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TIJDSCHRIFT VOOR NUCLEAIRE GENEESKUNDE

New [18F]radiofluorination methods

PET/CT characteristics in the diagnosis of an endobronchial lipomatous hamartoma

E-learningsplatform voor nucleair geneeskundigen en AIOS gelanceerd

1936

The official discovery of element 43

The discovery of element 43 was confirmed in a December 1936 experiment at the University of Palermo in Sicily by **Carlo Perrier and Emilio Segrè** (who won the Nobel Prize in Physics in 1959).

In mid-1936, Segrè visited the United States and persuaded cyclotron inventor Ernest Lawrence to give him some discarded cyclotron parts that had become radioactive, including a molybdenum foil that had been part of the cyclotron's deflector.

Segrè enlisted his colleague Perrier to attempt to prove, through comparative chemistry, that the molybdenum activity was indeed Z = 43. They succeeded in isolating the isotopes technetium-95 and technetium-97.

Segrè returned to Berkeley University in the US and met with **Glenn T. Seaborg**. They isolated the metastable isotope technetium-99m, which is now used in some 27 million medical diagnostic procedures annually.

In 1947, element 43 was named after the Greek word 'technetos', meaning 'artificial', since it was the first element to be artificially produced.

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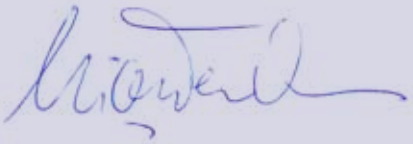
VAN DE REDACTIE

Future in motion

Dat ik trots ben op ons vak wist u natuurlijk al. Maar dat ik vind dat ons vak kracht heeft, en wel een middelpuntzoekende kracht, klinkt u misschien als grootheidswaanzin in de oren. Laat ik mijn standpunt eens grondig onderbouwen. Alle ziektes ontstaan door moleculair biologische veranderingen op celniveau, ten gevolge van een al dan niet bekende genafwijking. Waar wij tot dusver vooral in geïnteresseerd waren, zijn morfologische veranderingen die dus eigenlijk secundair zijn aan moleculair biologische veranderingen. En dat laatste is nu juist waar onze kracht ligt. Hoe langer hoe meer nieuwe generatie geneesmiddelen grijpen in op deze moleculair biologische veranderingen. Op dit punt kunnen wij als vakgebied van groot maatschappelijk èn economisch belang zijn. Door deze nieuwe geneesmiddelen radioactief te labelen kunnen we ervoor zorgen dat de farmacokinetiek in vivo gevisualiseerd en gekwantificeerd kan worden. We kunnen de imaging biomarkers gebruiken om upfront de geschikte patiëntenpopulaties te selecteren, zodat geneesmiddelen niet meer in de verkeerde c.q. ongevoelige patiëntenpopulaties getest worden. We kunnen farmacokinetische eindpunten definiëren, wat resulteert in dosering op basis van maximale receptorsaturatie. Proefpersonen hoeven niet langer belast te worden met onnodige bijwerkingen tengevolge van bepaling van de maximum tolereerbare dosis. Klinische trials kunnen bekort worden, doordat overleving geen eindpunt meer hoeft te zijn. Dit zorgt ervoor dat de kosten van nieuw te ontwikkelen geneesmiddelen drastisch teruggebracht kunnen worden en uiteindelijk veel vlotter en voor een lagere prijs beschikbaar zijn voor de patiënt. De patiënten krijgen therapie op maat, omdat zij met onze tools nauwkeurig geselecteerd worden voor het medicament, waarvan zij met grote waarschijnlijkheid profijt zullen hebben. Er zal geen geld en kostbare tijd meer verloren gaan en de patiënt zal niet meer hoeven te lijden onder de onnodige bijwerkingen van ineffectieve therapie. Therapie veranderingen zullen niet meer gebaseerd zijn op algemene protocollen, maar zullen geleid worden door de moleculair biologische veranderingen die optreden tijdens het vorderen van de desbetreffende ziekte en soms zelfs onder invloed van geneesmiddelen. Het klinkt te mooi om waar te zijn. Maar hoe labelen wij die nieuwe geneesmiddelen dan en met welke isotopen? Fluor-18 is zeer geschikt voor het labelen van o.a. nieuwe "small molecule" farmaca vanwege de ideale halfwaardetijd en de optimale positron energie. Klinkt eenvoudiger dan het is, want diezelfde halfwaardetijd kan ook nadelig zijn voor de radiochemische opbrengst. Je denkt dat de oplossing zit in het gebruik van snellere reactietechnieken, maar dat kan weer resulteren in bij-reacties en afbraak van het reactie product. Om deze en andere problemen op te lossen zijn nieuwe synthesemethoden vereist. Het hoofdartikel van Dr. Windhorst en Prof. Elsinga laat u de nieuwe mogelijkheden zien. Sommigen zijn zo nieuw dat we ze misschien zelfs futuristisch mogen noemen. Ik zal u niet langer ophouden, want ik voel dat u popelt om dit artikel te gaan lezen!



Lioe-Fee de Geus-Oei,
Hoofdredacteur

Bij de voorplaat (met dank aan Riemer Slart en Andor Glaudemans, Universitair Medisch Centrum Groningen): 18F-FLT PET van een patiënt met myelofibrose met sterke expansie van beenmergactiviteit naar het perifere skelet met tevens verhoogde opname in het axiale skelet en in een sterk vergrote milt.

New [^{18}F]radiofluorination methods

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Abstract

Windhorst AD, Elsinga PH. New [^{18}F]radiofluorination methods

Positron emission tomography (PET) with [^{18}F]FDG is nowadays routine practice in a modern Nuclear Medicine department. To move PET beyond applications with [^{18}F] FDG, new radiopharmaceuticals are required. Fluorine-18 is a well suited radionuclide for labelling and application of new –small molecule- radiopharmaceuticals, because of half life and adequate positron energy. Chemists, specialized in the development of radiopharmaceuticals, are developing new fluorine-18 labelled compounds for numerous diagnostic applications. An important drawback is the limitation in chemical possibilities of incorporating fluorine-18 in radiopharmaceuticals. However, new developments have appeared in literature during the last years, which give hope for the future. This review discusses these new developments in [^{18}F]radiofluorinations methods.

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Introduction

Fluorination chemistry with [^{18}F]fluoride or [^{18}F]F_2 is restricted to nucleophilic substitution reactions with [^{18}F]fluoride and electrophilic substitution reactions with [^{18}F]F_2. Because of the limited scope, new methodology is required in order to make optimal use of the possibilities to be able to radiolabel a larger variety of compounds with [^{18}F]F. The applicability of [^{18}F]F is further hampered by its chemical nature: as electrophile the reactivity is so strong that this limits its use and it can only act as nucleophile in very distinct reaction conditions. Another important limitation is the decay of the radioactive [^{18}F]F which has a strong influence on the maximal achievable radiochemical yield. Therefore fast reactions are required, this is often achieved by applying harsh reaction conditions, which often have the drawback that side reactions occur more frequently, or even breakdown of the reaction product or reactants.

The effect of reaction speed on radiochemical yield is illustrated in figure 1. In the left panel a graph is presented for a radiofluorination reaction which runs to completion within 60 minutes (line A), which is a fast reaction in itself, according to organic chemistry standards. Given the decay of the radioactive [^{18}F]F (line B), the maximum achievable yield is limited however to approximately 65% (line C). If one can achieve a faster reaction which already comes to completion at 20 minutes, the maximum theoretical radiochemical yield will be increase to approximately 80% (right panel of figure 1). This figure illustrates the need for very fast reactions when applying radiofluorination reactions. It goes without mentioning that the same is true for all radiochemistry reactions, but is especially relevant for radioisotopes with short half lives.

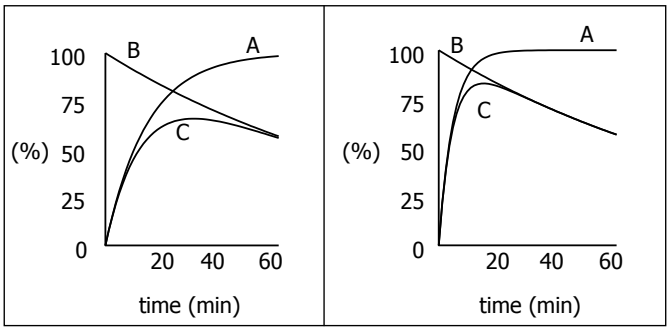


Figure 1.
Illustration of the effect of reaction speed on radiochemical yield. Y-axis presents the radiochemical yield expressed as percentage of the total radioactivity, X-axis is reaction time.

In order to improve on yield and selectivity of radiofluoridation reactions, new synthetic methods are required. Recently excellent reviews on new developments and trends in ^{18}F-radiochemistry were published (1,2).

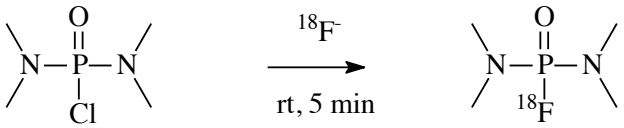
Several synthetic labelling methods are currently under development to further optimize ^{18}F-labelling chemistry and availability of ^{18}F-PET-tracers. Such developments are still needed to improve specific activity, increase radiochemical yield with shorter reaction times, simplify the labelling methods and finally disseminate application of ^{18}F-radiotracers worldwide.

In this review new developments will be discussed: click chemistry, microfluidics, chelation of Al[^{18}F]F in NOTA, use of silicon or phosphorous compounds, ionic liquids, fluorinase, developments in electrophilic radiofluorination and the influence of tertiary alcohols.

^{18}F-fluorinations using P or Si compounds

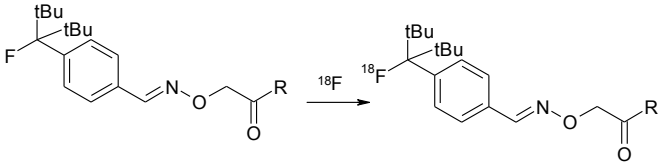
^{18}F-chemistry still holds intrinsic problems which may be the cause that compared to kit preparation for SPECT, it has not got the same impact. ^{18}F-chemistry still requires skilled

radiochemists and expensive synthesis modules. SPECT-chemistry is often characterized by relatively easy kit-type preparation yielding radiopharmaceuticals in quantitative yields. In addition no purification step is required for most SPECT-preparations. Some radiochemists have investigated the possibility to perform ^{18}F-labelling in the same kit-type manner. For this purpose, bond formation other than C-F has been investigated, namely P-F and Si-F.
The introduction of new radiolabelling chemistry utilizing the formation of a P-^{18}F bond has been reported by Studenov et al. (3). They demonstrated the synthesis of the ^{18}F-labelled cholinesterase inhibitor Dimefox in nearly quantitative radiochemical yields by [^{18}F]fluorination of the chloro precursor (Scheme 1). The P-^{18}F did not seem to be very stable *in vitro*, since 25% was hydrolyzed after 30 min at room temperature. *In vivo* stability still needs to be investigated.



Scheme 1.
Synthesis of ^{18}F-dimefox.

Substantially more work has been reported on the formation of a Si-^{18}F bond. The first reports originate already from 1985 when Rosenthal reported the reaction of chlorotrimethylsilane with [^{18}F]fluoride in aqueous acetonitrile yielding the Si-^{18}F compound in 65% radiochemical yield (4). It was shown that the *in vivo* stability was quite low. The corresponding silanol was formed quite rapidly. More sterically hindered Si-compounds were proposed to prevent hydrolysis. It was not until 2005 that Ting et al. described follow-up work on Si-^{18}F bond formation (5). High yield reactions by labeling biomolecules with arylfluoroborates and silicates were reported. They introduced biotinylated (aminopropyl) triethoxysilane for protein targeting of avidin. After treatment of these compounds with [^{18}F]fluoride they found formation of the corresponding tetrafluorosilicate. Labelling efficiency was very high (80-100%). The tetrafluorosilicate was moderately stable in vitro and in vivo tests were encouraging as well.
A breakthrough towards application for biomolecules was the development of *p*-(di-*tert*-butyl[^{18}F]fluorosilyl)benzaldehyde (6,7). Labelling with [^{18}F]fluoride was achieved by ^{19}F-^{18}F exchange yielding ^{18}F-compounds which were stable under physiological conditions (pH 7.4 in blood serum). Bulky *tert*-butyl groups on the Si-atom are still crucial to maintain stability (Scheme 2). A disadvantage of this method is dilution of ^{18}F with stable ^{19}F, resulting in decreased specific activity. An advantage is that the labelling yields in this SiFA (Silicon-Fluoride-Acceptor) are extremely high (>80%) within 15 min. To apply SiFA to peptides, Schirrmacher et al. reacted *p*-(di-*tert*-butyl(fluorosilyl)benzaldehyde with an oxoamino derivatized peptide resulting in the stable oxime. Radiochemical yields were >95% in 10-15 min at room temperature. Besides low specific activity (3-5 GBq/µmol) the high lipophilicity is a concern.



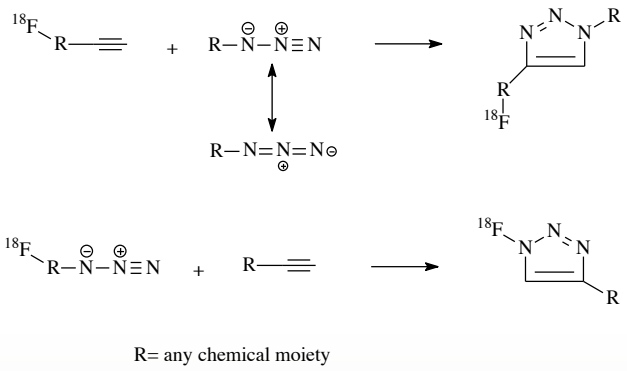
Scheme 2.
Use of SiFA in the synthesis of ^{18}F-tracers.

A next step forward was made by the Villigen group (8,9). This group developed new silicon-based building blocks to create high specific activity ^{18}F-biomolecules by nucleophilic displacement of either alkoxy, hydroxyl of hydride groups. The di-*tert*-butylsilyl functionalized peptides were prepared by standard solid phase peptide chemistry using the corresponding di-*tert*-butylsilyl acetic acid as building block. Reaction conditions for radiolabelling were that peptide and glacial acetic acid were added to the Kryptofix/[^{18}F]fluoride complex and heated at 90°C for 15-30 min. Acidic conditions were shown to be crucial. Radiochemical yields were 30-35%. Overall isolated yield was 13% with a reaction time of two hours and a specific activity of 62 GBq/µmol.
Based on disappointing in vivo biodistribution studies it was concluded that more potent and more hydrophilic peptides should be developed by preparation of reactive silicon groups bearing more polar substituents.

Click chemistry

Click chemistry is the popular term for a copper-catalyzed azide-alkyne reaction that makes it possible for certain chemical building blocks to "click" together in an irreversible linkage. Since its introduction in 2001 by Sharpless, the copper-catalyzed azide-alkyne reaction has proven extremely valuable for attaching small molecular probes to various biomolecules in a test tube or on fixed cells. However, its use for biomolecule labeling in living cells or organisms is prohibited by the requirement of a cytotoxic copper catalyst (10-12).
The most explored reaction is the Cu(I) catalyzed formation of 1,2,3-triazole using Huisgen 1,3-dipolar cycloaddition of terminal alkynes with azides. This reaction is highly regioselective leading to 1,4-disubstituted 1,2,3-triazoles (resembling an amide bond in vivo). Although the Cu(I) catalyzed 1,3-dipolar cycloaddition of terminal alkynes with azides provides the product in excellent yield and purity the transformation is still relatively slow and requires hours for completion (13-18).
Click chemistry using this Huisgen 1,3 cycloaddition can

be extremely useful for application to ^{18}F-radiolabelled pharmaceuticals (Scheme 3). Since the click reaction is orthogonal, no protective groups are required. In addition, reactions can be carried out in water possibly enabling ^{18}F-click reactions in vivo if suitable copper-free conditions are being developed.
Typically, temperature elevation is not required but the reaction can be performed over a wide range of temperatures (0–160°C), in a variety of solvents (including water), and over a wide range of pH values (5 through 12). It proceeds much faster than the uncatalyzed copper-free version, and purification essentially consists of product filtration (19). Furthermore, it is unaffected by steric factors.
^{18}F-labelled targeting peptides are becoming more widely used as in vivo imaging agents. Although a variety of ^{18}F-labelled prosthetic groups have been developed, only a limited number of chemical reactions have been utilized to incorporate the prosthetic groups into peptides including, acylation, alkylation, and oxime formation. Click chemistry with a Cu(I) catalyzed 1,3-dipolar cycloaddition has been used to prepare ^{18}F-radiolabelled peptides. The most commonly used acylation approach requires protection of other acylation prone groups within the peptide sequence.



Scheme 3.
^{18}F-Labelling using click chemistry.

The first application of ^{18}F-click chemistry for radiolabeling was published by Marik and Sutcliffe, describing a procedure for obtaining ^{18}F-fluoropeptides (20). They reacted ω-[^{18}F]fluoroalkynes with peptides bearing a *N*-(3-azidopropionyl)-group. The syntheses of the three different [^{18}F]fluoroalkynes, the butyne, pentyne and hexyne were accomplished by reacting the corresponding tosylalkynes. While the reported radiochemical purities were high (>98%) in all cases, the reaction yields varied significantly. The subsequent reaction of the [^{18}F]fluoroalkynes with the azide-derivatized peptides proceeded with radiochemical yields of 10% within 30 min using Cu(II)sulfate and sodium ascorbate as catalyst. Marik and Sutcliffe found that a Cu(I) iodide together with a nitrogen base resulted in drastically improved radiochemical yields of 54-99% in 10 min reaction time only.
Glaser and Årstadt published a similar approach (21). They also reported a click-labeling approach with the secondary labeling precursor 2-[^{18}F]fluoroethylazide. They decided on the ^{18}F-azide because alkynes are more readily available and less hazardous than organic azides. After 15 min the ^{18}F-azide was purified by distillation providing decay-corrected radiochemical yields of 54%. Glaser and Årstadt reported the use of this labeling synthon to obtain different 1,4-disubstituted triazoles in the presence of amine and carboxylic groups, among others. They tested different catalysts, Cu(II)-sulfate with sodium ascorbate and copper powder. The reaction was allowed to proceed for 15 min at room temperature, and yields varied considerably, depending not only on the catalyst, but also on the alkyne substrate used. After heating the reaction mixture to 80°C, the reaction was allowed to proceed for another 15 min, which then resulted in moderate to excellent yields (15-99%) of the triazoles. To prove that their approach also works satisfactorily for peptide labelling, Glaser and Årstadt labelled a model peptide derivatized with propargylic acid at room temperature in 15 min. The reaction yields reported were excellent (92%), but unfortunately HPLC purification was required to obtain the ^{18}F-labelled peptide.
Recently Sirion et al. describe an alternative synthetic approach for preparation of ^{18}F-labelled biomolecules using 'click reaction' with $CuSO_4$/Na-ascorbate and several model compounds such as small organic molecules, as sugar, amino acid and nucleotide (22). Preliminary studies to find optimal reaction conditions of the 1,3-dipolar cycloaddition for the two-step ^{18}F labeling procedure were performed using two Cu(I) species in four water-containing organic solvents: acetonitrile, dimethyl formamide, dimetheyl sulfoxide, and *t*-butanol, in which 1,3-dipolar cycloaddition of 4-methoxybenzyl azide and phenyl acetylene was employed as a model reaction. Finally they showed, the Cu(I)-catalyzed, 1,3-dipolar cycloaddition reaction was applied successfully to the synthesis of small, ^{18}F labelled, biomolecule-like compounds, and optimal reaction conditions were developed for one-pot, two-step reaction without intermediate purification. These conditions were employed in various 1,2,3-triazole syntheses of ^{18}F-labelled azides or acetylenes and their corresponding azide or acetylene compounds, including biomolecules.
Peptides prepared by ^{18}F-"click" radiolabeling and using 4-[^{18}F]fluorobenzoic and 2-[^{18}F]fluoropropionic acids were compared in relation to the effects on PET imaging and pharmacokinetics. The prosthetic groups did have an effect; metabolites with significantly different polarities were observed (23).
Although no *in vivo* data have yet been published, click chemistry for [^{18}F]fluorine labeling has the potential to develop into a versatile labeling tool.

