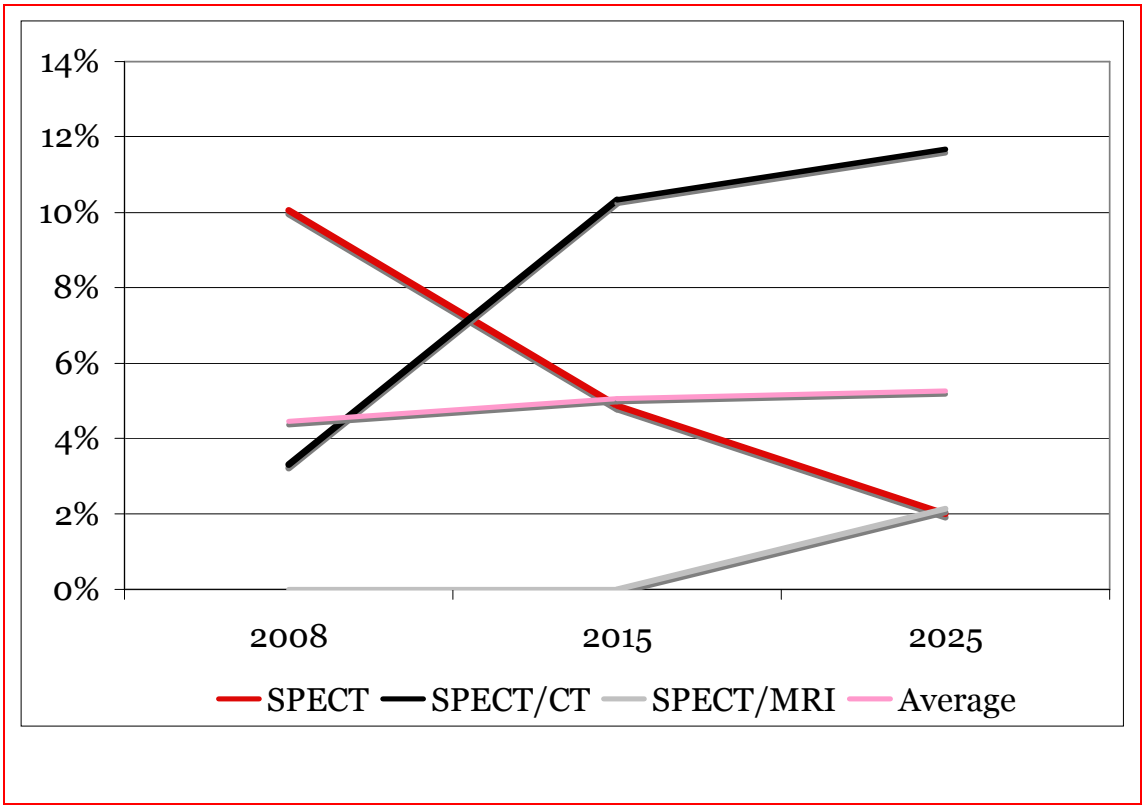
Figure 2 Expectations of future use of modalities, share of scans by basic modalities



Technopolis Group. n=23

Figure 2 shows that the respondents expect the combined use of PET to increase significantly, as well as the use of MRI. The decrease in “single” PET and MRI is substituted by the use of multimodality techniques. The combined use of CT will increase considerably at first and then slightly decrease again, at the expense of for instance MRI multi-modalities. The share of this modality will remain more or less stable.
The considerable decrease of the SPECT share (see figure 3) is compensated by the use of multi-modalities: first in particular by SPECT/CT and after 2015 by SPECT/MRI.
Since SPECT is the modality that uses reactor isotopes, the SPECT share is further split in figure 3.