Aluminum [^{18}F]fluoride

Peptides are usually labelled by using a ^{18}F-labelled prosthetic group, which requires multiple synthetic steps. A very facile

method was recently reported by McBride et al. wherein ^{18}F is first attached to aluminum as Al^{18}F, which is then bound to a NOTA-chelator which is already attached to a peptide (24). As a consequence a stable Al^{18}F-chelate-peptide complex can be synthesized in an efficient 1-pot synthetic procedure.
First, a solution of $AlCl_3$ in a pH 4.0 sodium-acetate buffer was mixed with aqueous ^{18}F to form the Al^{18}F complex which was added to a solution of a NOTA-conjugated pretargeting peptide (IMP 449). Followed by heating at 100 °C for 15 min. Radiochemical yields were 5%-20% with a specific activity of 18,500-48,100 GBq/mmol. The Al[^{18}F]F-IMP 449 was stable for 4 h in serum in vitro, and in animals. Radioactivity isolated in the urine 30 min after injection was only bound to the peptide.
As a follow-up to this promising and simple fluorination method several new NOTA ligands were investigated. Reaction parameters were optimized by variation of temperature, reaction time, and reagent concentration. Using four different forms of the NOTA ligand resulted in radiolabeling yields ranging from 5.8% to 87%. All of the Al[^{18}F]F NOTA complexes were stable *in vitro* in human serum, and those that were tested *in vivo* also were stable. The radiolabeling reactions were performed at 100 °C, with reaction times of 5 min. Amounts of 40 nmol peptide still yielded satisfactory yields. The peptide could be labelled up to 115 GBq/µmol with a total synthesis time of 30 min without chromatographic purification (25). This labeling technique has proved to be a simple one step [^{18}F]fluorination method for peptides and proteins and has the potential to become a kit-type preparation.

Microfluidics

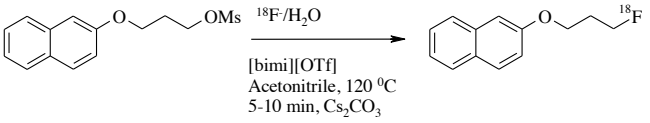
Microreactor technology has shown enormous potential for optimizing synthetic efficiency, particularly in the preparation of sensitive compounds. The high surface-to-volume ratios in microfluidics offer many possibilities to more efficient syntheses. Advantages of the use of very small quantities include simplification of purification steps and increased specific activity. Furthermore, microfluidic reactors offer possibilities to increase reaction speed dramatically, improve reproducibility, and reduce costs.
A few papers have appeared on the application of microfluidics for PET-radiochemistry. The most striking paper was published in Science (26). The authors achieved the synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG), in an integrated microfluidic device. Five sequential processes: [^{18}F] fluoride concentration, water evaporation, radiofluorination, solvent exchange, and hydrolytic deprotection proceeded with high radio-chemical yield and purity and with shorter synthesis time relative to conventional automated synthesis.
Gillies et al. applied microfluidic technology for the synthesis of [^{18}F]FDG (27,28). These reactions involved established methods of nucleophilic substitution on a mannose triflate precursor. [^{18}F]FDG was synthesised with a 50% incorporation of the available ^{18}F radioactivity in a very short time of 4 s.
Carboxylic esters were also successfully labelled with ^{11}C and ^{18}F, within a hydrodynamically-driven micro-reactor. The non-radioactive methyl ester was obtained at room temperature; its yield increased with higher substrate concentration and with reduced infusion rate. Radioactive methyl ester was obtained from the reaction of (10 mM) with in 56% decay-corrected radiochemical yield at an infusion rate of 10 µL.min^{-1}, and when the infusion rate was reduced to 1 µL.min^{-1}, the radiochemical yield increased to 88%. The synthesis of the non-radioactive fluoroethyl ester required heating of the micro-reactor on a heating block at 80 °C (14-17% RCY), whilst the corresponding radioactive form was obtained in 10% radiochemical yield.
Further work was presented in abstract form. A lot of work was presented using a MinuteMan device from NanoTek/Advion. A MinuteMan LF, liquid-flow microfluidic reactor system, was used to label, hydrolyze and purify [^{18}F]FLT from a commercially available thymidine precursor (29). The MinuteMan LF is a modular flow-based microreactor assembly, capable of up to four reaction steps with in-line purification via HPLC-based column. Syringe pumps were used to load and drive reagents through the glass microreactors at pressures up to 50 bar with microliter precision.
The rapid preparation and purification of [^{18}F]FLT was achieved in under 4 minutes with high radiochemical yields of 82%±5% and radiochemical purities >98%.
The average reported decay corrected yield for the production of [^{18}F]FLT is 20-40% using the standard macroscale labeling procedures. Compared to these methods, the microfluidic-based production of [^{18}F]FLT has been shown to be an improvement in both yield and time of synthesis.
The NanoTek MinuteMan microreactor was also used to provide improved synthesis of ^{18}F-setoperone, a potent PET serotonin antagonist with moderate dopaminergic activity (30). Due to the high cost and limited availability of the precursor (nitrosetoperone), microfluidic preparation of ^{18}F-setoperone was seen as an attractive alternative for the production of this radiopharmaceutical. Radiochemical yields were 70 to 80% as determined by radioTLC. Non-optimized final product yields after HPLC purification were 35-40% with a radiochemical purity >95%, as compared to regular production yields at TRIUMF of 10-20%.
GE Healthcare also presented a microscale solution for conducting [^{18}F]fluoride phase transfer and subsequent radiosynthesis of 2-[^{18}F]FDG eliminating the azeotropic drying process (31). A solution of [^{18}F]fluoride (1 mL) was passed at differing flow rates (100–1000 µL/min) through a volume of resin (1-15 µL) contained within a microscale device. The [^{18}F] fluoride was eluted from the resin at flow rates up to 250 µL/min. The elution mixture was reacted with a solution of mannose triflate using a microfluidic 'T'- mixer heated to 85 °C. The reaction mixture was collected in a solution of NaOH (0.3 M) and analysed by HPLC to determine the yield of 2-[^{18}F]FDG. The [^{18}F]fluoride trapping efficiencies were 80-97%, using resin

volumes of 6-13 µL. At a flow rate of 1000 µL/min, 1 mL of cyclotron produced [^{18}F]fluoride solution was extracted from the resin in 60 s. The elution efficiencies of [^{18}F]fluoride were up to 90% and were achieved at a flow rate of 250 µL/min. When the extracted [^{18}F]fluoride solution was passed directly onto the subsequent microfluidic 'T'- mixer and reacted with mannose triflate, acetyl protected [^{18}F]FDG was synthesised in 6 min with radiochemical yield of 83%. The deprotection reaction was performed in >80% yield to give 2-[^{18}F]FDG.
In conclusion, the application of microfluidics in ^{18}F-radiochemistry is still in its infancy. Information on the obtained data in the public domain is scarce, especially the number of full papers is surprisingly low. A lot of research needs to be done before it is possible to produce sufficient amounts for human studies. This research includes capturing high amounts of activity from the ^{18}F-target. Up to now microfluidic PET-radiochemistry holds promise which is demonstrated by the strategy of several companies who envision tailor-made PET-radiotracer production on individual patient basis (32) in combination with a table-top minicyclotron.

Ionic liquids

Regular nucleophilic radiofluoridation reactions will only occur if the [^{18}F]fluoride is free of water, however [^{18}F]fluoride is made by irradiation of ^{18}O enriched water by high energy protons. So before the [^{18}F]fluoride can react as nucleophile it needs to be worked up to remove any traces of water. Therefore the [^{18}F]fluoride is extracted from the H_2[^{18}O]O target via anion exchange extraction, followed by elution from the anion exchange resin with carbonate. Any residual water is removed from the reaction mixture by azeotropic distillation with acetonitrile. One needs such a non-protic solvent, else the [^{18}F]fluoride will behave as a base and will not give nucleophilic substitution. In order to solvate the [^{18}F] fluoride ion in a non-protic solvent, a phase transfer catalyst is applied, often the aza-crownether Kryptofix[2.2.2]. This work up procedure is required for the synthesis of all [^{18}F]F labelled compounds which are obtained via nucleophilic substitution. However, Kim et al (33,34) showed that with the aid of ionic liquids this workup procedure can be omitted. They showed that the addition of an ionic liquid to the reaction mixture of a nucleophilic fluorination with KF in acetonitrile on an aliphatic mesylate, the yield was improved and reaction time shortened (Scheme 4). Moreover, the addition of ionic liquid resulted in tolerance for water in the reaction mixture. This was an unprecedented finding, because it is generally accepted that nucleophilic fluoridations only occur in water free reaction conditions. A year later the same research group published the first radiofluorination method where several ionic liquids were applied in the radiofluorination of an aliphatic mesylate, as a model reaction for this new procedure (35).

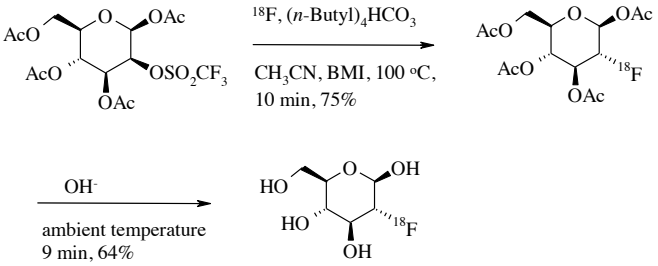
It was shown that this procedure yields over 90%



Scheme 4.
Radiofluorination in protic solvents.

incorporation of the [^{18}F]fluoride and does not require complete removal of water from the reaction mixture, thus proving that also in radiofluorination, where the concentration of the nucleophile [^{18}F]fluoride is very low and residual water may have a large influence on the reactivity of the [^{18}F]fluoride, the addition of a ionic liquid allows for residual water to be present in the reaction mixture. In 2004 this group published the first practical use of ionic liquids in the synthesis of [^{18}F]FDG, (Scheme 5) (36).

For this synthesis procedure the workup of the fluoride was



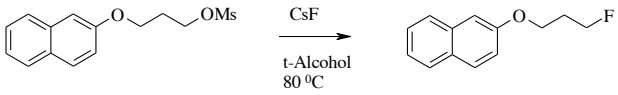
Scheme 5.
Synthesis of [^{18}F]FDG utilizing an ionic liquid.

discarded and still the radiochemical yields were moderate (49 % overall). Hydrolysis with sodium hydroxide on a Waters SepPak *t*C18 cartridge resulted in a radiochemical purity > 95%. Major advantage of this procedure is that the total synthesis time is shortened to 19 minutes in total, which is of great importance when dealing with short-lived radioisotopes. The authors also claim an increased nucleophilicity of the fluoride ion, due to the presence of the ionic liquid, although no evidence for this hypothesis was given.
In conclusion, ionic liquids have been shown to be of much interest for radiofluoridation reactions and the procedure has a high potential. However the procedure has not yet been reported to be successful in the hands of other research groups. Still research is needed to elaborate on the applicability of this new procedure and to determine the reason why ionic liquids have such benefits like the authors have reported. Finally the toxicity of ionic liquids may be an issue of concern.

Radiofluorination promotion by tertiary alcohols

It has been generally accepted that radiofluorination reactions cannot be performed in protic solvents, because fluoride

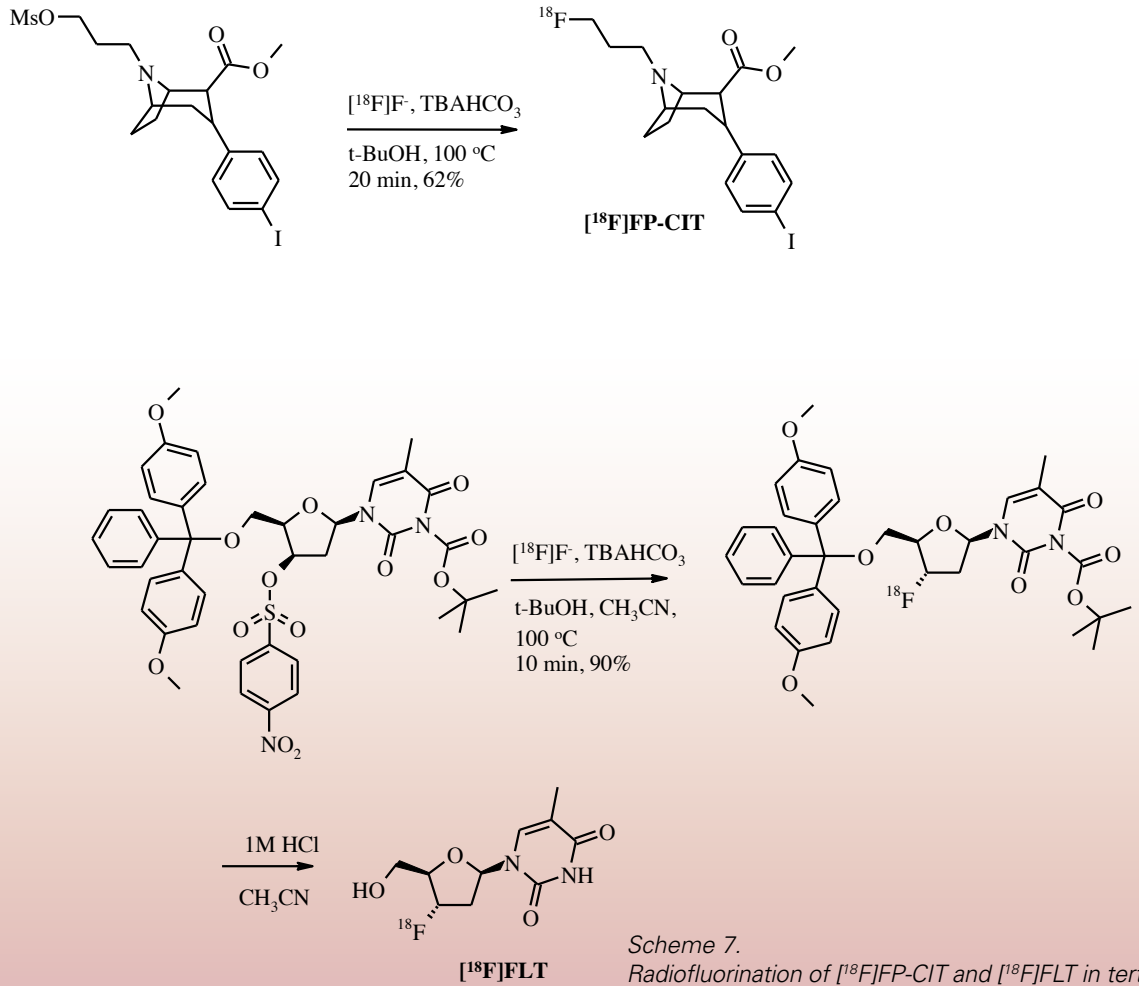
will in that case act as a strong base by abstracting the acidic proton of the protic solvent and thus the nucleophilic character of fluoride will be diminished. A nucleophilic substitution reaction will be impossible in that case. However, in contradiction to this general accepted rule, it has been found recently by Kim et al (37) that radiofluorinations in protic tertiary alcohols is possible nonetheless. A model reaction was used (Scheme 6) to show that in several tertiary alcohols and with alkali metal fluorides a S_N2 substitution on a primary mesylate could be done in high yields.
They found that tertiary alcohols give much better results



Scheme 6.
Model reaction for fluorination in tertiary alcohols.

compared to other protic solvents, Cs^+ works better than K^+ as cation, F^- is more reactive than Br and the effect of the solvent on the leaving group is increased. As explanation for these atypical results they hypothesize a catalytic effect by the tertiary alcohol. This hypothesis was further investigated by quantum chemical methods (38,39). They conclude that the catalytic effect of tertiary alcohols is caused by a combination of interactions: the tertiary alcohol acts as a Lewis base for the cation, thus shielding the protic solvent from the nucleophile and acts as a Lewis acid towards the leaving group, thus bridging the nucleophile and the leaving group. Moreover they calculated that the interaction of the tertiary alcohol with the cation reduces the reaction barrier and that the fluoride ion is much better solvated than the bromine ion. These findings let them conclude that they have found a new S_N2 reaction mechanism.
These recent findings did not yet lead to a broad application of this new method in radiolabeling with [^{18}F]fluoride. In literature only a few reports are known where a catalytic effect was observed by the use of tertiary alcohols. It has been reported with the synthesis of [^{18}F]-*N*-fluoropropyl-carbomethoxy-4-iodophenyl-nortropane ([^{18}F]FP-CIT) (40) and in the case of radiofluorination of [^{18}F]FLT (41) (Scheme 7).

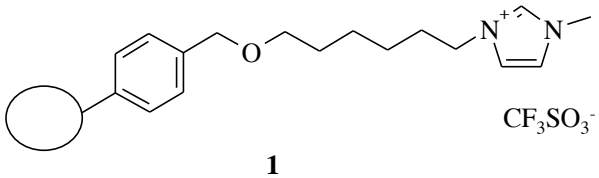
However, others did not find this catalytic effect (42) in their



Scheme 7.
Radiofluorination of [^{18}F]FP-CIT and [^{18}F]FLT in tertiary alcohols.

reaction or even found reduced reactivity (43), in both cases for unexplained reasons.
An interesting synergistic effect of the application of tertiary alcohols in combination with ionic liquids was reported in 2 recent publications, either by using a tertiary alcohol in combination with a polymer supported ionic liquid (44) or by combining the two features of ionic liquids and tertiary alcohol within one molecule (45) (Scheme 8).

Kim et al. (44) conclude that the combination of a tertiary



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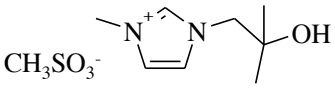

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Scheme 8.
Polymer supported ionic liquid (1) and combination of t-alcohol with an ionic liquid in one molecule (2).

alcohol with a polymer supported ionic liquid significantly enhances the alkali metal fluoride as well as the reactivity of the halide leaving group in a series of model reactions, whereas Shinde et al. (45) demonstrate that with the application of a same level of yield and chemoselectivity could be observed in comparison with reactions in *t*-butanol or in an ionic liquid/acetonitrile mixture, but reaction times were much shorter. This is important for the radiosynthesis of short lived isotopes like ^{18}F.

Developments in electrophilic radiofluoridation reactions

Elemental $[^{18}F]F_2$ and reagents derived from $[^{18}F]F_2$ like $[^{18}F]$ acetylhypofluorite (46,47) or $[^{18}F]$-*N*-fluorobenzenesulfonimine (48) amongst others, are described in literature as sources of electrophilic ^{18}F.

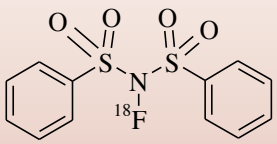


Figure 2.
Reagents for electrophilic radiofluorination reactions.