Figure 3. Substitution effects of SPECT by multi-modalities



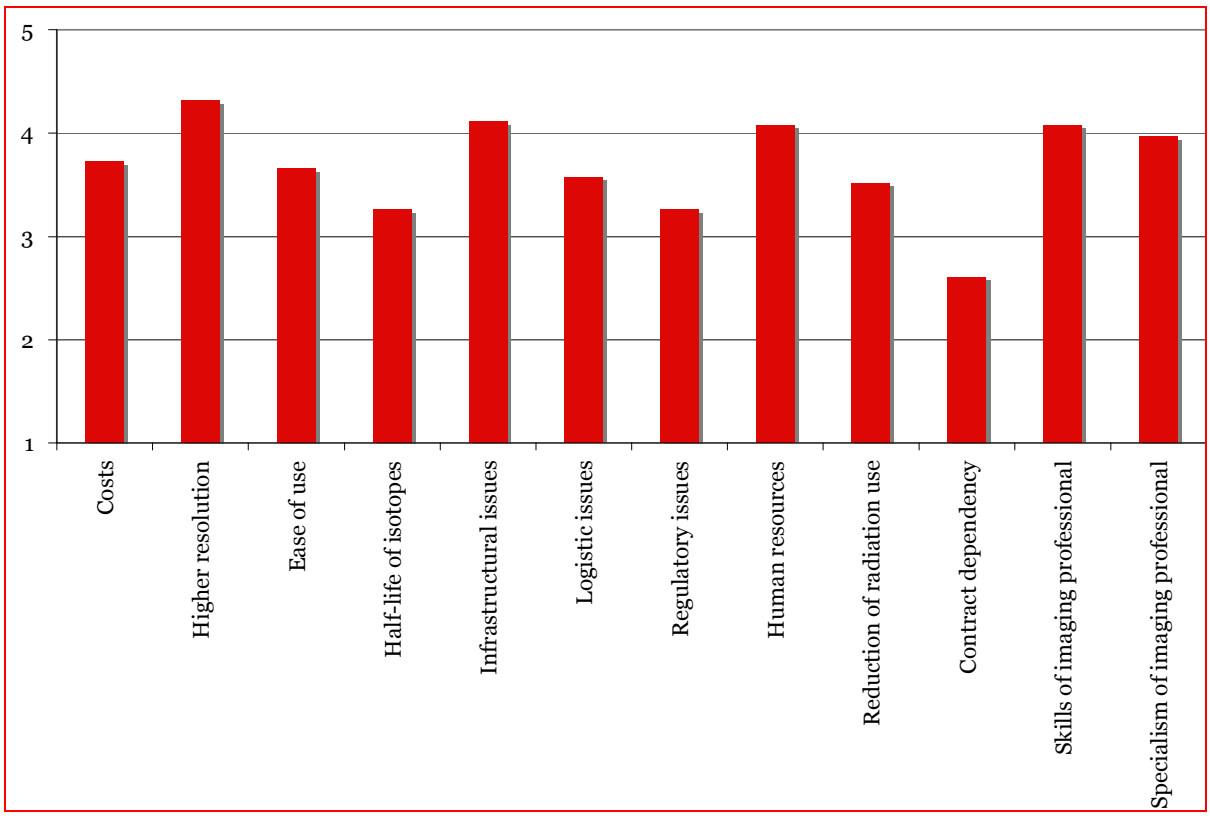
Source: survey Technopolis Group. n=23

Innovation dynamics

The implementation of innovative technologies is driven by technological (e.g. resolution) but also by non-technological factors (e.g. logistical and infrastructural issues related to the use of isotopes). In order to determine which technological or non-technological factors are decisive in the choice of a specific modality in the clinic, the respondents in the questionnaire were asked to indicate which of these factors are (very) important or unimportant. See figure 4.

Figure 4 shows that only dependency on contracts is assessed as less important. The higher resolution is a technological driver, but human factors are of high importance for determining the success of that technology. This also means that the pace of the wider application of PET mainly depends on sufficiently trained staff and infrastructure. Apart from that, the 'cost' issue has not been further defined; it can concern the cost of one single action as well as the investment costs for a hospital to obtain the technology in question.