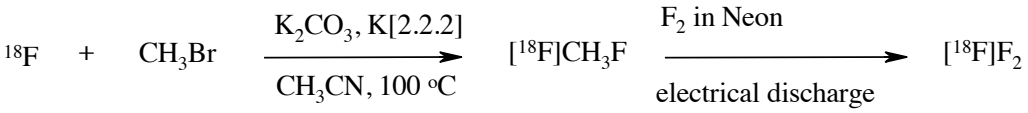
Although in organic chemistry electrophilic fluorination is the main route for introducing carbon-fluorine bonds, in radiochemistry it is not. Mainly because the use of $[^{18}F]F_2$ has two major limitations: the yield of the nuclear reaction ($^{20}Ne(d,\alpha)^{18}F$ or $^{18}O(p,n)^{18}F$) is relatively low and secondly carrier F_2 is required to retrieve the $[^{18}F]F_2$ from the cyclotron target system. Both these limitations results in a low specific activity of labelled compounds obtained via an electrophilic substitution reaction (in the range of 0.1-1.0 GBq/µmol), therefore making these products unsuitable for tracer studies where a receptor is the biological target for which a lower limit of 18.5 GBq/µmol is generally accepted. For non-receptor targets the specific activity is of less relevance, hence radiolabelled compounds synthesized with $[^{18}F]F_2$ or derivatives have only been successfully applied in such cases, like $[^{18}F]$FDOPA or $[^{18}F]$-5-fluorouracil.

Cyclotron production of $[^{18}F]F_2$ is relatively low yielding compared to the cyclotron production of $[^{18}F]$fluoride. While for the latter production yields of 500 GBq are achievable, for the $^{20}Ne(d,\alpha)^{18}F$ production of $[^{18}F]F_2$, a maximum yield of 40 GBq is achieved and for the $^{18}O(p,n)^{18}F$ production of $[^{18}F]F_2$, a maximal yield of approximately 100 GBq can be achieved. Furthermore, carrier F_2 has to be added to the target content, in the order of 0.1–2% in order to retrieve the maximum amount of $[^{18}F]F$ from the target. By using this procedure up to 100 µmoles of carrier F_2 are present in the final mixture for the substitution reaction.

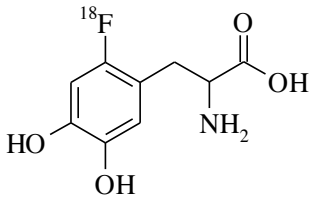
Bergman et al. (49) recognized this issue and developed a method for the conversion of $[^{18}F]$fluoride into $[^{18}F]F_2$, thereby utilizing the higher yield of the $[^{18}F]$fluoride production (Scheme 9). They reported a method in which the obtained $[^{18}F]$fluoride was, after standard workup for nucleophilic substitutions, reacted with bromomethane to yield $[^{18}F]$ fluoromethane. This intermediate product was converted to $[^{18}F]F_2$ by promoting an isotopic exchange reaction of the $[^{18}F]$ fluoromethane with F_2 in neon by an electrical discharge.

Despite the fact that in this case the addition of carrier F_2 is required, like is also the case with the in-target production of $[^{18}F]F_2$, the obtained $[^{18}F]F_2$ has a relative high specific activity of 55 GBq/µmol. They used this method for the synthesis of several radiolabelled compounds (Scheme 10). In all cases electrophilic fluorination is performed on stannylated precursors. They were isolated with a specific activity approximately 15 GBq/µmol at end of synthesis (50). The dopamine transporter ligand $[^{18}F]$CFT was obtained in even higher specific activity and in amounts allowing for 2 PET studies from one production in a routine synthesis situation. Drawback of this method is that dedicated instrumentation is required which is not commercially available and therefore widely spread use of this procedure is limited.

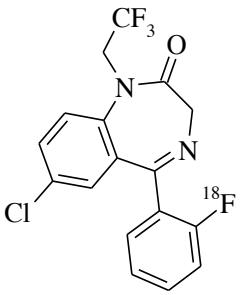
Fluorinase



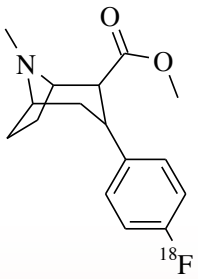
Scheme 9.
Synthesis of [^{18}F]F_2 according to Bergman.



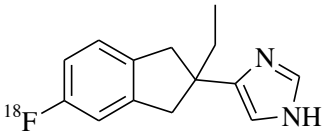
[^{18}F]FDOPA



[^{18}F]oxoquazepam



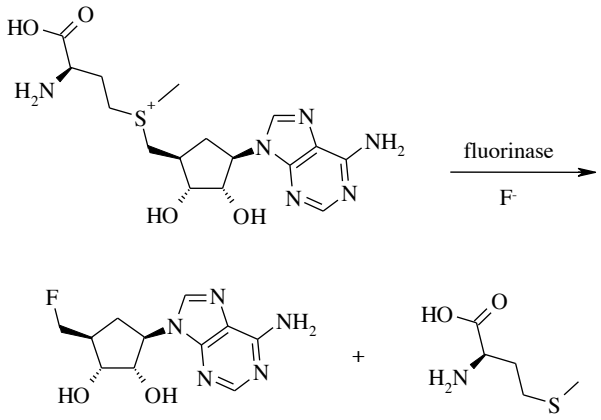
[^{18}F]CFT



[^{18}F]Fluoroatipamezole

Scheme 10.
Electrophilic fluorination of several compounds, according to Bergman (50).

Fluorinase is an enzyme firstly characterized by O'Hagan et al (51-53). It was isolated from Steptomyces cattleya, and its official name is 5'-fluoro-5'-deoxyadenosine synthase (E.C. 2.5.1.63). Already in 1986 it was found by Sanada et al. (54) that Steptomyces cattleya was able to biosynthesise organo-fluorine bonds, which was quite unique in itself. It was shown that the reaction mechanism in the biosynthesis of 5'-fluoro-5'-deoxyadenosine was as depicted in scheme 11. The fluorinase amino acid sequence was identified (55) and



Scheme 11.
Biosynthesis of 5'-fluoro-5'-deoxyadenosine by fluorinase.

subsequently the enzyme was expressed in *E.Coli* BL21(DE3). The overexpression of fluorinase in this cell system allowed isolation of a large amount of fluorinase for recrystallization. The crystal structure of the enzyme was published in the same paper. It was shown elegantly (56) that the reaction mechanism follows an S_N2 substitution by the use of the deuterium labelled substrate (S-adenosyl-L-methionine). NMR measurements showed that the configuration of the substituted carbon atom was inverted.
Fluorinase has also been applied successfully in radiofluorination with the synthesis of [^{18}F]-5'-fluoro-5'-deoxyadenosine, by incubating fluorinase and *S*-adenosyl-L-methionine in the presence of [^{18}F]fluoride (57), according to the same reaction as presented in scheme 11. Although still in low yields, due to the fact that Steptomyces cattleya was used, it was the first enzymatic radiolabeling with [^{18}F] fluoride. After fluorinase was over-expressed in *E.Coli*, more efficient conversion of the [^{18}F]fluoride was found. The reaction speed was dependent on enzyme concentration and temperature and proceeded quite fast with over 95% conversion of the [^{18}F]fluoride within 2 hours to yield [^{18}F]-5'-fluoro-5'-deoxyadenosine (58). A major advantage of using fluorinase with [^{18}F]fluoride is that the enzyme is in a large excess compared to the fluoride (µmoles of enzyme vs pmoles of [^{18}F]fluoride), thus enhancing the conversion of the [^{18}F]fluoride. Increasing the amount of fluoride by the addition of [^{19}F]fluoride to the reaction mixture reduced the speed of conversion.
The major advantage of radiofluorination with fluorinase is that [^{18}F]fluoride directly from the target can be applied. It is a very simple and effective method of radiofluorination. Drawback of fluorinase is that is specific for its precursor *S*-adenosyl-L-methionine, in this way it can only be applied for the biosynthesis of [^{18}F]-5'-fluoro-5'-deoxyadenosine or breakdown products thereof, e.g. fluoroacetic acid.
It would be a great challenge to modify the reactive site of the enzyme by biochemical engineering of the enzyme while maintaining its reactivity, in order to be able to use a larger variety of substrates, thus yielding a diversity in (radio)fluorinated product possibilities. For now, fluorinase can only be applied of the synthesis of [^{18}F]-5'-fluoro-5'-deoxyadenosine.

Concluding remarks and future perspectives

In this article several new developments from recent literature has been described that are still in its infancy. Despite these improved possibilities, there is still an urgent need for new developments. Additional issues to be addressed should be, amongst others, mild reaction conditions to reduce formation of side products or break-down products; improving specific activity when applying electrophilic radiofluorination; kit-type chemistry in order to have easy and wide applicable radiofluorination methods; an easy to handle general radiofluorination reagent, like diethylaminosulphur trifluoride is for non-radioactive fluorination chemistry
All these options will improve radiofluorination in general and will make the use of [^{18}F]fluoride more easy and more efficient. However it will take quite some effort to achieve these goals, if possible at all.

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PET/CT characteristics in the diagnosis of an endobronchial lipomatous hamartoma: a case report

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Abstract
Van der Zant FM, Knol RJJ, Heitbrink MA, Boer RO. PET/CT characteristics in the diagnosis of an endobronchial lipomatous hamartoma: a case report.
We describe a case of endobroncheal lipomatous hamartoma. We discuss the results of the PET/CT examination in this patient and we describe the usefulness of the PET and CT characteristics, Hounsfield Units and FDG-avidity, in making the diagnosis. Furthermore, we describe some general aspects of hamartomas.
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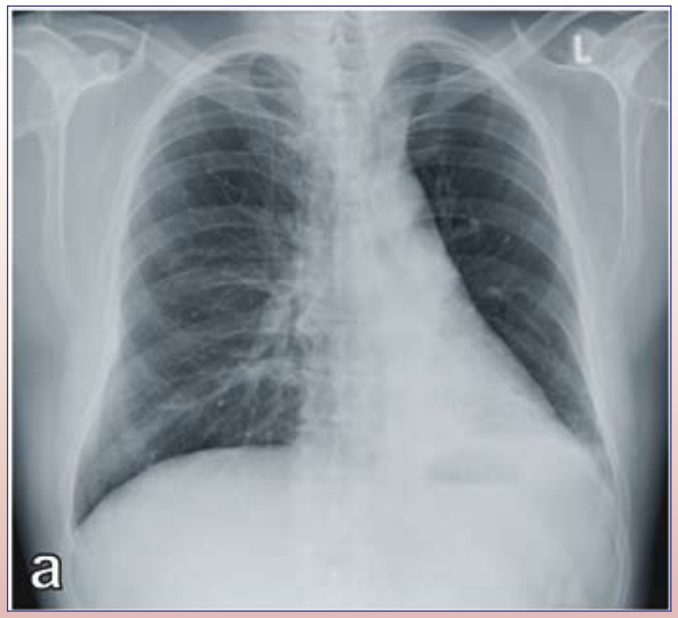
Introduction

Hamartomas may occur in any organ and originate from mesenchymal cells, naturally expressed in these organs. The cell proliferation may either be a developmental disorder or neoplasm, but certainly is not malignant in nature. The term hamartoma was introduced by Albrechts in 1904, but frequently these masses are named after the principal mesenchymal cell type found in the proliferation (chondromatous, lipomatous etc.) (1). In lung, the vast majority of all parenchymal benign tumours have been shown to be hamartomas (>70%) (2). Of the hamartomas that occur in lung, more than 90% are located in the parenchyma (3). endotrachial or intrabronchial hamartomas, however, are relatively rare. Of all pulmonary hamartomas within the lungs, these account for approximately 1.4% of the cases (4). While most parenchymal hamartomas are non-symptomatic, endobronchial hamartomas usually give rise to complaints such as coughing, infection, hemoptysis, or dyspnea due to obstruction of the bronchi. Here, we report a case of an endobronchial polypoid lesion in a 50-year-old male. Furthermore, we describe how PET/CT characteristics, Hounsfield units (HU) and FDG-avidity, assist in making the diagnosis.

Case Report

A 50-year-old male patient was referred to our hospital in the second half of January 2011. Relevant history of the patient included left-sided traumatic pneumothorax in 1990, pneumonia in 2007 followed by a period of recurrent bronchitis for a few months. The patient developed general discomfort at the end of December 2010. In the beginning of January 2011, the general discomfort was accompanied by coughing, exercise dyspnea and fever. Physical examination revealed fever of 38 °C and decreased breath sound of the left lower thorax at auscultation. The chest X-ray, ordered by the general practitioner, showed pneumonia of the left lower lobe. Based on these findings, the general practitioner started with antimicrobial treatment by means of amoxicillin clavulanate potassium (augmentin) for one week. The complaints of the patients did not resolve after this treatment and the general practitioner ordered a control chest X-ray. The control chest X-ray (figure 1) showed aggravation of the retrocardial infiltrate in the left lower lobe and the radiologist suggested consultation of a pulmonologist.
Patient's complaints did not change until the visit to the pulmonologist. Physical examination now showed decreased breath sounds on the whole left thorax while temperature had risen to 38.5 °C. Therefore, the patient was scheduled for bronchoscopy. The bronchoscopy revealed a polypoid lesion (figure 2) in the left main bronchus which could not be passed with the bronchoscope. Five biopsies were taken from the



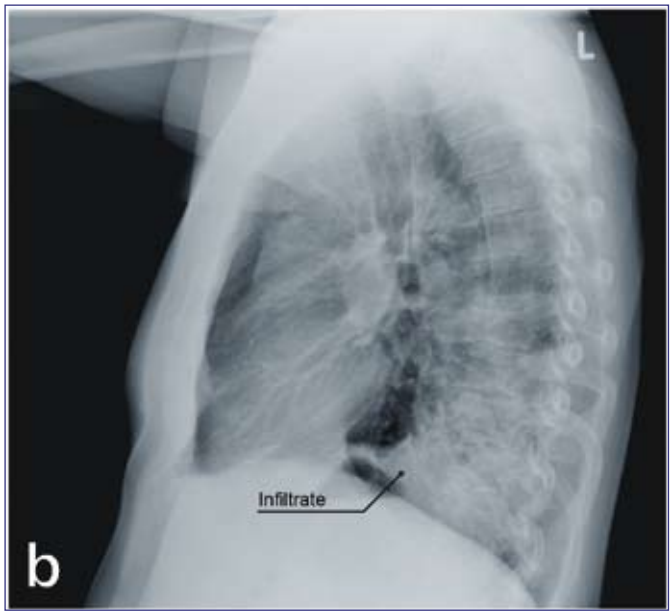


Figure 1a and 1b.
Chest X-ray (AP and lateral view) showing an infiltrate in the left lower lobe.

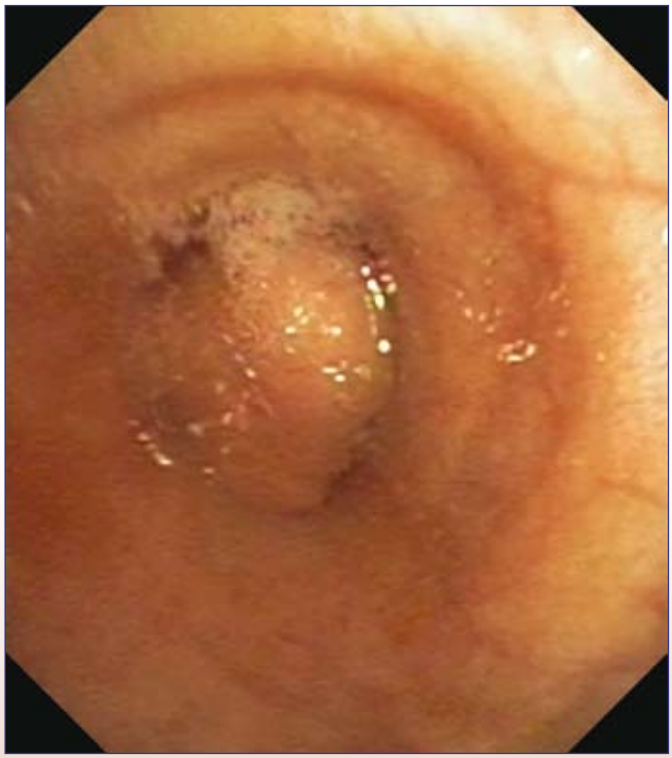


Figure 2.
Bronchoscopic view of the lipomatous hamartoma.

lesion and bronchial fluid was harvested for microbiological examination. The specimens from biopsy were distorted in the procedure but clearly showed reactive changes and chronic inflammation. Microbiological examination showed Haemophilus para-influenza and staphylococcus aureus.

Based on these findings the pulmonologist ordered a PET/CT scan to clarify the patient's problem.

PET/CT

A PET/CT from head to mid-thigh was performed on a Siemens Biograph 2, using an intravenous contrast agent (Ultravist 300) and 370 MBq ^{18}F-FDG. The PET/CT (figure 3) clearly indicated moderate hypermetabolism of the post-stenotic infiltrate in the lower lobe of the left lung. Careful attention was paid to the endotracheal lesion that was discovered during bronchoscopy. This particular lesion was not FDG-avid on the PET-images, but could easily be recognized on the CT-series in the left main bronchus since it had a density of approximately -85 HU, as compared to the adjacent air containing bronchus (-650 HU). Resembling the density of subcutaneous fat on the CT (-100 HU), the CT- as well as the PET-characteristics of the mass, were suggestive of a benign, lipomatous endobronchial lesion. Although very rare in the general population, the most common cause is a hamartoma. In this case it turned out to be a lipomatous hamartoma. Based on the findings of the PET/CT, the patient was referred to an academic hospital for bronchoscopic debulking. The debulking was performed using a diathermy snare and a cryoprobe. The debulking procedure of this patient was recorded in the academic hospital and can be viewed on YouTube (http://www.youtube.com/v/8Qccm1VR1s0) or www.bronchoscopy.nl under 'teaching files', subhead 'advanced bronchoscopy', 'hamartoma'.