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



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Conclusion

Based on the identified trends and of the proportions of modalities, it can be concluded that the experts anticipate that PET-modalities in particular will increase significantly. Industrial respondents as well as interviewees that use the techniques indicate that this is currently the strongest development. Multi-modal developments seem to promote the progress of PET.
The share of SPECT-modalities will remain more or less stable. The number of SPECT-scans will decrease in the next few years; the share of multi-modalities that combine SPECT with other modalities will however increase. The industrial interviewees indicate that people are working hard on a SPECT/CT-scanner and the questionnaire shows that it is expected in the clinical practice that this scanner will have a substantial share.
Concerning the mix of modalities, it has become evident that reactor isotopes continue to fulfill an important function. From the stable share of SPECT-scans it can be concluded that the relative demand for reactor isotopes (in relation to the total number of scans) will remain more or less the same.
Implementation of a technology is decided by technological as well as non-technological factors. From their choice for a specific modality in the clinic it shows that a higher resolution is a technological driver, but that it is nevertheless human factors which determine the success of a technology.

Future technetium use

Total number of scans

The total number of scans in medicine will increase in the coming years. An increase of prosperity leads to a higher standard of living, better medical science and to a higher life expectancy. As people get older and the ageing population increases, the total number of medical treatments will increase as well. Moreover, a higher standard of living leads to an increased use of medical technology.
Combined with a growing population this will lead to an increase in imaging procedures.
This trend has already commenced, and the total number of scans will continue to increase especially due to ageing and population growth. This image is supported by the estimations of the experts. They almost unanimously expect an increase to a high increase in the total number of scans over time.
Figure 5 shows the expectations of the experts about the total number of scans in 2008-2010, 2010-2015 and 2015-2025.

Figure 5 Expert expectations of the total number of scans for medical use

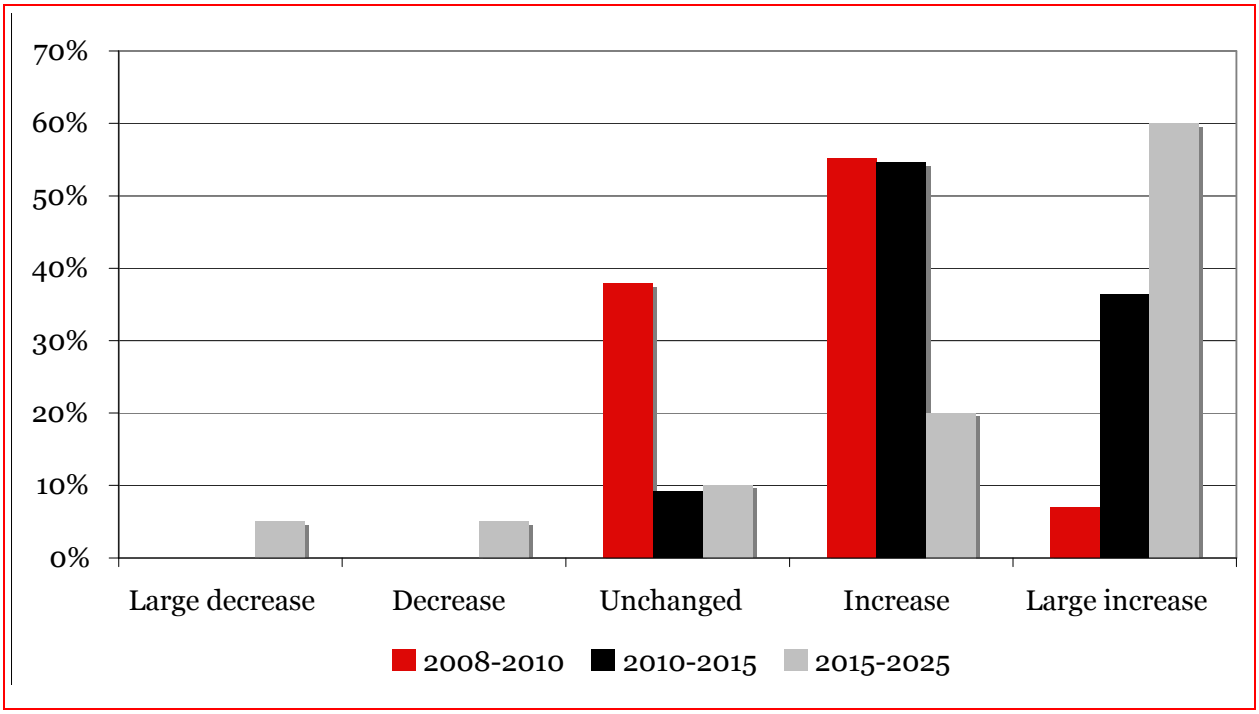

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Figure 6 Weighted average of the expert expectations on the total number of scans in 2008-2010, 2010-2015, 2015-2025. 1= large decline, 2= decline, 3= unchanged, 4= increase, 5= large increase

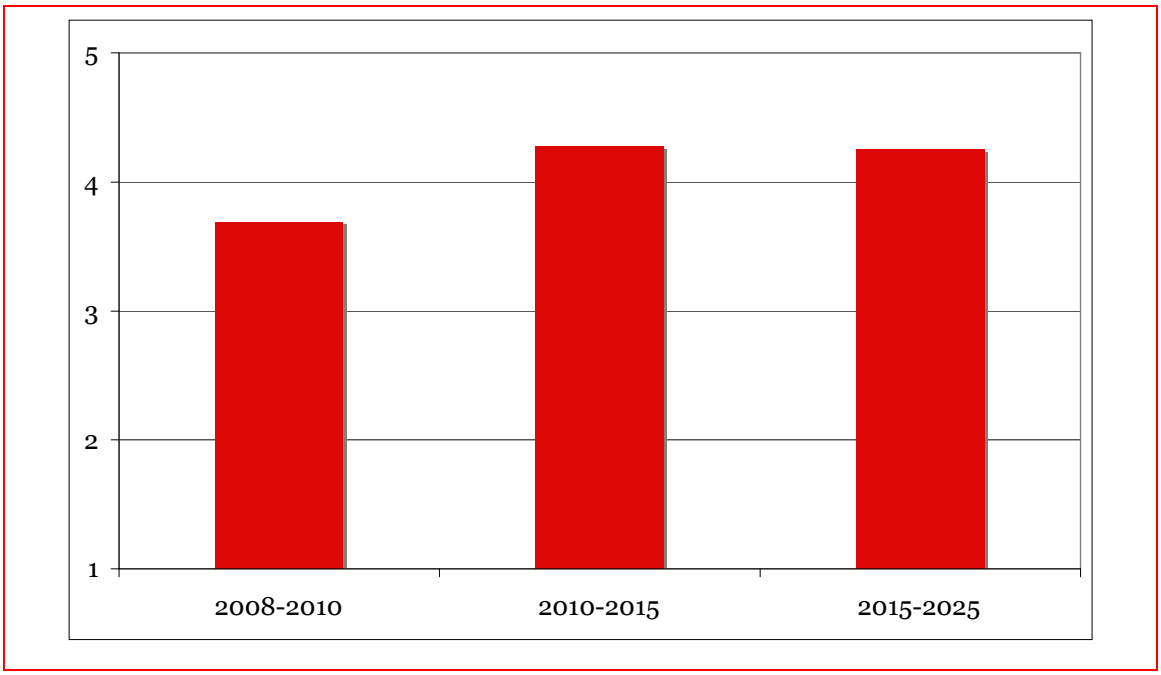

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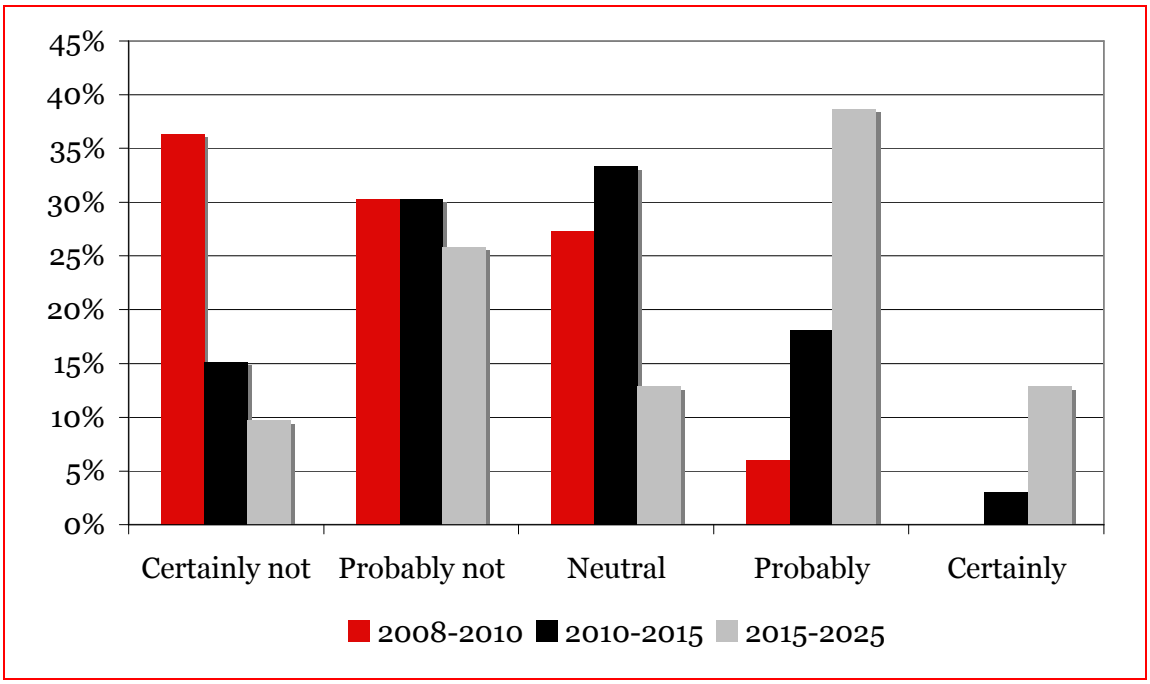
Figure 6 shows the same results, but this time represented as the weighted, more certain average of the answers of the respondents. Almost all experts foresee an increase in the total number of scans in the future. On average, the experts expect an increase; for 2015-2025 60% of the respondents expect a significant increase.

The questionnaire also asked about the probability that an important part of technetium procedures will be replaced by modalities that do not require any technetium.

Figure 7 shows how probable the respondents think it is that technetium will be replaced during the period until 2010 (red), from 2010-2015 (black) and from 2015-2025 (grey).