Discussion

Between 7-14% of all coin lesions in lungs prove to be pulmonary hamartomas (5,6). Pulmonary hamartomas are most often diagnosed in the fifth or sixth decade of life and seldom in childhood (2,4,7). A male predominance has been reported in the incidence of these benign tumors, with a M/F ratio of approximately 2 (4). The majority of the lesions are asymptomatic and are incidental findings on imaging studies, found during chest surgery performed for other reasons, or show up as an incidental finding at autopsy (4). The small subgroup of endotracheal or endobronchial hamartomas are more likely to be symptomatic due to bronchial obstruction, bleeding or irritation. The most frequently encountered symptoms are recurrent respiratory infections or obstructive pneumonia and hemoptysis, with or without cough or dyspnea (8). Peels and co-workers reported 171 hamartomas between 1960 and 1987 in the Saint Antonius Hospital in Nieuwegein, 12 (7%) of the 171 hamartomas were located endobrochially (9). Another study, performed by Le Roux et al. showed two endobronchial hamartomas in a population of 27 (8%) (10). In a study population of 215 cases of pulmonary hamartomas, Gjevre and colleagues found only three endobronchial hamartomas (1.4%) (4).
In the study by Peels et al., the endobronchial hamartomas were characterized and proved to be of the chondromatous type in 67% (8 patients) whereas in 33% the predominant

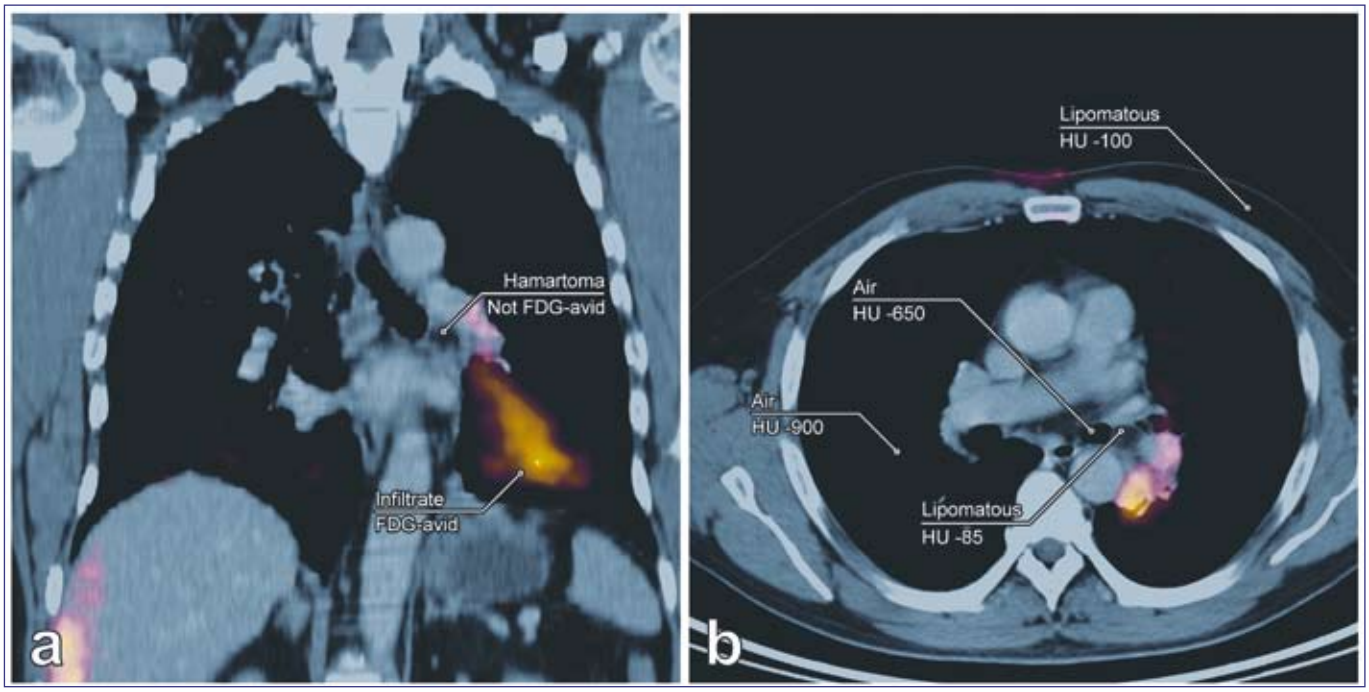


Figure 3a and 3b.
Coronal and transversal slice of PET/CT showing the PET and CT characteristics in i.e. FDG-avidity and Hounsfield Units of the lipomatous hamartoma.

tissue type was lipomatous (9). Cosío and co-workers reported a group of 43 patients with endobronchial hamartomas, who all underwent bronchoscopy. Histologic characterization showed that of these hamartomas, 37% were chondroid, 30% were lipoid, whereas in 33% there was no predominant cellular component (8).
For intrapulmonary hamartomas the typical radiological abnormality is a round homogeneous opacity in the periphery of the lung, although occasionally it appears lobulated. Calcification is evident radiologically in only 10%, particularly at the periphery (11). Popcorn calcification is virtually diagnostic of a hamartoma with chondrosarcoma being the only differential diagnosis (12). Radiological abnormalities in patients with endobronchial tumors are usually the result of bronchial obstruction, and include post-obstruction pneumonia or atelectasis (11). Hamartomas usually show no or little FDG uptake on PET scans and can be differentiated from malignant lung tumors (13,14). However, atypical hamartomas can show increased FDG accumulation, thereby mimicking a pulmonary malignancy (15).
For treatment of endobronchial hamartomas endoscopic approach should be the first choice, especially because the lesions are benign (16). Electrocautery followed by cryotherapy for removal of residual tumor is preferred (16). Only when bronchoscopic treatment fails, surgical resection can be considered. In the study of Cosío 17 of 36 (47%) patients were treated with rigid bronchoscopy and laser, 5 of 36 (14%) were treated with thoracotomy, 2 of 36 (6%) were treated with fiberoptic bronchoscopy with forceps resection and 12 of 36 (33%) were not treated. Only 4 of the 24 treated patients showed a recurrence within 72 months. All other endoscopic procedures were considered either successful or partially successful (8).

Conclusion

Endobronchial, lipomatous hamartoma show HU comparable with fat density and hamartoma are not FDG-avid.
Endobronchial, lipomatous hamartoma are very rare and can cause FDG-avid postobstruction pneumonia.

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E-learningsplatform voor nucleair geneeskundigen en AIOS gelanceerd

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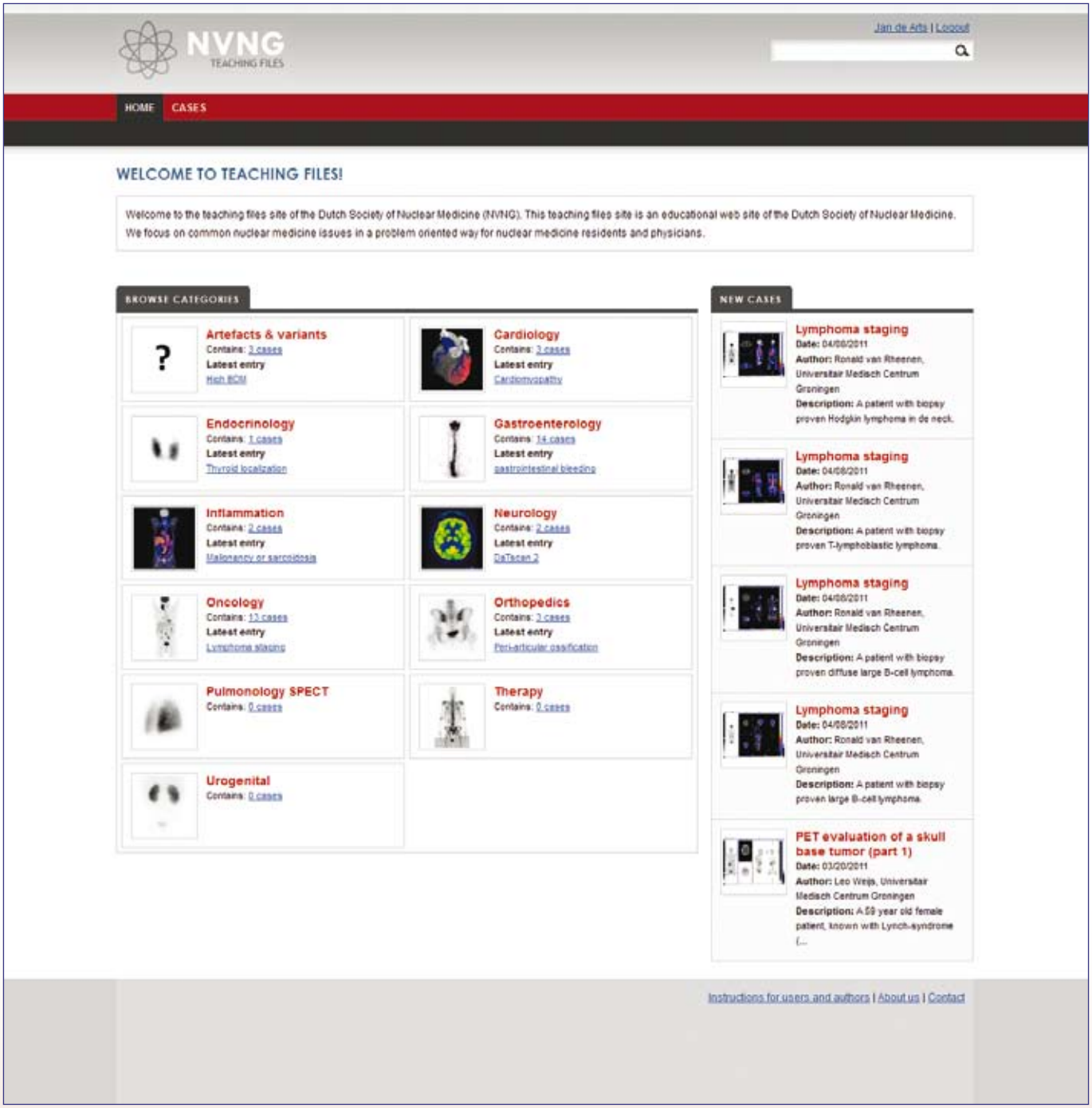
Vanaf februari 2011 is de E-learningwebsite van de NVNG geactiveerd. Er zijn op dit moment ongeveer 40 cases op de site geplaatst. Er zijn drie soorten cases beschikbaar: multiple choice cases, lokalisatiecases en diagnostische cases. Op dit moment zijn de aangeleverde cases vooral multiple choice cases en de meeste zijn door AIOS aangeleverd. Er zijn elf verschillende categorieën waarin de casus geplaatst c.q. bekeken kan worden. Deze categorieën kunnen ook weer in verschillende scantechnieken ingedeeld worden.
Van de AIOS wordt verwacht dat deze minimaal een vijftal cases per jaar op de site plaatst. Van de supervisoren van de AIOS, waarvan diversen opgenomen zijn in de redactie (zie bijgevoegde lijst Associate Editors), wordt verwacht dat deze de aangeleverde casuïstiek controleren op de vereiste structuur en volledigheid en eventueel redigeren, dan wel vragen om invulling van bestaande hiaten. Van belang bij het plaatsen van de casus is dat deze gevalideerd is door histologie, follow up of bevestiging met andere beeldvorming.
Het uitwerken en aanleveren van een casus kan onderdeel vormen van de opleiding, waardoor de AIOS een actieve rol is toebedacht. Vooral het opstellen van goede lokalisatiecases en diagnostische cases kan erg leerzaam zijn.
Natuurlijk mag ook elke supervisor en elke nucleair geneeskundige zelf casuïstiek plaatsen, sterker nog: Hoe meer casuïstiek, hoe beter de site wordt.
Diverse NVNG leden hebben de site (te vinden onder **www.nvng.nl,** onder leden staat de link naar de e-learning site) al bezocht. De huidige opzet heeft als voordeel dat casuïstiek voortdurend vernieuwd wordt zodat onderwijs steeds state-of –the-art zal zijn.
Op een later tijdstip zullen er officiële oefenexamens toegevoegd worden waarmee punten behaald kunnen worden. Door middel van deze oefenexamens kan de AIOS en de nucleair geneeskundige zelf bijhouden hoe zijn/haar kennisniveau is, hoe dit is veranderd in de tijd (vergelijking met zichzelf) en hoe het niveau is ten opzichte van andere nucleair geneeskundigen (benchmarking). Het is het streven om het deelnemen aan het E-learning- en benchmarkingprogramma een onderdeel te maken van het accreditatieprogramma van de nucleaire geneeskundige (directe GAIA koppeling) en na verloop van tijd ook van het onderwijsprogramma van de AIOS.
Nog enkele praktische zaken: als je andere bezigheden hebt terwijl de casus nog niet af is, de casus altijd even tussentijds opslaan (button "save" onderaan te vinden bij de casus), zodat de casus niet verloren gaat. Sommige ziekenhuizen kunnen geen afbeeldingen inladen op de E-learning website, waarschijnlijk ten gevolge van een hoogdrempelige fire wall. Als alternatief kan dit thuis gedaan worden, of eventueel kunnen de afbeeldingen doorgestuurd worden naar de redactie.
Door de Editors in Chief zal twee keer per jaar de auteur van de in hun ogen meest leerzame casus gevraagd worden een uitgebreide versie van deze casus te schrijven voor plaatsing in het Tijdschrift voor Nucleaire Geneeskunde.



Figuur 1
De E-learningwebsite van de NVNG.

Dr. I.M.E. Desar

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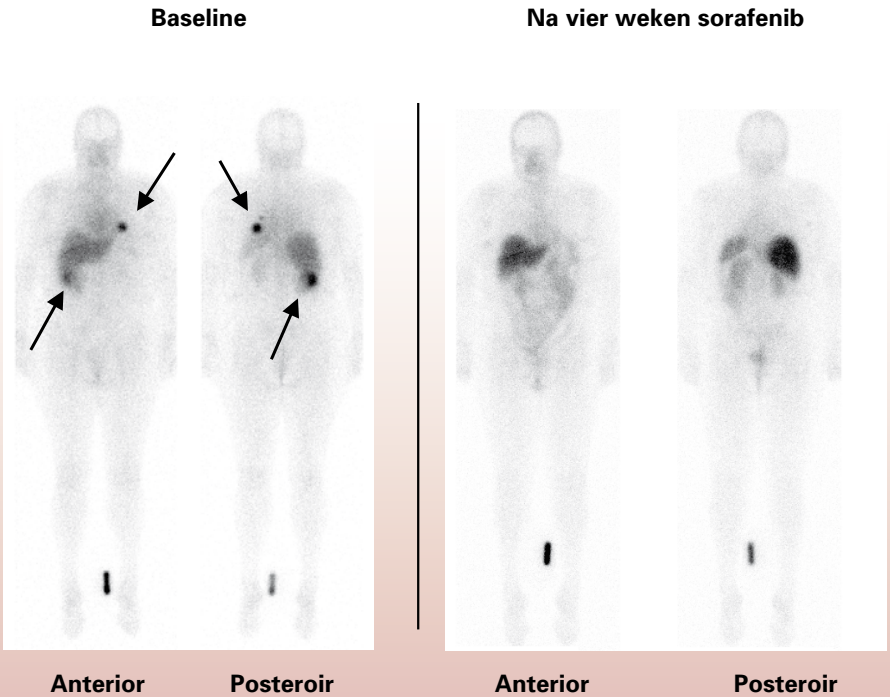
Advanced monitoring of targeted therapy in cancer

De recente ontwikkeling van zogenaamde '*targeted therapy*' vormt een doorbraak in de behandeling van maligniteiten. *Targeted therapy* richt zich op zeer specifieke eigenschappen van de kankercel, of op (elementen uit) processen die essentieel zijn voor de ontwikkeling en groei van kanker, zoals proliferatie, angiogenese, vascularisatie en apoptose. De effecten van *targeted therapy* bestaan niet alleen uit volume veranderingen, maar ook uit bijvoorbeeld necrose en cavitatie. Om al in een vroeger stadium deze effecten te evalueren, voldoet anatomische beeldvorming niet en zijn er betere moleculaire en functionele beeldvormende technieken nodig. Uit de beschikbare literatuur bleek dat moleculaire en functionele beeldvormende technieken, m.n. ^{18}F-FDG PET en dynamic contrast enhanced (DCE)-MRI, in staat zijn om al vroeg respons te meten, maar de optimale timing was onduidelijk. Maar ook bleek dat het tot dusver ontbreekt aan standaardisatie en inzicht in de reproduceerbaarheid van dergelijke beeldvormende technieken.
In een klinische studie werd de toepassing van Indium-111 (^{111}In) gelabeld bevacizumab scintigrafie onderzocht voor de evaluatie van neoadjuvante behandeling met "vascular endothelial growth factor receptor" (VEGFR)-remmer sorafenib bij patiënten met een heldercellig niercelcarcinoom. Bevacizumab is een monoklonaal antilichaam tegen "vascular endothelial growth factor" (VEGF). ^{111}In gelabelde bevacizumab scintigrafie is een moleculaire beeldvormende techniek die enerzijds informatie geeft over VEGF expressie en anderzijds over permeabiliteit, vascullariteit en necrose aangezien de penetratie van ^{111}In gelabeld bevacizumab in de tumor afhankelijk is van de neovasculatuur. ^{111}In gelabeld bevacizumab scintigrafie bleek in staat om niercelcarcinoom laesies te visualiseren in alle veertien patiënten. Negen van



Figuur 1. Indium-111 Bevacizumab scintigrafie voor en na vier weken neoadjuvante behandeling met sorafenib bij een patiënt met pulmonale metastasen van een heldercellig niercelcarcinoom rechts.

hen werden gedurende vier weken neoadjuvant behandeld met 2 dd 400 mg sorafenib. Bij hen werd voor start van de behandeling en na afloop van de behandeling een ^{111}In gelabeld bevacizumab scintigram gemaakt. Neoadjuvante behandeling met sorafenib leidde tot een significante afname van de ^{111}In-bevacizumab accumulatie in de niercelcarcinoom laesies (gemiddelde afname -60.5%, range +1.5 tot -90.1%). Deze afname was het gevolg van destructie van de tumor neovasculatuur. De VEGF-A expressie bleef intact.
Ook werd de hypothese onderzocht, dat de vasculaire veranderingen die geïnduceerd worden door VEGFR remmer sunitinib voorafgaan aan de volumetrische veranderingen op CT-scans. Deze vroege vasculaire veranderingen werden gemeten bij tien patiënten met abdominale laesies van een niercelcarcinoom met drie typen functionele MRI scans; diffusie gewogen MRI (DWI), DCE-MRI en T2* perfusie MRI, en werden gecorreleerd met progressievrije overleving. Er waren reeds op dag drie veranderingen meetbaar en deze correleerden met progressievrije overleving.
De biologische processen na het staken van angiogenese remmers in het geval van radiologisch bewezen progressieve ziekte zijn onduidelijk, maar wel belangrijk mede gezien het optreden van flare-up syndromen. Flare-up syndroom is een snelle toename van ziektegerelateerde klachten zoals pijn en dyspnoe direct na het staken van een angiogeneseremmer. In een groep van tien niercelcarcinoom patiënten met volgens de "Response evaluation criteria in solid tumors" (RECIST) radiologisch progressieve ziekte tijdens behandeling met een angiogenese remmer, staakte de helft direct de behandeling en de rest ging nog twee weken door. In de totale groep was er sprake van groei van de tumoren en toename van metabole activiteit gemeten met ^{18}F-FDG PET/CT. Dit leek meer uitgesproken in de groep die direct stopte, maar dit was in deze kleine aantallen nog niet significant. De resultaten van de DCE-MRI scans waren nog te beperkt. De C-reactive protein en d-dimeer namen meer toe in de groep die direct stopte. Samenvattend kunnen moleculaire en functionele beeldvormende technieken worden ingezet om de optimale timing van start, staken en volgorde van *targeted therapy* mede te bepalen.

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Sentinel nodes in complex areas: innovating radioguided surgery

Retroperitoneale sentinelnodes en sentinelnodes in het hoofd-halsgebied en bekken zijn op conventionele lymfoscintigrafiebeelden vaak moeilijk te lokaliseren, als gevolg van de complexe anatomische verhoudingen.

SPECT/CT

SPECT/CT toont meer sentinelnodes en identificeert extra-nodale opname van het radiofarmacon, zoals contaminatie van de huid. Met behulp van SPECT/CT kunnen ook onduidelijkheden op conventionele planaire beelden worden opgehelderd (non-visualisatie of onduidelijke locatie van de klieren). Achtendertig patiënten met een hoofd-halsmelanoom ondergingen conventionele lymfoscintigrafie gevolgd door hybride SPECT/CT. SPECT/CT detecteerde een extra sentinelnode bij 16% van de patiënten en toonde duidelijk de anatomische locatie van de hete klieren bij alle patiënten. Ook omdat bij meer dan de helft van de patiënten de chirurgische aanpak werd aangepast op basis van de SPECT/CT beelden, is het verrichten van een SPECT/CT aan te bevelen bij patiënten met een hoofd-halsmelanoom. Bij patiënten met

prostaatcarcinoom toonde SPECT/CT extra sentinel nodes in 63% van 46 patiënten en ook hier heeft de preoperatieve anatomie informatie tot betere peroperatieve identificatie van sentinelnodes geleid.