Figure 7. Probability of the substitution of technetium



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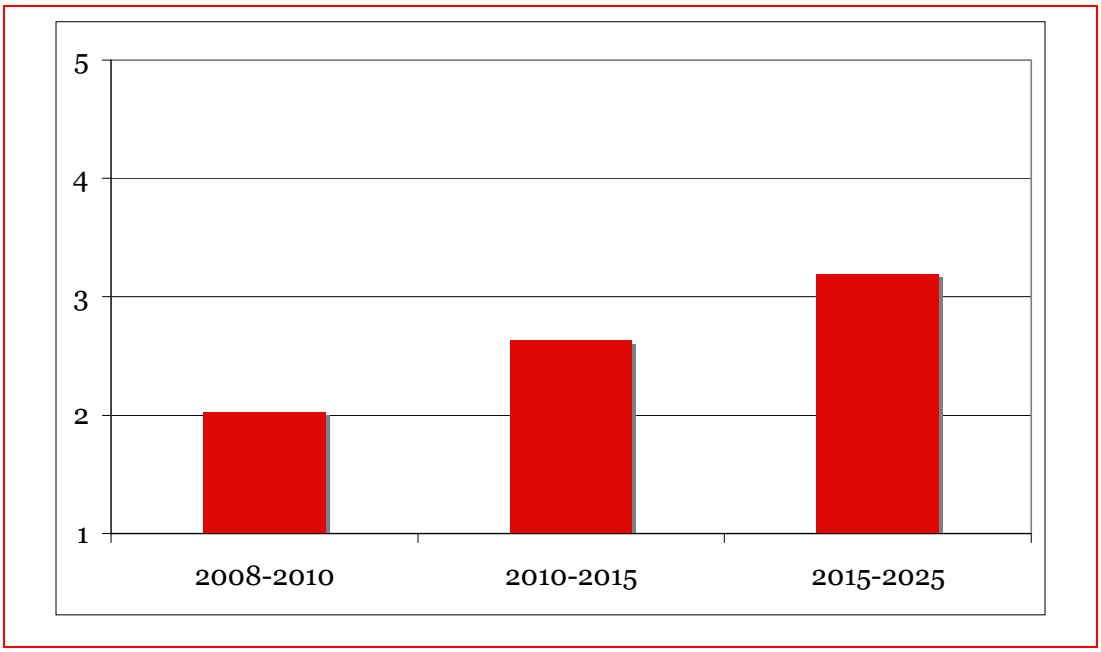
For the period up to 2010, 65% of the respondents deem it improbable that technetium will be partly replaced. For the period from 2010-2015, 30% of the respondents still do not consider it probable, although an equal number now give a neutral answer. The respondents expect an increasing chance that technetium will be replaced for the far future. On the one hand, this can be explained by an increasing uncertainty: predictions of the future always entail certain insecurities. This becomes evident from the increasingly divergent responses when looking at time: for the period from 2015-2025 the spread is considerably larger than for the earlier periods (see figure 7).