Mini-gammacamera

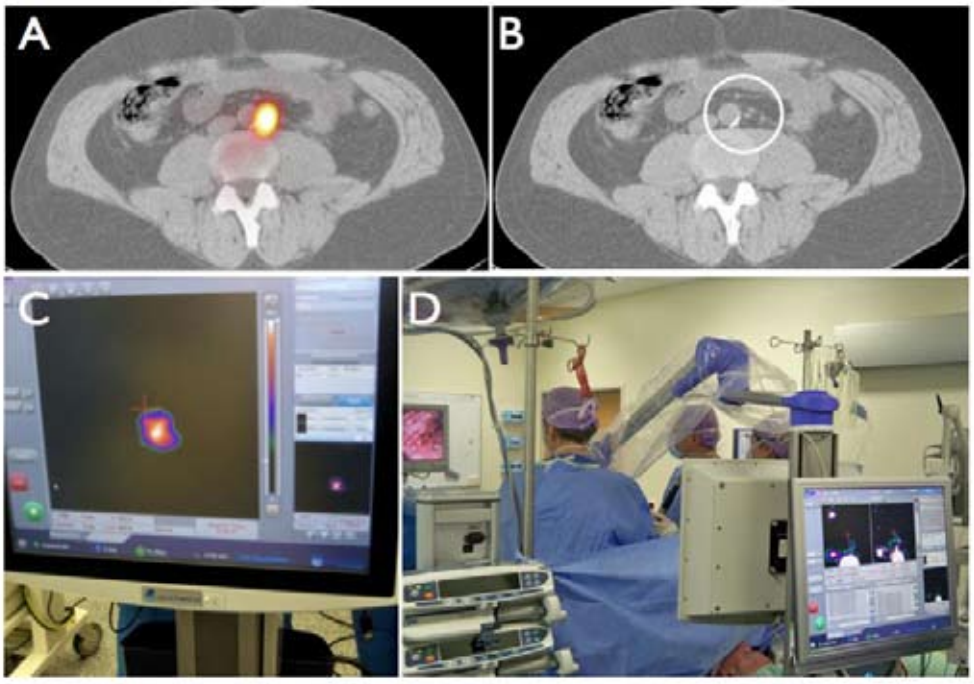
Een mini-gammacamera maakt peroperatieve beeldvorming van sentinelnodes mogelijk, waarbij na excisie van een sentinelnode resterende radioactiviteit getoond wordt. Een Jodium-125 bron, geplaatst op een chirurgisch instrument, blijkt tevens op het scherm van de gammacamera als pointer voor het zoeken naar de sentinelnode te kunnen fungeren. Bij 25 patiënten met een hoofd-halsmelanoom of mondholtecarcinoom bracht de mini-gammacamera alle 70 preoperatief geïdentificeerde sentinelnodes peroperatief in beeld. Klieren op lastige locaties konden efficiënter gelokaliseerd worden. Bij zes patiënten werden negen extra sentinelnodes (één tumorpositieve sentinelnode) verwijderd door te checken op resterende radioactiviteit na excisie. Deze beeldvorming draagt ook bij aan de detectie van meer sentinelnodes bij patiënten met prostaatkanker en bij deze patiënten kunnen klieren op moeilijke locaties gelokaliseerd worden door het gebruik van de Jodium-125 bron als pointer.

Nieuwe mogelijkheden voor sentinelnode detectie

Voldoende tracer uptake is noodzakelijk voor sentinelnode detectie. Het vermeerderen van de deeltjes van de radiotracer heeft geleid tot een significante verbetering van pre- en peroperatieve sentinelnode visualisatie bij 50 patiënten met prostaatkanker. In het proefschrift wordt daarnaast de haalbaarheid van sentinelnode detectie bij para-aortale sentinelnodes, lymfoscintigrafie bij patiënten met niertumoren en sentinelnode biopsie bij patiënten met een recidief prostaatcarcinoom na eerdere behandeling aangetoond. Ook onderzochten we nog de lymfedrainage en sentinelnode diagnostiek bij patiënten met meer dan één tumor in de borst, door gebruikmaking van multipele intratumorale injecties met de radiotracer in iedere tumor afzonderlijk. Wij vonden een hoog percentage (71%) van aanvullend gevonden sentinelnodes, drainerend van de kleinere tumoren. Dit suggereert dat het bepalen van lymfedrainage van iedere aanwezige tumor kan leiden tot meer betrouwbare stadiëring.

Algemene conclusies en toekomstvisie

SPECT/CT kan potentieel als routine procedure worden aangewend voor patiënten met lastig te interpreteren planaire beelden. Een mini-gammacamera maakt peroperatieve beeldvorming van sentinelnodes mogelijk en leidt eveneens tot de detectie van meer sentinelnodes. Verdere aanpassing van detectiesystemen is mogelijk. Gangbare radiotracers kunnen worden verbeterd door aanpassing van de deeltjesconcentratie en het toevoegen van fluorescente kleuring aan het radiofarmacon en daarnaast is er ruimte voor nieuwe indicaties voor sentinel-nodediagnostiek.



Figuur 1.
Sentinelnode-procedure bij een patiënt met prostaatkanker. De axiale coupes van de SPECT/CT (A) tonen een para-aortale sentinel-node, welke ook op de corresponderende CT-coupe geidentificeerd kan worden (B). De klier kan tijdens de operatie duidelijk in beeld gebracht worden op het scherm van de minigammacamera (C). De opstelling tijdens de operatie wordt rechts-onder getoond (D), waarbij op het scherm de situatie voor en na excisie van de para-aortale sentinelnode te zien is. Na excisie resteert nog radioactiviteit in de prostaat en sentinelnodes in het bekken.

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Synthesis and evaluation of radiolabeled peptide multimers for tumor targeting

The interest in peptides as tumor targeting vehicles is derived from their favorable pharmacokinetic profile, ease of preparation and their flexibility in chemical modifications. Based on the RGD (arginyl-glycyl-aspartic acid) tripeptide sequence several radiotracers have been developed for the non-invasive detection and visualization of $\alpha_v\beta_3$ expression in tumors (1). Among these analogs several dimeric and tetrameric RGD derivatives have been introduced and evaluated (2). By increasing the number of RGD units a significant increase in affinity for $\alpha_v\beta_3$ was observed, presumably due to multivalent interaction with the target cell. The encouraging results obtained with multimeric RGD analogs have prompted us to explore this concept in the development of multimeric peptide-based radiotracers for other target receptors.

In this thesis, the chemical synthesis and biological evaluation of a series of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-conjugated monomeric, dimeric and tetrameric peptide derivatives of (Tyr^3)octreotide and (Tyr^3) octreotate are described. These mono- and multimeric somatostatin analogs were prepared via chemoselective coupling of peptidyl azides to dendrimeric alkynes by the Cu(I)-catalyzed azide/alkyne 'copper-Click' cycloaddition reaction. To eliminate Cu-DOTA complex formation, the DOTA moiety was subsequently introduced via a metal-free thio acid/sulfonyl azide 'sulfo-Click' amidation reaction (3). The final products could be labeled with $^{111}In^{3+}$ very efficiently. Furthermore, in vivo studies showed that radiolabeled (Tyr^3)octreotide dimer exhibited improved tumor retention (Figure 1), which can be exploited for therapeutic applications.

Additionally, the spacer effects of a series of dimeric (Tyr^3) octreotate derivatives on the somatostatin receptor affinity were determined (4). From an in vitro displacement assay two (Tyr^3)octreotate dimers were selected, based on their high binding affinity, for further in vivo evaluation. Employing the two-stage 'Click' chemistry, DOTA-conjugated (Tyr^3)octreotate

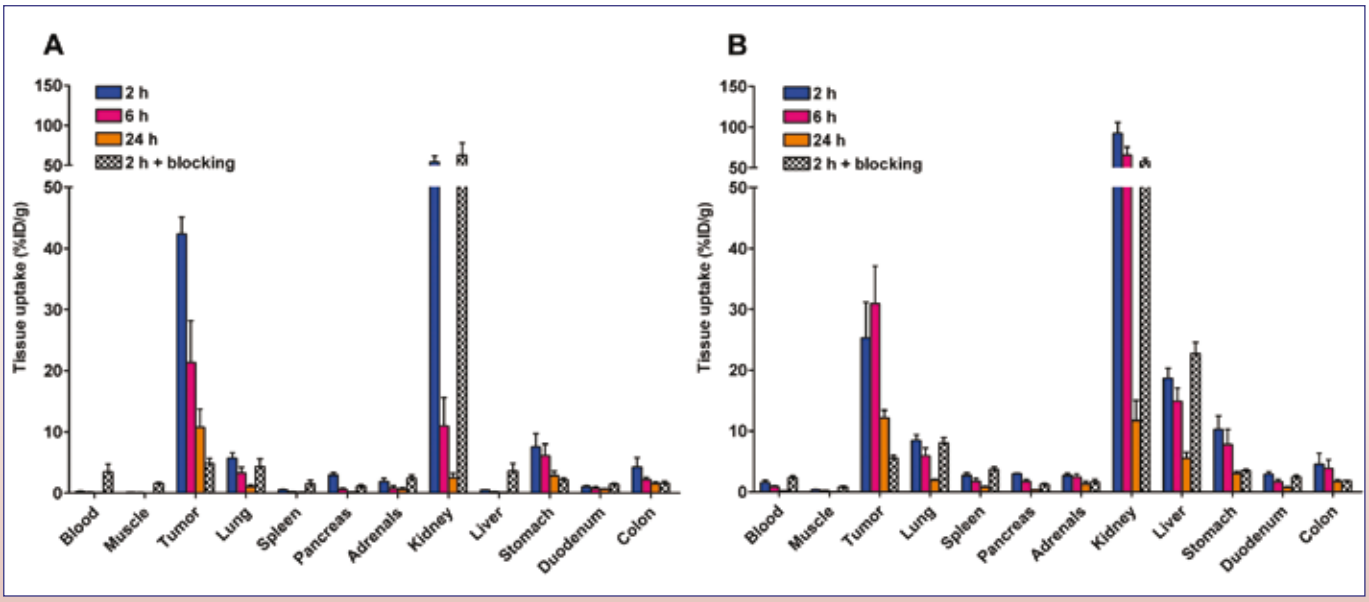

Figure 1. Biodistribution of a monomeric (^{111}In-DOTA^0,Tyr^3)octreotide analog (A) and a dimeric (^{111}In-DOTA^0,Tyr^3)octreotide analog (B) in BALB/c nude mice bearing subcutaneous AR42J expressing tumors.

dimers with a short spacer (9-atoms) and a long spacer (57-atoms) were synthesized, radiolabeled and evaluated for its tumor targeting and pharmacokinetic properties. Tumor uptake of the ^{111}In-labeled DOTA-conjugated (Tyr^3) octreotate dimer with the short spacer was high, specific and prolonged compared to the monomeric analog. However, the introduction of the long hydrophilic spacer resulted in faster clearance from the blood and lower tumor accumulation. These findings provide important information about spacer effects of dimeric (Tyr^3)octreotate peptides on tumor targeting and pharmacokinetics, which can help to design and develop dimeric (Tyr^3)octreotate-based conjugates with improved in vivo properties.

In conclusion, a promising method to develop improved peptide-based diagnostic and therapeutic probes is to adopt the concept of multivalency in the preparation of multimeric peptide conjugates using innovative chemical strategies. In this regard, the combined approach using first 'copper-Click' chemistry followed by a metal-free 'sulfo-Click' reaction with DOTA-derived sulfonyl azide is a powerful method for the versatile synthesis of DOTA-conjugated mono- and multimeric peptides. Despite significant progress in the design and synthesis of potent multimeric analogs, their application to clinical imaging and therapy is still in its investigative stage.

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Strategies to reduce uptake of radiolabeled peptides in the kidneys

Neuroendocrine tumors overexpressing somatostatin receptors can be treated with peptide-receptor radionuclide therapy (PRRT) using ^{90}Y-DOTA-octreotide or ^{177}Lu-DOTA-octreotate. Other radiolabeled peptides can be used for imaging and therapy of various other tumors. However, high renal retention of radiolabeled peptides in PRRT can cause kidney failure, limiting the maximum radiation dose that can safely be administered, thereby also limiting the anti-tumor effect. Coinfusion of basic amino acids can reduce the renal retention of radiolabeled somatostatin analogues by 50%, but nephrotoxicity remains a problem in current clinical PRRT. Furthermore, basic amino acids do not reduce the renal uptake of other radiolabeled peptides such as minigastrin.

We aimed to clarify the mechanisms involved in the renal uptake of radiolabeled peptides, focusing on the role of megalin, a large endocytotic receptor located in the kidney proximal tubules. In addition, we designed and studied new strategies to reduce the renal uptake of different radiolabeled peptides.

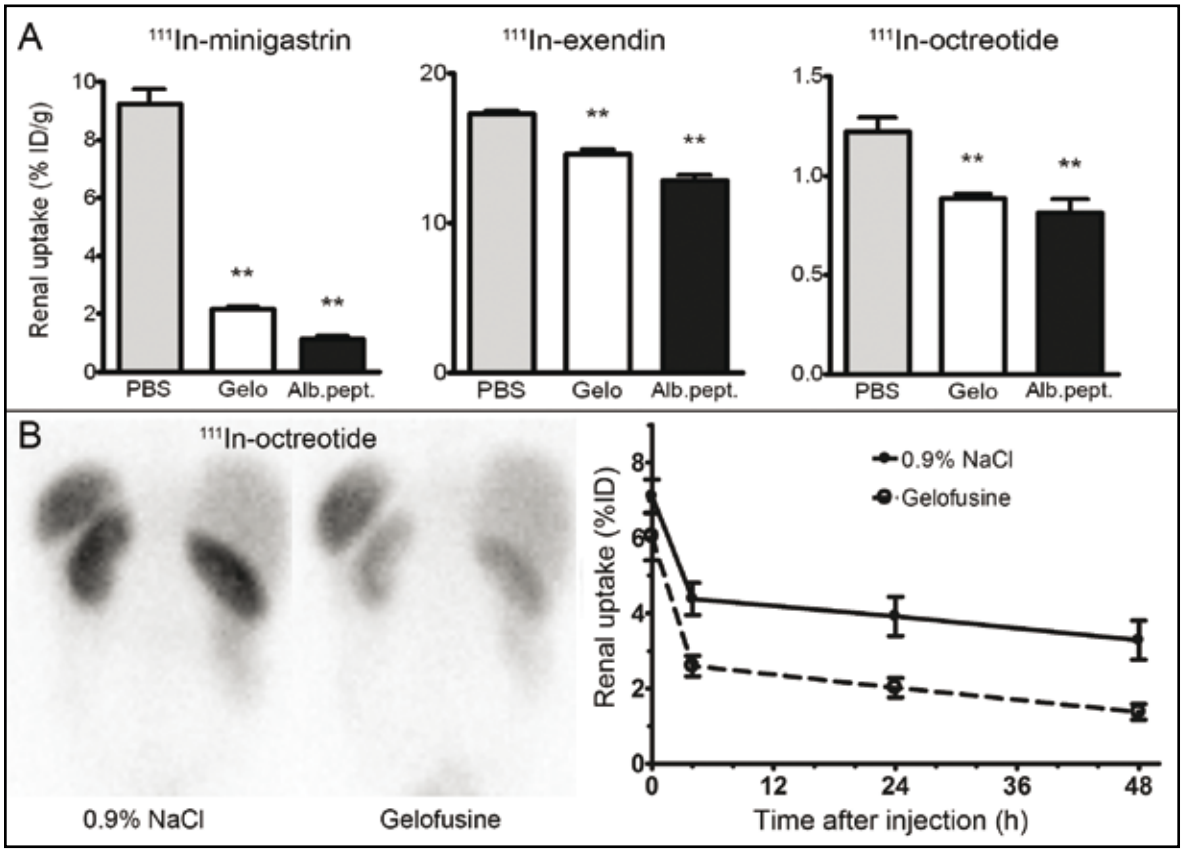

Figure 1. Kidney uptake of ^{111}In-labeled peptides in rats (A) and of ^{111}In-octreotide in human volunteers (B). Subjects were injected with placebo (phosphate buffered saline (PBS) or 0.9% NaCl) compared to Gelofusine (Gelo) or albumin derived peptides (Alb.pept.; rats only). Retention of the radiolabeled peptides in the kidneys was significantly reduced after injection of Gelofusine or albumin derived peptides (p=0.006). Data are depicted as mean + SD.

Role of megalin

The renal uptake of various ^{111}In-labeled peptides (octreotide, octreotate, exendin, minigastrin and neurotensin) was measured in megalin-deficient mice and in wild type mice. Uptake was measured in vivo by SPECT and ex vivo by biodistribution studies.
The renal uptake of all peptides was significantly lower in megalin-deficient mice than in wild types, ranging from 23% (neurotensin) to 62% of normal (exendin). This indicates that megalin plays an important role in renal uptake of these radiopeptides.

Reduction of renal uptake of radiolabeled peptides

To reduce the uptake of ^{111}In-labeled octreotide, exendin and minigastrin, we aimed to saturate renal endocytotic receptors (e.g. megalin) by simultaneous administration of other peptide or protein solutions. Studied solutions were the plasma expander Gelofusine (succinylated gelatin), fragmented albumin (a ligand of megalin), and synthesised albumin-derived peptides. Their effect on the uptake of the radiolabeled peptides was studied in megalin-expressing cultured cells and in rats and mice. The effect of Gelofusine (registered for patient use) on the renal uptake of ^{111}In-octreotide was subsequently studied in human volunteers. Gelofusine, fragmented albumin, and one of the albumin-derived peptides significantly reduced the uptake of all studied radiolabeled peptides in vitro and in vivo. Gelofusine also caused a 50% decrease in the renal retention of ^{111}In-octreotide in humans (Figure 1).

Conclusions

Megalin is essential for the renal uptake of ^{111}In-octreotide and other radiopeptides.
Gelofusine can reduce the renal retention of various radiolabeled peptides. Albumin-derived peptides have potential as well, but their safety and toxicity need to be determined before human use becomes possible.
Reduction of nephrotoxicity enables administration of higher activity doses, increasing the anti-tumor effect of PRRT.

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Surgical implications of novel PET technologies in breast cancer, lung cancer and melanoma

Breast cancer

The first part of the thesis describes, amongst others, the role of ^{18}F-FDG PET/CT for the detection of axillary and extra-axillary lymph nodes in stage II-III primary breast cancer. In 28% of the included patients extra-axillary lymph nodes were detected by ^{18}F-FDG PET/CT, whereas ultrasound guided cytology had detected extra-axillary lymph node involvement in only 12% of these patients. Radiotherapy treatment was altered in 12% of the patients with extra-axillary involvement. The sensitivity and specificity of ^{18}F-FDG PET/CT in detecting axillary involvement were 97% and 100%, respectively. The results of this study show that ^{18}F-FDG PET/CT may be useful as an additional imaging tool to assess axillary and extra-axillary lymph node metastasis in stage II-III breast cancer patients, with impact on adjuvant radiotherapy management. The thesis shows that ^{18}F-FDG PET/CT changed the clinical management in almost half of the patients with locoregional breast cancer recurrence and that ^{18}F-FDG PET/CT could potentially replace conventional staging imaging in patients with a locoregional breast cancer recurrence. Furthermore, the thesis shows that a dedicated high-resolution breast PET (MAMMI-PET) is able to visualize breast carcinomas in nearly all stage II-III breast cancer patients. This promising technique will be further evaluated.

Lung cancer

The second part of the thesis describes, amongst others, the role of ^{18}F-FDG PET/CT for the monitoring of response to neoadjuvant erlotinib, an epidermal growth factor receptor - tyrosine kinase inhibitor (EGFR-TKI), in operable non-small cell lung cancer (NSCLC) patients. The results suggest that early during the course of EGFR TKI therapy, ^{18}F-FDG PET/CT can predict response to erlotinib treatment in patients with NSCLC. Changes measured during treatment by diagnostic CT show no relation to the response of treatment.

Melanoma

In this part the role of ^{18}F-FDG PET/CT in melanoma patients is described. In high-risk melanoma patients with an elevated serum S-100B during follow-up, S-100B has a modest 50% positive predictive value for recurrent disease. Subsequent PET/CT can identify patients with recurrent disease. Twenty-six percent of the patients with a true positive ^{18}F-FDG PET/CT scan received surgical treatment with curative intent; the other 74% received palliative treatment or supportive care. Furthermore, the diagnostic value and impact on management of ^{18}F-FDG PET/CT in melanoma patients with palpable lymph node metastases was described. ^{18}F-FDG PET/CT lead to a change in the planned regional node dissection in 37% of the patients and ^{18}F-FDG PET/CT findings correlate with survival.

In conclusion, ^{18}F-FDG PET/CT has proven to be an important imaging modality for certain patient categories with breast cancer, lung cancer and melanoma. Although it is essential to evaluate efficacy and costs critically, to my belief, indications for ^{18}F-FDG PET/CT in oncology will expand as ^{18}F-FDG PET/CT can contribute to patient-tailored treatment and will gain a standard role in the management of patients with breast cancer, lung cancer and melanoma for specific indications.

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Radiolabelled monoclonal antibodies for molecular imaging of chronic inflammatory diseases

Clinical diagnosis is slowly but continuously shifting towards the molecular level. Such molecular diagnosis can in principle be provided by nuclear medicine, via specific radiopharmaceuticals. To improve diagnosis, nuclear medicine therefore remains in the search of high affinity and specific radiopharmaceuticals. This continuous development has explored a variety of intelligent approaches to establish the foundation of future molecular imaging modalities. As a result, new multidisciplinary modalities are being developed for more specific diagnostic imaging and targeted molecular therapy. These techniques aim to detect the pathological changes at a very early stage and to increase the understanding of the pathophysiology of different diseases. Amongst these new techniques, scintigraphic imaging with radiolabelled

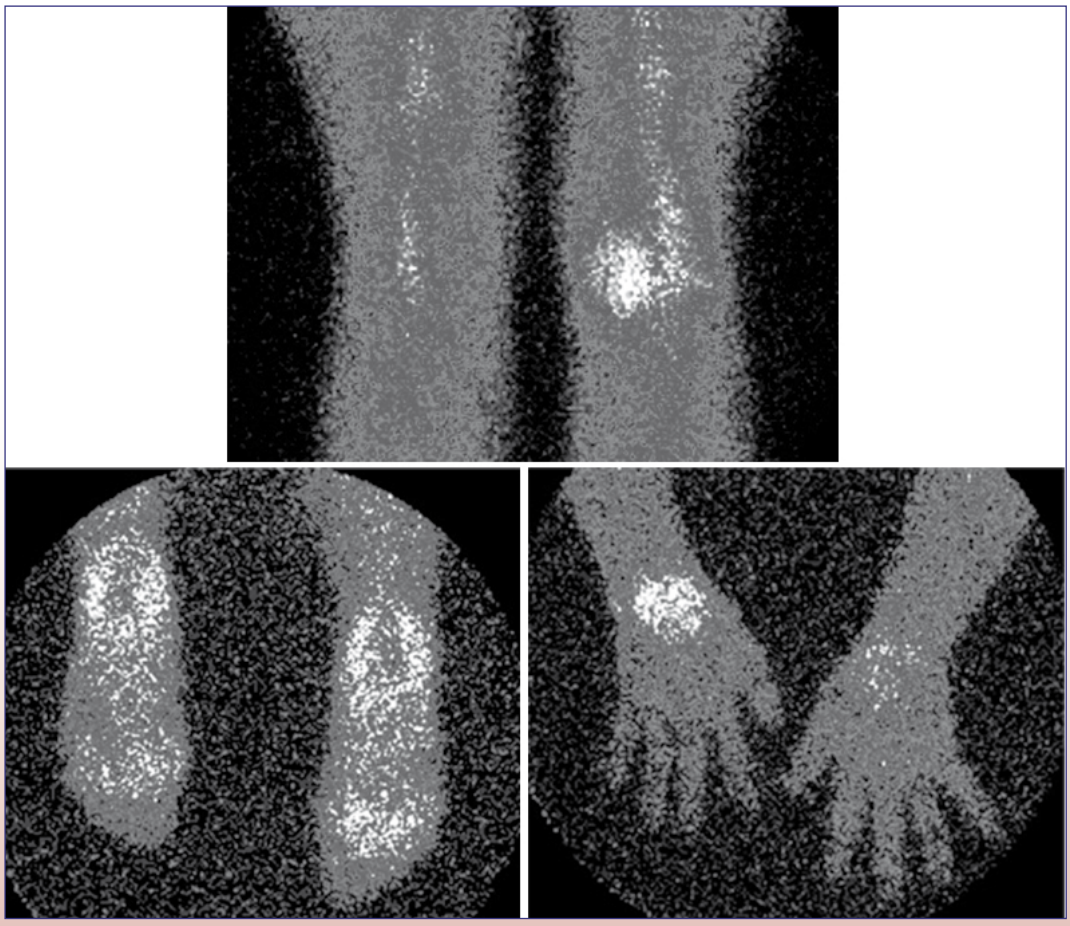

Figure: Multiple joint (knee, ankle, wrist) involvement in patients with Rheumatoid Arthritis, as demonstrated by scintigraphy with ^{99m}Tc-TNFα monoclonal antibody.

monoclonal antibodies (mAbs) may provide the sensitivity and specificity that is required for molecular diagnosis.
This thesis describes the synthesis and clinical application of different ^{99m}Tc labelled mAbs, including anti-TNFα mAb, anti-CD20 mAb, anti-CD3 mAb and anti-HLA-DR mAb, for receptor mapping and therapy decision making in patients affected by organ-specific autoimmune diseases.

The radiolabelled anti-TNFα mAb, infliximab, was successfully used in patients with active Crohn's Disease (CD). These scintigraphic studies evaluated the presence of TNFα in the affected bowel of patients. In another study, role of scintigraphy with ^{99m}Tc-infliximab in predicting and monitoring the response to TNFα antagonists in patients with refractory knee monoarthritis was investigated. We also investigated the role of ^{99}mTc-rituximab (anti-CD20 antibody) as a prognostic tool for therapy decision-making in different autoimmune rheumatic disease patients. This study showed that ^{99m}Tc-rituximab can be used for imaging B-lymphocyte infiltration, thus providing a rationale for anti-CD20 therapy. The most remarkable finding is that both radiolabelled monoclonal antibodies, anti-TNFα and anti-CD20, show the presence or absence of their respective target molecules in inflammatory lesions, and allow assessing whether an antibody will accumulate in an inflammtory lesion before using a high dose of the same unlabelled antibody for therapeutic purposes. A low expression of a particular inflammatory target molecule suggests that a different therapy directed against another inflammatory target should be employed. This approach would not only be of great benefit for the patient to avoid ineffective, expensive and potentially harmful biological therapy, but could also significantly reduce the ever growing healthcare costs.

Other investigated mAbs were ^{99m}Tc-visilizumab (anti-CD3 mAb) and ^{99m}Tc-1D09C3 (anti-HLA-DR mAb) for human lymphocytes imaging. Our *in-vitro* and *in-vivo* results in mice animal models demonstrated that these radiolabelled mAbs could provide a valuable tool for the study of human lymphocyte trafficking and lymphocytic infiltration of tissues and organs.

These preliminary data from these different radiolabelled mAbs, indicate that this molecular approach to disease diagnosis and therapy decision making could have revolutionary impact on the management of chronic inflammatory diseases, although, these results need to be confirmed in larger prospective studies.

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PET and SPECT imaging of bone marrow disorders

Non-invasive imaging of the bone marrow cellularity has been pursued using many tracer methods. Bone marrow scintigraphy can be divided into three categories based on the three target cell systems: red cell precursors, white cell precursors, and tracers for the reticuloendothelial system (RES). The PET tracer 3'-fluoro-3'-deoxy-L-thymidine (^{18}F-FLT) has been developed to image the proliferative activity. Uptake of this tracer is directly related to the rate of DNA synthesis. The specificity of ^{18}F-FLT uptake for cycling cells, the whole body imaging aspect, the high resolution of PET, and the quantification possibilities may support the relevance of ^{18}F-FLT-PET as diagnostic procedure in with bone marrow disorders.

Uptake of ^{18}F-FLT was clearly higher in patients with

myelodysplastic syndrome (MDS) and myeloproliferative disorders but was lower in patients with myelofibrosis (MF), multiple myeloma (MM) and aplastic anemia (AA) , in agreement with the cycling activity of the bone marrow compartment of the affected areas. FLT scans showed various degrees of bone marrow expansion with exception of patients with AA. Higher uptake in the spleen and liver with distinct hepatosplenomegaly was characteristic of MF. ^{18}F-FLT-PET provides a highly distinctive picture that might be helpful to distinguish AA patients from other hematological bone marrow disorders. In addition, it might be helpful to monitor the treatment response. ^{18}F-FLT-PET can also be used to detect extramedullary hematopoiesis.

^{18}F-FLT-PET demonstrated a significant increase in SUV measured at different points of the bone marrow compartment in the post-transplantation in a group of patients with lymphoma. In addition, a significant expansion of the bone marrow compartment was noticed. These findings correlated with in vitro data showing a higher proliferative activity of hematopoietic progenitor cells even when the peripheral blood cells have been normalized to great extent.

^{18}F-FLT-PET can be used to visualize the effect of therapy-related bone marrow toxicity in patients being treated for malignancy, and might be a tool to define the residual hematopoietic activity. A significant decrease in ^{18}F-FLT uptake was observed in the cervical region of the adjacent bone marrow compartment after radiotherapy in patients with laryngeal carcinoma.

Somatostatin receptor expression has been demonstrated on a number of plasma cell lines. Positive somatostatin receptor scintigraphy (SRS) was seen in patients with MM reflecting the enhanced disease activity. SRS seems not only be of value to assess disease activity in multiple myeloma but might also be used for therapy response.

In summary these data show that different aspects of the bone marrow can be non-invasively imaged. In addition the imaging techniques might be used during and following specific therapies dependent on the underlying haematological disorder.

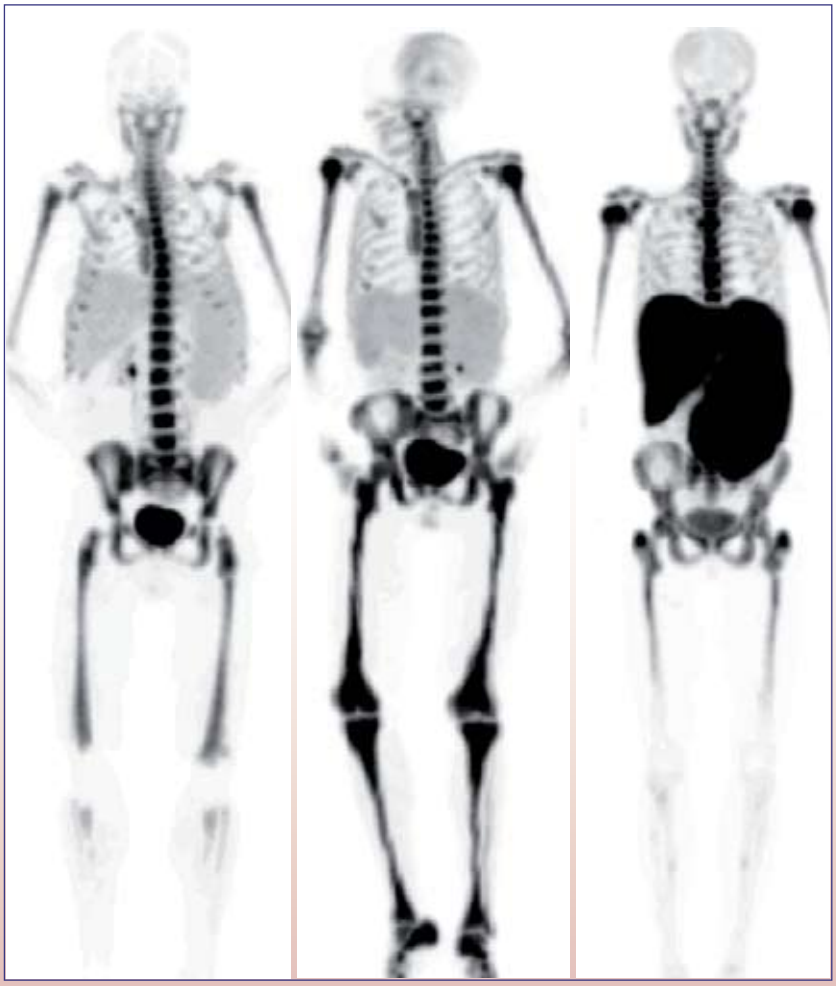

Figure 1 Figure 2 Figure 3

Figure 1: ^{18}F-FLT PET in patient with myelodysplasia, showing homogeneously increased uptake and modest peripheral bone marrow expansion into the peripheral bones.

Figure 2: ^{18}F-FLT PET in patient with myeloproliferative disorder showing homogeneously increased uptake and extensive peripheral bone marrow expansion into the extremity bones.

Figure 3: ^{18}F-FLT PET in patient with myelofibrosis showing low uptake in the bone marrow compartment, hepatosplenomegaly with increased uptake as a result of extramedullary hematopoiesis and minor bone marrow expansion into the extremity bones.

Incidental colonic ^{18}F- FDG uptake: colonic cancer detected in a patient with locally advanced breast cancer

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A 41-year old female underwent a fluor-18 fluorodeoxyglucose positron emission tomography / computed tomography (^{18}F-FDG PET/CT) as a part of the work-up for locally advanced breast cancer (1). Contrast enhanced ^{18}F-FDG PET/CT showed a ^{18}F-FDG avid tumor in the lateral upper quadrant of the right breast and a conglomerate of enlarged ^{18}F-FDG positive lymph nodes in the right axilla (figure 1, panel B, C, E and F). As an incidental finding, a localized focal ^{18}F-FDG uptake, projecting over a thickened sigmoid wall, was found (figure 1, panel D and G). Patient was asymptomatic in relation to the sigmoid mass and there was no evidence for a positive family history of colorectal cancer. Colonoscopy was performed to exclude synchronic malignancy as this could compromise the treatment of the breast cancer.
Colonoscopy revealed in the rectosigmoid a semicircular, non-stenosing, tumour-like mass, suspect for colorectal cancer. Histology revealed an adenocarcinoma (figure 2).
Patient underwent a laparoscopic low anterior rectosigmoid resection prior to the start of neoadjuvant chemotherapy. Histology of the tumour confirmed a T2N0 sigmoid carcinoma.

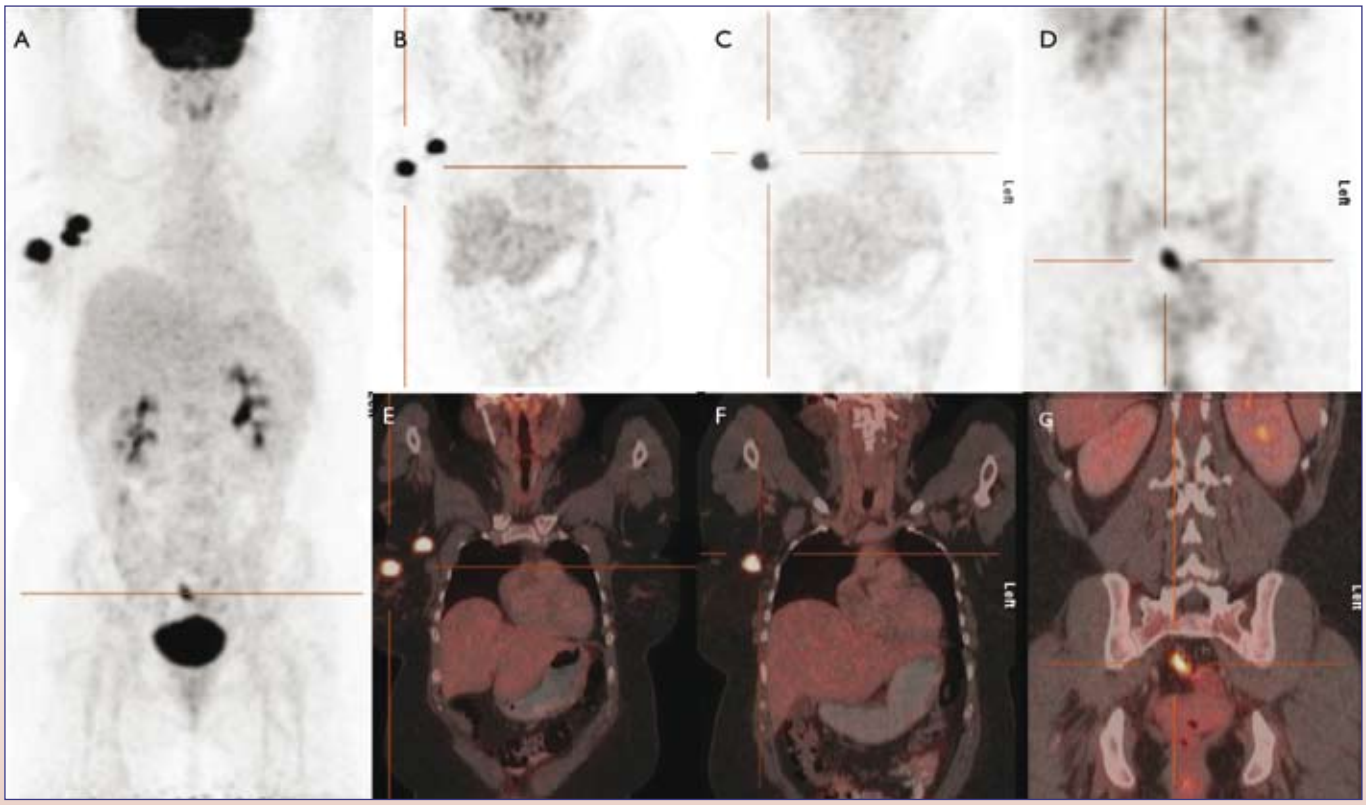

Figure 1.
^{18}F-FDG PET/CT scan in 41-year old woman with locally advanced breast cancer. Maximum Intensity Projection (A), correlating attenuation corrected coronal PET (B, C, D) and CT fusion (E, F, G) of the right breast, right axilla and pelvic cavity respectively. This confirms the hypermetabolic mass in the right breast and in the right axilla and the unexpected hypermetabolic focus in the pelvic cavity, projection over the sigmoid wall. Localization of the pathological uptake is marked with partial crosses.

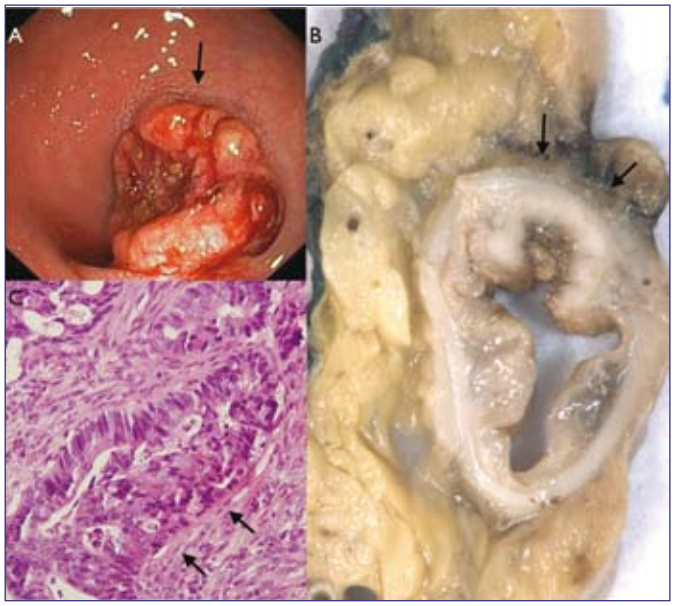

Figure 2.
The colonoscopy shows the non-obstructive ulcerating mass occupying about 2/3 of the colon lumen (panel A). The corresponding fragment of the rectosigmoid resection specimen shows tumour growing into muscularis propria (black arrows, panel B). Histology with hematoxylin and eosin stain shows mild differentiated adenocarcinoma (black arrows, panel C).

Discussion

^{18}F-FDG PET/CT is increasingly used for staging and follow-up of an expanding number of malignancies. In oncology, ^{18}F-FDG PET/CT is known to be more accurate than CT in detecting unexpected metastases or recurrences that either were not yet visible or were difficult to interpret on CT alone (1). Furthermore abnormal incidental foci of increased ^{18}F-FDG uptake, unlikely to be related to the primary tumour, represent a well known phenomenon during a routine interpretation of ^{18}F-FDG PET/CT. Those foci are known to be related to unusual tumour spread in regard to common metastatic pathways, synchronous malignancies, or to the various spectrums of physiological variants.