However, the weighted replacement average shifts from 'probably not' for 2008-2010 to 'neutral' for 2010-2015, with a slight inclination towards 'probably yes' for the period from 2015-2025.
The average value shifts from 2.0 in 2008-2010 to 3.2 in 2015-2025 (see figure 8).

Figure 8. Weighted average probability of the substitution of technetium. (1= certainly not, 2= probably not, 3= neutral, 4= probably, 5=certainly)



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The interviews show that this shift can be explained in particular by the estimation that other modalities will have a higher functionality in this period (see also figure 1).

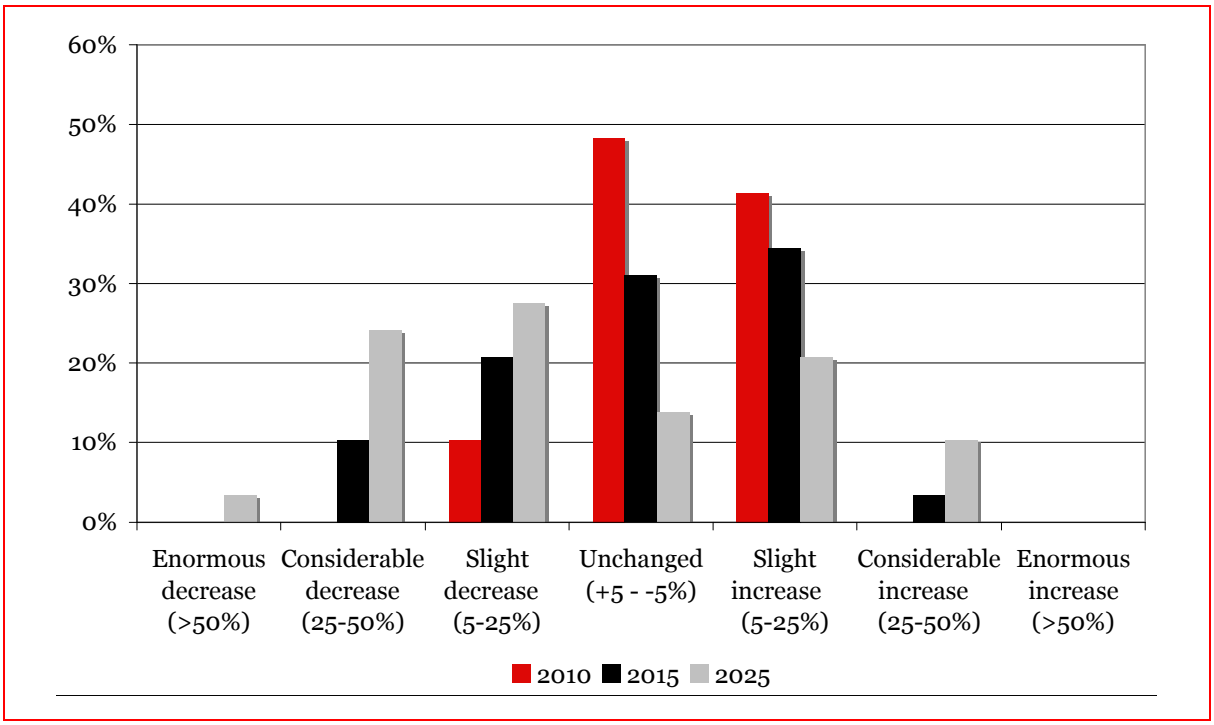
Nuclear physicians expect large developments for PET in particular. Experts from other areas in medical imaging expect breakthroughs in the field of MRI, which will image metabolisms. There is no consensus on these ideas. In general, experts have no total view of all these future developments. The average estimation shows that the use of technetium will slightly decrease as time passes by.