One common site of such incidental activity is the colon. This activity is suggested to be related to physiologically active smooth muscles, reactive leucocytes in inflammation sites, as well as benign or malignant processes. It has been reported in 1.3 to 2.7% of the patients (2).

Diagnostic significance of these finding was broadly discussed during the past decade (2, 3-8). For example, Kei et al. showed that hyper-metabolic foci in the bowel were frequently associated with clinically relevant abnormalities, such as tubular and tubulovillous adenomas and colon carcinoma. In addition they demonstrated that a positive predictive value of 84% in 25 foci of unexpected bowel uptake in 2250 consecutive patients with non-gastrointestinal malignancy (8). On the other hand, Weston and co-workers emphasize the high false positive rate of ^{18}F-FDG PET/CT in regard to colonic uptake as no abnormalities were found during the colonoscopic evaluation in at least a third of the patients (4). This group has also assessed the false negative rate of ^{18}F-FDG PET/CT in detection of significant colonic pathology by evaluating all the patients who underwent ^{18}F-FDG PET/CT and colonoscopy within three months after ^{18}F-FDG PET/CT. They reported a sensitivity, specificity, positive predictive value and negative predictive value of ^{18}F-FDG PET/CT to detect significant colonic pathology of respectively 53%, 93%, 65% and 89%. Although a relatively high negative predictive value was found the authors emphasize how important it is to realize that a negative ^{18}F-FDG PET/CT does not rule out significant neoplastic or inflammatory pathology of the colon.

Conclusion

Whole body ^{18}F-FDG PET/CT imaging may identify unexpected foci of hyper-metabolism, particularly within the colon, many of which may have clinical relevance, especially if performed in patients with present or suspected malignancy, thus justifying the need of follow up, preferably to the point of tissue conformation.

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Wetenschappelijke Vergadering van de NVNG

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^{89}Zr-Nanocoll based PET/CT lymphoscintigraphy in head and neck cancer: preclinical results

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Introduction
The sentinel node (SN) procedure appears to be a reliable diagnostic procedure in early stage oral cavity carcinoma. However, for floor of mouth tumours the sensitivity is significantly lower compared to other sites. This may be due to limitations of the current tracer for lymphoscintigraphy, technetium-99m (^{99m}Tc-) Nanocoll. This study describes the development and the in vivo evaluation in tumour-bearing rabbits of a tracer specific for lymphoscintigraphy by positron emission tomography (PET), which has the potential to improve the SN procedure in head and neck cancer.

Methods
The positron emitter zirconium-89 (^{89}Zr) was coupled to Nanocoll via the chelate desferal. Radiochemical purity and particle size were compared with the currently used tracer ^{99m}Tc-Nanocoll. For in vivo evaluation of ^{89}Zr-Nanocoll a lymphogenic metastatic tumour model in the rabbit was used. SN identification by ^{89}Zr-Nanocoll was evaluated by dynamic PET or PET/computed tomography (CT) imaging and results were compared with conventional planar lymphoscintigraphy. To allow for comparative biodistribution studies, ^{89}Zr- and ^{99m}Tc-Nanocoll were coinjected around 12 tumours, followed by obduction 0.5, 1 and 3 h later. Draining lymph nodes and non-lymphatic tissues were collected and the uptake of the radiocolloids assessed and expressed as percentage of the injected dose per gram tissue.

Results
Coupling of ^{89}Zr to Nanocoll appeared to be possible. Radiochemical purity and particle size were comparable with ^{99m}Tc-Nanocoll. PET(/CT) showed clear uptake of ^{89}Zr-Nanocoll in the SN lymph nodes. Biodistribution of both tracers was similar.

Conclusion
^{89}Zr-Nanocoll is a potential tracer for SN detection by PET.

Inter-observer agreement of neck lesions on ^{124}I-NaI PET scans of patients with differentiated thyroid carcinoma

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Introduction
Patients with differentiated thyroid carcinoma (DTC) are often up-staged after the detection of metastases by iodine-124 sodium iodide (^{124}I-NaI) positron emission tomography (PET). There are, however, no guidelines on how to interpret PET-positive lesions in these cases, and until now staging by this method has relied on 'expertise from experience'. We sought to assess the inter-observer variability in the interpretation of ^{124}I-NaI PET and discover differences between observers with different levels of experience.

Methods
The pre-ablation ^{124}I-NaI PET/computed tomography (CT) scans of 15 patients with DTC and suspected of metastases on ^{124}I-NaI PET by an initial reviewer were assessed by 5 independent blinded observers with varying degrees of familiarity with the ^{124}I-NaI PET tracer. The observers were asked to label each lesion they found as residual thyroid tissue, central lymph node metastasis, lateral lymph node metastasis, physiological uptake, or artefact. They consistently scored their certainty on a five-point scale.

Results
There was an excellent (80-100%) inter-observer agreement for the detection and discrimination of lesions as lateral lymph node metastases (N1b nodes). However, there was a significantly lower agreement for lesions in region VI (residual thyroid tissue or N1a nodes). Inexperience with ^{124}I-NaI PET did not correlate with lower sensitivity for pathological lesions, though region VI abnormalities were less often considered N1a nodes than with more experienced observers.

Conclusion
There is variable inter-observer agreement of neck lesions on ^{124}I-NaI PET-CT. There is excellent agreement on N1b lymph node metastases, whilst criteria for the interpretation of region VI lesions need to be established.

Predictive factors of ^{131}I-NaI treatment failure in Graves' hyperthyroidism: single dose (3.7 MBq/ml) versus double dose (7.4 MBq/ml)

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Introduction
Graves' hyperthyroidism is a common autoimmune disease of the thyroid with an incidence of over 16.000 new patients each year in the Netherlands. The goal of this study was to compare two different iodine-131 sodium iodide (^{131}I-NaI) therapy dosage schemes (single dose versus double dose) and to assess which patient characteristics are most predictive of ^{131}I-NaI treatment failure, defined as recurrent hyperthyroidism. For double dose treatment various indications applied, among which increased radioiodine turnover.

Methods
We analysed the prospectively collected data of a total of 554 patients with Graves' hyperthyroidism, treated with ^{131}I-NaI at our institution between January 2000 and December 2008. All patients with sufficient follow-up (n=381) were included in this study. The cohort was divided into group 1 (n=240), patients receiving 3.7 (SD±0.44) MBq/ml thyroid volume, and group 2 (n=141), patients receiving 7.4 (SD±1.09) MBq/ml (both corrected for 24h uptake). We assessed the clinical treatment outcome within one year in relation to thyroid volume, 5h/24h Iodine-131 (^{131}I) uptake ratio and 24h ^{131}I uptake.

Results
In group 1 the overall treatment results were: hypothyroidism in 98 (41%) patients, euthyroidism in 70 (29%) patients and recurrent hyperthyroidism in 72 (30%) patients. In group 2 the overall treatment results were: hypothyroidism in 76 (54%) patients, euthyroidism in 29 (21%) patients and recurrent hyperthyroidism in 36 (26%) patients. Treatment failure in patients with thyroid volume >50ml was 59% in group 1 (n=34), and 44% in group 2 (n=39). Treatment failure in patients with ^{131}I uptake ratio >0.8 was 47% in group 1 (n=78) and 29% in group 2 (n=117). Treatment failure in patients with 24h ^{131}I uptake >75% was 43% in group 1 (n=56) and 31% in group 2 (n=78).

Conclusion
Patients with large thyroid volumes, high 5/24h turnover ratio, and/or high 24h ^{131}I uptake have an increased risk of treatment failure both with traditionally advised administered activity of 3.7 MBq/ml and with a higher administered activity of 7.4 MBq/ml.

Phase I clinical study of the feasibility of pre-targeted radio-immunotherapy in patients with colorectal cancer: first results

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Introduction
Pre-targeted radio-immunotherapy (PT-RAIT) is being investigated in this phase I clinical trial to determine the optimal dose schedule using a humanised bi-specific monoclonal antibody, TF2, targeting CEACAM5, and the hapten, histamine-succinyl-glycine (HSG), conjugated with lutetium-177 (^{177}Lu-) labelled di-HSG-DOTA-peptide IMP288, in advanced colorectal cancer (CRC) patients.

Methods
The intervals between the infusion of TF2 and the intravenous. injection of ^{177}Lu-IMP288 was 5 days (n=5)

in the first cohort and 1 day (n=5) in the second cohort. A pre-therapy cycle with indium-111 (^{111}In-) labelled IMP288 was used to predict the radiation dose and assure the safety of high ^{177}Lu-doses (1st and 2nd cohorts: 3.7 and 7.4 GBq, respectively). Toxicity was determined by NCI-CTC v3.0. Whole-body planar scintigraphy and single photon emission computed (SPECT) were acquired up to 3 days post-injection (p.i.).

Results

In both cohorts TF2 administration was safe, with only mild grade 2 infusion reactions in 3 patients, controlled with antihistamines and corticosteroids. TF2 cleared quickly from the circulation (< 1% ID in the serum 1 day p.i.), as did ^{111}In/^{177}Lu-IMP288 (1st and 2nd cohorts of 0.014 and 0.25% ID/L in the blood 1 day p.i.). Localisation of tumour masses was seen, without evidence of targeting any normal tissue. Absorbed kidney doses for the 2 cohorts were 0.21 and 0.30 mGy/MBq, and red marrow doses 0.011 and 0.035 mGy/MBq, respectively. Bone marrow toxicity was very mild, apart from one grade 4 thrombocytopenia in the 2nd cohort, with fast and complete recovery.

Conclusion

These first results confirm that CEACAM5-expressing CRC can be targeted with TF2 and ^{177}Lu-IMP288 with minimal radiation exposure to normal organs.

^{18}F-FDG PET/CT as a staging procedure in primary breast cancer stage II and III: comparison to conventional imaging techniques

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Introduction

The occurrence of distant metastases in primary breast cancer depends on stage at presentation. It is recommended to perform a staging procedure prior to treatment in patients with large or locally advanced tumours. The aim of the present study was to compare fluor-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) to conventional imaging techniques in the detection of distant metastases before the start of neoadjuvant chemotherapy.

Methods

106 patients with stage II and III breast cancer, scheduled for neoadjuvant therapy, underwent an ^{18}F-FDG PET/CT scan and conventional imaging, consisting of bone scintigraphy, ultrasonography of the liver and a chest x-ray. Suspect lesions were confirmed with histopathology or additional imaging. A minimal follow-up of six months was required for occult metastases.

Results

Additional lesions were seen in 17 patients (16%) with PET/CT and could be confirmed in 15 of 106 patients. In 13 patients distant lesions were exclusively seen with PET/CT, leading to a change in treatment in 12 of them (11%): six patients were treated palliatively, four patients underwent additional surgical intervention and the field of radiation was changed in two patients. PET/CT showed no distant lesions in 89 patients, which was confirmed by additional imaging and follow-up.

Conclusion

^{18}F-FDG PET/CT is superior to conventional imaging techniques in the detection of distant lesions in patients with primary breast cancer stage II and III. PET/CT should be the starting procedure in the staging of these patients.

Initial clinical validation of a multimodal radioactive / fluorescence imaging agent for simultaneous radioguided and optical sentinel node detection

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Introduction

This study aims to clinically validate a multimodal imaging agent obtained by adding indocyanine green (ICG) to technetium-99m (^{99m}Tc-) nanocolloid in order to optimise intraoperative sentinel node (SN) identification.

Methods

So far, 18 patients (10 head/neck melanoma, 1 melanoma on the trunk, 7 penile carcinoma) scheduled for SN biopsy were prospectively included in the analysis. After peritumoural injection of ^{99m}Tc-Nanocoll, lymphoscintigraphy was performed on the basis of a 10 minute dynamic study

and static images at 10 minutes and 2 hours post-injection, followed by single photon emission computed tomography/computed tomography (SPECT/CT). The following day the procedure was repeated with injection of the hybrid imaging agent (ICG-^{99m}Tc-Nanocoll) in an identical fashion. The images of both procedures were compared. Intraoperative imaging was performed using a portable gamma camera and a dedicated fluorescence camera. After excision, radioactive and fluorescent signal intensities were quantified and correlated ex vivo.

Results

Lymphatic drainage was visualised in all (18/18) patients. A total of 49 SNs were preoperatively identified after the first scintigraphic study. The second scintigraphic study revealed the same number of SNs at the same locations in all patients (100% reproducibility). In total, 62 SNs were surgically removed. Intra-operatively, 60 SNs (96%) could be visualised by fluorescence imaging, of which 4 contained metastases. Ex vivo analyses showed a strong intensity correlation of the radioactive and fluorescent content in all excised SNs.

Conclusion

ICG-^{99m}Tc-Nanocoll has an identical lymphatic distribution pattern compared to ^{99m}Tc-Nanocoll, whilst simultaneously enabling intraoperative fluorescence imaging of radioactive SNs.

Optimal time point of sentinel node scintigraphy: results of routine scintigraphy 1 and 2 hours post-injection

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Introduction

There is ample evidence that tumour-negative sentinel lymph nodes are a reliable predictor for the absence of tumour invasion in other lymph nodes. One of the most often used methods in western countries is radionuclide sentinel node (SN) detection. There is a lot of controversy about different aspects of the implementation of this procedure and guidelines do not always provide strict protocols. One of those aspects comprises the time point of image acquisition. We evaluated the performance of our protocol in which images are acquired 1 and 2 hours post-injection (p.i.).

Methods

All images of patients who underwent a SN procedure

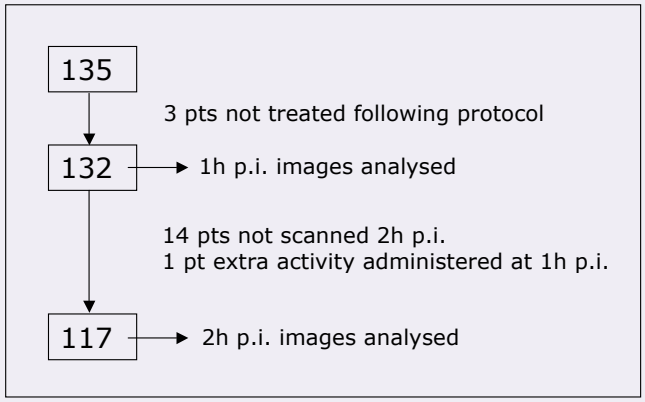


Figure 1. Flowchart

	Number of patients	%	Average number of nodes if specific side shows uptake (range)
Images 1h p.i.	**132**		
Axillary nodes	**105**	**79.5**	**3.00 (1-10)**
SN	105	79.5	1.49 (1-3)
Higher echelon	57	45.5	
Parasternal	**35**	**26.5**	**2.77 (1-5)**
SN	35	26.5	1.14 (1-2)
Higher echelon	27	20.5	
Images 2h p.i.	117		
Axilary nodes	**111**	**94.8**	**2.64 (1-10)**
SN	111	94.8	1.45 (1-3)
Higher echelon	66	56.4	
Parasternal	**38**	**32.5**	**2.78 (1-5)**
SN	38	32.5	1.08 (1-2)
Higher echelon	29	24.7	

Table 1.
Visualisation of lymph nodes categorised on imaging time, anatomical site and echelon.

	Number of patients	%	Average number of nodes if specific side shows uptake (range)	Dissected
All procedures 2h p.i.	**131**	**100**		
Axillary nodes	**125**	**95.4**	**2.66 (1-10)**	
SN	125	95.4	1.46 (1-3)	1.86 (1-4)
Parasternal	**42**	**32.5**	**2.73 (1-5)**	
SN	42	32.5	1.10 (1-2)	1.00 (0-9)

Table 2.
Visualisation of lymph nodes of all completed procedures without administration of extra activity and the number of nodes dissected.

following the standard protocol were evaluated and the number of SNs per anatomic localisation and the interpretability of the images were scored.

Results

The images of 132 patients were analysed. An axillary SN was visualised in 79.5% and 94.8% of the patients, respectively one and two hours p.i. In a large number of patients (20.5%) the images acquired one hour p.i. provide no information for identification of a SN. Furthermore, in all procedures there was no added value of the images one hour p.i. to those acquired one hour later.

Conclusion

Scintigraphic imaging two hours after a single peritumoural or intratumoural administration of about 120 MBq technetium-99m albumin nanocolloid yields an axillary SN in over 95% of the procedures. Imaging one hour p.i. is of no additional value and can be omitted.

Cardiac sympathetic nervous system function and activity as a predictor for appropriate ICD therapy in patients with chronic heart failure: The SYMPATHETIC study

SYmpathetic Myocardial Prediction of Appropriate Therapy in HEarT failure for ICd

coördinatoren	participerende ziekenhuizen	patiëntenaantal
Dr. J.R. de Groot Dr. G.A. Somsen Dr. H.J. Verberne Drs. D.O. Verschure	4 centra in Nederland 2 centra in België 1 centrum in Oostenrijk	300

Chronisch hartfalen is een complex syndroom waarbij er een slechtere functie is van het hart. In een poging van het lichaam om deze slechtere functie van het hart te herstellen treden er een aantal compensatie mechanisme in werking. Een van de compensatie mechanismen is het activeren van het sympathisch zenuwstelsel. De behandeling van patiënten met hartfalen bestaat uit het geven van geneesmiddelen soms in combinatie met een intern defibrillator (ICD). De ICD is een soort pacemaker die mogelijk fatale ritmestoornissen herkent en in staat is deze ritmestoornissen te stoppen. Een aantal grote klinische trials hebben aangetoond dat deze ICD's in patiënten met hartfalen (NYHA II of III en een linkerventrikelejectiefractie van minder dan 35%) een gunstig effect hebben op de overleving. Sindsdien is er een enorme toename in het gebruik van de ICD's. Het is alleen zo dat bij ongeveer 2/3 van patiënten die nu in aanmerking komen voor een ICD deze ICD nooit "afgaat". Daarnaast is het van belang om te realiseren dat de kosten van een ICD ongeveer € 30.000, - bedragen. Het is dus wenselijk om op zoek te gaan naar een test of combinatie van tests die nog beter in staat zijn om patiënten te selecteren voor een ICD.

Er zijn op dit moment aanwijzingen dat de mate waarin het sympathisch zenuwstelsel geactiveerd is in patiënten met chronisch hartfalen een belangrijke rol kan spelen in het voorspellen of iemand een mogelijk fatale ritmestoornis krijgt. De activiteit van het sympathisch zenuwstelsel kan worden gemeten met een radioactief gelabelde stof die lijkt op noradrenaline (^{123}I-metaiodobenzylguanidine, ^{123}I-MIBG).

Het doel van de huidige prospectieve internationale (Nederland, België en Oostenrijk) observationele studie is om te onderzoeken in hoeverre de sympathische activiteit van het hart zoals gemeten met ^{123}I-MIBG kan helpen om patiënten te identificeren die het meest baat hebben bij een ICD.

In 300 patiënten met chronisch hartfalen die op grond van de huidige richtlijnen in aanmerking komen voor een ICD zal de sympathische activiteit van het hart worden bepaald met ^{123}I-MIBG. Deze bepaling zal plaats vinden voor de ICD implantatie waarbij de uitkomst van de ^{123}I-MIBG scintigrafie geen invloed heeft op de ICD indicatie stelling. De patiënten zullen vervolgens iedere 6 maanden gedurende 2 jaar worden vervolgd. Tijdens deze bezoeken zal het geheugen van de ICD worden uitgelezen en geanalyseerd op het voorkomen van mogelijk fatale ritmestoornissen. Als patiënten een ICD discharge hebben gehad moeten zij zich volgens de geldende richtlijnen binnen 24 uur melden op de eerste (hart)hulp. Ook dan zal het geheugen van de ICD worden uitgelezen en geanalyseerd op het voorkomen van mogelijk fatale ritmestoornissen. Pas na afsluiting van de studie zal de voorspellende waarde van ^{123}I-MIBG worden bepaald.