Future use technetium

The probability of substitution is further examined in the questionnaire by means of a quantitative estimation of the future use of technetium. The questionnaire asked the experts to estimate the total use of technetium in the future compared with 2008..

In the short term (Figure 9, 2008-2010, red) almost 90% of the respondents expect that the use of technetium will slightly increase or remain stable. On average it is 105% of the current use. After that, in the period from 2010-2015 (black), the number of respondents who think the use will decrease is increasing, but actually the use is remaining the same as present.
For the period 2015-2025 (grey) the spread in answers is, just as for the previous question, large.

Figure 9 Quantitative estimates on the use of technetium in 2010, 2015 and 2025, as a percentage of the current use (2008).



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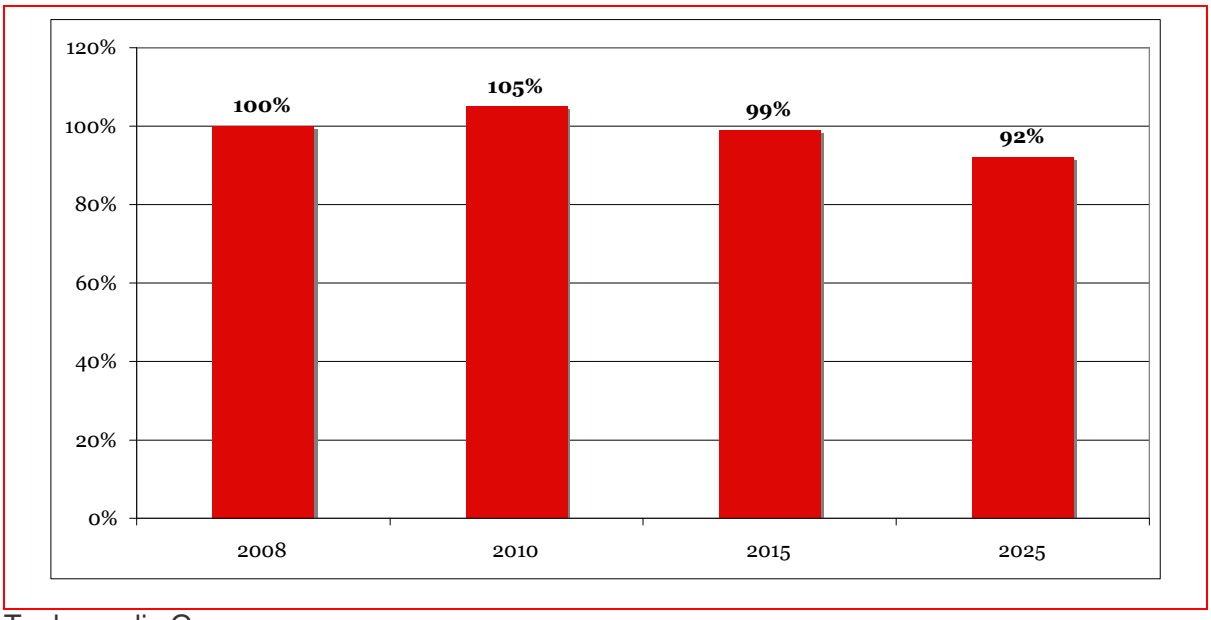
The weighted average shows a slight decrease of 92% for the use of technetium compared to the level of today (see Figure 10).

Figure 10. Weighted average of the quantitative estimates on the use of technetium-using modalities in 2010, 2015 and 2025 (reference year: 2008).



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Summary of findings

All experts unanimously expect a strong to very strong increase in the total number of diagnostic imaging scans in the future. This is connected to the increasing ageing population and population growth.

As for the expectations regarding the replacement of imaging modalities that use technetium, no major change (substitution) is to be expected yet. For the period after 2015 the experts have a divided opinion; the average answer however shifts from 'probably not' to more or less neutral, with a slight inclination towards 'probably yes' in 2025.
This trend can also be seen in the total use of technetium: in the coming years the use of technetium will definitely not decrease, it is more likely to increase slightly. In the period from 2015-2025, the experts expect that the use of technetium will slightly decrease (<10%), but the spread in expectations is large.

With regard to the use of reactor isotopes for therapy: the experts expect an increase in the use of lutetium-177 and yttrium-90, and this increase will already start now and continue far into the future after 2015.
The use of holmium-166 and samarium-153 will also increase, but this will take place after 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.

Conclusions

This study, commissioned by the Ministry of VROM, has tried to answer the following research questions:

- 'What is the predicted market size of imaging technologies for medical applications in the future, i.e. from now until 2025, and what will be the relative share of technetium-based imaging in these technologies?'
- '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?'

On the basis of interviews, the results of an online survey and validation by the committee of experts, it can be concluded that:

Current developments

- At present, there is a range of imaging modalities available (CT, MRI, SPECT and PET), each of which has a specific application in the medical domain. Technetium is used for SPECT and planar nuclear technologies.
- Multi-modality imaging which combines nuclear and radiological techniques in a single device is on the rise. For the future shifts are expected in the use of modalities; in which it's expected that there is a decrease in "non-hybrid" modalities in favour of "multi-modalities".
- At the moment, there is no new technology in sight that could influence the use of technetium. If there should be such a technology, then the experts expect that it would take at least 18 years before it can be used in clinical practice. On top of that there is the fact that 'old' techniques usually do not disappear.
- Even though high resolution of imaging modalities is an important technological driver, human factors to a great extent influence the success of a technology.

Expectations

- A strong increase of PET-modalities is expected, especially in combination with CT or MRI. Also because of the high resolution the current applications for PET will be extended, but probably not at the expense of the total share of SPECT modalities. The pace of the developments around PET also depends on the development of new radiopharmaceuticals, necessary infrastructure and expertise.

- The relative share of SPECT-modalities probably remains stable, but single SPECT will be replaced in time by SPECT/CT and later SPECT/MRI (not yet available).

- The experts are convinced that the total number of scans will (strongly) increase in the future. This increase has already started in the past few years.

- The experts consider it unlikely that imaging which uses technetium will be replaced on medium-term (until 2015) by other technologies; it will probably slightly decrease in the period from 2015-2025. This also becomes evident from the expectations about the total use of technetium: This will remain the same for now, but will slightly decrease (<10%) in the period 2015-2025. A number of experts also indicated that until now no imaging modality has ever been replaced.

In summary, it can be concluded that the demand for radiopharmaceuticals that are produced in a nuclear reactor will continue to exist until 2025. In the field of nuclear medicine, the experts expect that the current accelerated development of PET will continue, which will cause a relative decrease in the use of reactor isotopes. However, due to the lower costs and relative simplicity of SPECT and planar nuclear imaging technology, these technologies will continue to exist and, in absolute terms, will be used just as much.

Remark: This exclusively concerns a summary of the original 42-page report of Technopolis commissioned by VROM (December 2008).
The editing of this report has not affected its content. The entire report can be found on the website of the Dutch Society for Nuclear Medicine (NVNG: www.nvng.nl, only for members) ; the respondents are also mentioned in this report.

Footnotes

1. NRG: http://www.nrg-nl.com/product/fuel/isotopes/index.html, visited in August, 2008.
2. Meanwhile the Jülich research reactor has been closed.
3. Report on the consequences of the (longer) closure of the high flux reactor in Petten for the provision of radionuclides for medical applications. Inspection for Health Care, 2002.
4. L. Kid, 2008. Cures for Patients, Nuclear Engineering International.
5. 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
6. Advanced Molecular Imaging and Therapy, 2008. Preliminary Draft Report of the SNM Isotope Availability Task Group.
7. Triumf, 2008. Making Medical Isotopes.
8. Multi-modal scanners are imaging devices that combine different modalities in one device.

9. A complete image of the use of the different modalities now (and in the past) can only be given by requesting the production figures of the radiology and nuclear medicine departments of all Dutch hospitals, categorized according to modality.