Inmiddels zijn de eerste patiënten in het AMC geincludeerd. Andere deelnemende centra zijn nu bezig met toetsen van lokale haalbaarheid. Het is de verwachting dat in de loop van 2011 het merendeel van deze centra ook patiënten zal gaan includeren.

Verdere informatie kunt u opvragen via:
Drs. D.O. Verschure, AIOS cardiologie
(d.o.verschure@amc.uva.nl) of
Dr. H.J. Verberne, nucleair geneeskundige
(h.j.verberne@amc.uva.nl)

Groene Hart Ziekenhuis (GHZ), Gouda

Geesje Abels-Fransen, *Nucleair Geneeskundige*
Gerrit Sloof, *Nucleair Geneeskundige*

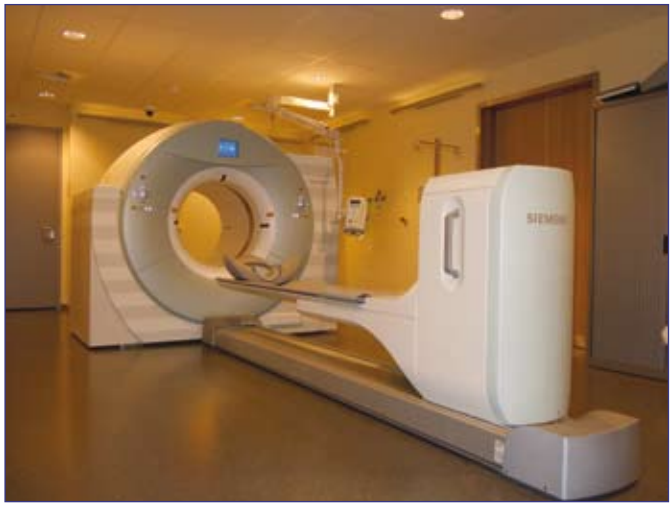
Het GHZ is een algemeen ziekenhuis met zo'n 450 bedden. Er werken ruim 130 medisch specialisten, 2000 medewerkers en 75 vrijwilligers. Het GHZ beschikt over drie locaties: de Bleulandlocatie, de Jozeflocatie en de polikliniek Nieuwerkerk aan den IJssel. Het GHZ is bezig met nieuwbouw op de Bleulandlocatie. De nieuwbouw biedt ook ruimte aan de afdelingen die nu op de Jozeflocatie zijn gehuisvest.
Het GHZ is georganiseerd in resultaat verantwoordelijke eenheden, kortweg RVE's. In de RVE-structuur liggen de besluitvormingsprocessen, inclusief de bijbehorende verantwoordelijkheden en bevoegdheden, daar waar de kennis van de patiëntenzorg het grootst is: bij de medisch specialist. Het GHZ heeft voor RVE's gekozen om continuïteit van patiëntenzorg te kunnen bieden en om markt- en klantgerichter te kunnen werken.
Elke RVE wordt geleid door een medisch leider. Dit is een medisch specialist. Deze wordt bijgestaan door een manager bedrijfsvoering. De leiding van de RVE rapporteert rechtstreeks aan de Raad van Bestuur. De afdeling nucleaire geneeskunde is een zelfstandige RVE, Geesje Abels-Fransen is de medisch leider, Anita Schoonderwoerd-Lok is de manager bedrijfsleider, zij is tevens manager bedrijfsleider van de RVE radiologie.

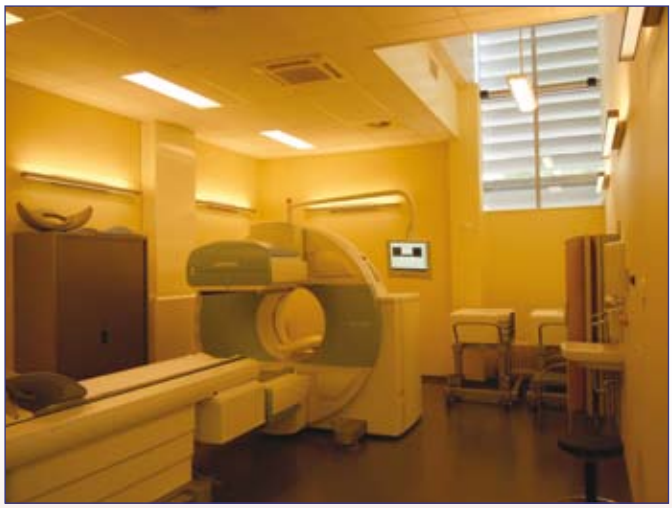
Afdeling nucleaire geneeskunde

De afdeling nucleaire geneeskunde is in de zeventiger jaren van de vorige eeuw opgericht in Gouda door Arie van Dalen, klinisch chemicus. In de negentiger jaren is Henny Peltenburg, internist in de staf van de afdeling gekomen. Rond het millennium is Geesje Abels-Fransen als eerste nucleair geneeskundige in Gouda begonnen, in 2005 gevolgd door de tweede nucleair geneeskundige, Gerrit Sloof.

Coöperatie en de afdeling nucleaire geneeskunde

Samen met drie andere ziekenhuizen participeert het GHZ in de Samenwerkende Ziekenhuizen West-Nederland Coöperatief U.A. (hierna: de Coöperatie). De andere drie ziekenhuizen zijn de stichting Bronovo-Nebo te Den Haag, stichting Medisch Centrum Haaglanden te Den Haag (Westeinde) en Leidschendam (Antoniushove) en Stichting





't Lange Land Ziekenhuis te Zoetermeer. De Coöperatie is (formeel) opgericht in oktober 2008. In de praktijk zijn de vier leden al sinds begin 2008 bezig met gezamenlijke activiteiten. De samenwerking biedt vele kansen om, vanuit de gedachte van concentratie en spreiding van zorg, een toename in kwaliteit en tegelijkertijd een kostenbesparing te realiseren. In 2008-2010 zijn circa 25 projecten gestart. Eén van de koplopers is het PET/CT project. De PET/CT is eind 2010 in het GHZ geïnstalleerd in samenwerking met de vier ziekenhuizen. De in begin 2011 geplaatste SPECT/CT is ook in een gezamenlijk inkooptraject binnen de Coöperatie met het Medisch Centrum Haaglanden aangeschaft. Daar wordt de SPECT/CT medio 2011 geplaatst.

De afdeling nucleaire geneeskunde in 2011

De afdeling nucleaire geneeskunde levert nucleair geneeskundige zorg over de gehele breedte. Van botdichtheidsmetingen tot SPECT/CT en PET/CT en daarnaast diverse nucleair geneeskundige therapieën. Met een heel enthousiast team van medewerkers wordt deze klus geklaard. De apparatuur en de accommodatie is modern en efficiënt. Er is intensieve samenwerking met vooral de cardiologen en de radiologen, maar ook met meerdere andere, verwijzende specialismen. Er zijn diverse multidisciplinaire overleggen (MDO): dagelijks cardiologie (na ochtendrapport, bij iedere angiobespreking met aanwezige (assistent)cardiologen) en wekelijks oncologie, longziekten, endocrinologie en orthopedie (io) en maandelijks schildkliercarcinoom. Alle beelden zijn na verslaglegging beschikbaar door het hele huis. De afdeling is gelokaliseerd op de Bleulandlocatie van het Groene Hart Ziekenhuis. De afdeling nucleaire geneeskunde is vorig jaar verhuisd naar het nieuwe polikliniek gebouw van de Bleulandlocatie op de begane grond. De afdeling heeft een eigen ingang en heeft een bijzondere architectuur met deels heel hoge plafonds met daardoor een aparte lichtinval.

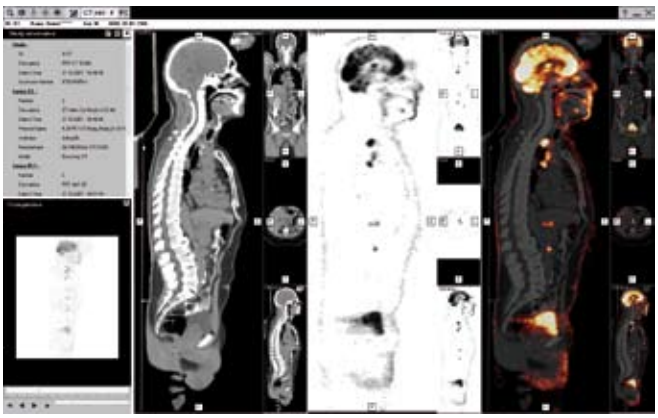
Enkele feiten en cijfers:

Nucleair geneeskundige verrichtingen (2010)	
conventionele nucleaire geneeskunde en therapie	6000
PET/CT	1200
Staf:	
Nucleair geneeskundigen	2
Manager bedrijfsleider	1
Klinisch fysicus	1
Klinisch fysicus in opleiding	1
Coördinator nucleaire geneeskunde	1
Medisch beeldvormend en stralingsdeskundigen	9
Administratieve medewerkers	4
Apparatenpark en voorzieningen:	
Siemens Symbia T SPECT/2msCT	1
Siemens PET/40msCT (extended FOV, TOF/UHD)	1
GE Infinia SPECT 2kopsgammacamera	2
Hologic Discovery bot densitometer	1
Medrad Intego PET Infusion System	1
Gamma probe	2
Ergometriekamer voor nucleaire cardiologie	2
Wachtkamers	2
PET voorbereidingskamers	3

iSOFT Radiology:

Snelheid en Kwaliteit in Nucleaire Geneeskunde

De afgelopen jaren groeit het aantal radiologische verrichtingen sterk in Nederland. Stijgingen van meer dan 10% zijn geen uitzonderingen en in het aantal Sanderspunten zien we zelfs stijgingen van 150%. Ook het aantal te diagnosticeren beelden is de afgelopen jaren explosief gegroeid. Gelijkertijd verandert de complexiteit van de zorgvraag. De discipline ontwikkelt zich: nieuwe behandelmethoden dienen zich in een snel tempo aan hetgeen grote flexibiliteit van de clinicus en de radioloog verlangt.



iSOFT Radiology speelt in op deze continue verandering in de radiologische discipline. Deze procesgeoriënteerde softwareoplossing is speciaal afgestemd op de eisen van de hedendaagse radiologie. De oplossingen voor nucleaire geneeskunde, radiotherapie en radiologie zijn dusdanig ontwikkeld dat deze direct bijdragen aan een efficiënte organisatie en communicatie op uw radiologieafdeling. Met iSOFT Radiology heeft u volledig controle over uw proces, waardoor de patiëntveiligheid binnen de zorgketen significant verbetert.

Omvangrijke verwerking
iSOFT Radiology heeft PACS-integraties met alle bekende wereldspelers, ook spraakherkenning wordt diep geïntegreerd in de workflow van het RIS. Bovendien maken de functies DICOM Modality Worklist en Performed Procedure Step een automatische informatie-uitwisseling mogelijk met de modaliteiten. Op die manier wordt de betrouwbaarheid van data aanzienlijk verbeterd en betekent dit een besparing in tijd en van personeelskosten.

Snelle, effectieve communicatie
Het webgerelateerde portaal voor verwijzers dat is geënt op moderne internettechnologieën, waarborgt de papierloze gegevensuitwisseling met externe of interne doorverwijzers en afdelingen. Bevoegde doorverwijzers kunnen onderzoeken boeken of worden geïnformeerd over wijzigingen in of afzeggingen van afspraken. De planning van afspraken geschiedt met gebruik van de sterke boekings-functionaliteit van UltraGenda Pro, zodat er ook rekening gehouden wordt met de individuele wensen van patiënten.

Connectiviteit
iSOFT Radiology is door het gebruik van HL7-informatiestandaarden compatibel met talloze andere systemen (PACS, laboratorium-systemen, modaliteiten, netwerken van artsen) en verbetert de communicatie tussen de afzonderlijke zorgverleners dankzij een gemakkelijke uitwisseling van verslagen en andere relevante gegevens. iSOFT Radiology is ook compatibel met Veenstra ten behoeve van de Nucleaire geneeskunde. De gegevens van de patiënt worden naar Veenstra verzonden. Na het onderzoek worden de meetgegevens vanuit Veenstra terug naar iSOFT Radiology verzonden. Hierdoor is er uitgebreide naslag in iSOFT Radiology beschikbaar.

DemoNavigator
Nieuw is de DemoNavigator, een speciaal ontwikkelde module om het interdisciplinair overleg voor te bereiden en te leiden. Met de DemoNavigator kunt u alle informatie van een patiënt (beelden, vorige onderzoeken, aantekeningen e.d.) aan een demonstratielijst toevoegen en deze overzichtelijk presenteren tijdens patiëntbesprekingen.

Overzicht van de mogelijkheden:
- Afspraak- en uitslagennavigator
- Workflowondersteuning
- Digitale opdrachten-, beelden- en uitslagencommunicatie
- DemoNavigator

Meer informatie over iSOFT Radiology? Neem contact op met iSOFT: 071-52 56 789 of via salesoffice@isofthealth.com

Annual PET/CT meeting: PET/CT in the practice of oncology

Deze tweedaagse cursus vond plaats op 14 en 15 maart 2011 in Londen en werd georganiseerd door de sectie radiologie van de Royal Society of Medicine.

Inschrijfkosten:	€290,- p.p. (inclusief koffie/thee en lunch)
Deelnemersaantal:	circa 120
Website organisatie:	www.rsm.ac.uk
Accreditatie:	11 punten

Voor de locatie van deze cursus was gekozen voor een sfeervol oud gebouw met moderne inrichting, in de buurt van Oxford Street.

Het programma was inhoudelijk zeer gevarieerd met fysische voordrachten, lopende en afgeronde wetenschappelijke projecten, klinische indicaties voor PET/CT scans en interactieve voordrachten waarbij PET/CT scans uit de dagelijkse praktijk werden getoond.

De fysische voordrachten gingen over tumor response assessment en de factoren die semikwantitatieve analyse beïnvloeden, met aandachtspunten voor gebruik van ^{18}F-FDG PET scans bij radiotherapieplanning.
De rol van ^{18}F-FDG PET scans in de kliniek bij slokdarmkanker, pancreascarcinomen, hersentumoren, cervixcarcinomen en melanomen werd behandeld, en verder kwamen radiotherapieplanning en het beleid bij patiënten met HIV aan de orde.

In voordrachten werd behalve aan ^{18}F-FDG ook aandacht besteed aan het gebruik van tracers als ^{18}F-FLT, ^{18}F-Tyrosine en ^{18}F-MISO, met name bij hersen- en hoofdhalstumoren. Tijdens een voordracht over neuro-endocriene tumoren werd de nadruk gelegd op tracers als ^{18}F-DOPA PET en ^{68}Ga-DOTATOC.

De interactieve sessies waren gericht op lymfomen, hersentumoren en de nieuwe stadiëring van het oesophaguscarcinoom. Bij de lymfomen werd veel aandacht besteed aan de beoordeling van interim ^{18}F-FDG PET/CT scans (dus beoordeling van de respons op chemotherapie na enkele kuren) en de prognostische rol van PET/CT scans bij lymfomen.

Drie sessies van twintig minuten werden gewijd aan nationale (dus Britse) PET/CT onderwerpen, zoals een researchnetwerk. Dit was voor de continentale deelnemers minder interessant en had wellicht beter ingeroosterd kunnen worden als een soort pre-conference meeting.

Al met al was het een leerzame bijeenkomst. De impact ervan op de dagelijkse werkzaamheden van een perifeer nucleair geneeskundige leek niet groot te zijn, maar het bijwonen ervan was wel interessant omdat het zicht gaf op de ontwikkelingen van PET in de oncologie; eenmaal meer uitgekristalliseerd zullen deze ook bruikbaar zijn in een niet-academisch ziekenhuis.

Dr. C.D.L. Bavelaar-Croon
Nucleair geneeskundige, Ziekenhuis Gelderse Vallei, Ede

Making bone inflammation/infection simpler to detect

Scintimun® 1mg ▲▼

PRESCRIBING INFORMATION: Scintimun 1 mg kit for radiopharmaceutical preparation. Please refer to the full Summary of Product Characteristics (SPC) before prescribing Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/. **PRESENTATION:** Vial containing 1 mg of besilesomab, anti-granulocyte monoclonal antibody (BW 250/183), produced in murine cells. Excipients: contains 2 mg of sorbitol / vial of Scintimun. **DIAGNOSTIC INDICATIONS:** Scintigraphic imaging, in conjunction with other appropriate imaging modalities, for determining the location of inflammation/infection in peripheral bone in adults with suspected osteomyelitis. Scintimun should not be used for the diagnosis of diabetic foot infection. **DOSAGE AND METHOD OF ADMINISTRATION:** Scintimun should be reconstituted with the solvent provided and then radiolabelled with sodium pertechnetate (^{99m}Tc) injection in order to obtain a clear and colourless technetium (^{99m}Tc) besilesomab injection. In adults, the recommended activity of technetium (^{99m}Tc) besilesomab should be between 400 MBq and 800 MBq. This corresponds to the administration of 0.25 to 1 mg of besilesomab. Scintimun is not recommended for use in children below the age of 18 years due to insufficient data on safety and efficacy. Scintimun should be given to sufficiently hydrated patients. In order to obtain images of best quality and to reduce the radiation exposure of the bladder, patients should be encouraged to drink sufficient amounts and to empty their bladder prior to and after the scintigraphic examination. SPECT imoging should start 3 to 6 hours after administration. 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Only limited data is available about binding of technetium (^{99m}Tc) besilesomab to CarcinoEmbryonic Antigen (CEA) expressing tumours in vivo. In vitro, besilesomab cross-reacts with CEA. False positive findings in patients with CEA expressing tumours cannot be excluded. False results may be obtained in patients with diseases involving neutrophil defects and to patients with haematological malignancies including myeloma. Scintimun contains sorbitol therefore patients with rare hereditary problems of fructose intolerance should not be administered this product. Human Anti-Mouse Antibodies (HAMA): Administration of murine monoclonal antibodies can lead to the development of Human Anti-Mouse Antibodies (HAMA). Patients who are HAMA positive may have a greater risk for hypersensitivity reactions. Inquiry on possible previous exposure to murine monoclonal antibodies and a HAMA test should be made prior to administration of Scintimun; a positive response would contraindicate the administration of Scintimun. Repeated use: Scintimun should only be used once in a patient's lifetime. Hypersensitivity reactions: Anaphylactic or anaphylactoid reactions may occur after administration of the medicinal product. Appropriate cardiopulmonary resuscitation facilities and trained personnel should be available for immediate use in the event of an adverse reaction. Since allergic reactions to the murine protein cannot be excluded, cardiovascular treatment, corticosteroids, and antihistamines must be available during administration of the product. **INTERACTIONS:** Active substances which inhibit inflammation or affect the haematopoietic system (such as antibiotics and corticosteroids) may lead to false negative results. 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Exposure to ionising radiation is linked with cancer induction and a potential for hereditary defects and must be kept as low as reasonably achievable. **DOSIMETRY:** Effective dose from 800 MBq is 6.9 mSv. **OVERDOSE:** Encourage frequent micturition and defecation. **MARKETING AUTHORISATION HOLDER:** CIS bio international, B.P.32, F-91192 Gif-sur-Yvette Cedex, France. **CLASSIFICATION FOR SUPPLY:** subject to restricted medical prescription. **MARKETING AUTHORISATION NUMBERS:** EU/1/09/602/001 and EU/1/09/602/002. **DATE OF REVISION OF TEXT:** 11 January 2010.

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Cursus- en Congresagenda

19th International Symposium on Radiopharmaceutical Sciences
28 August - 2 September, 2011. Amsterdam, The Netherlands. www.isrs2011.org

EANM Course on PET/CT in Oncology, basic
1 - 3 September, 2011. Vienna, Austria. www.eanm.org

World Molecular Imaging Congress – WMIC
7 - 10 September, 2011. San Diego, USA. www.wmicmeeting.org

Nuclearie dagen Urologie
8 - 9 September, 2011. Amsterdam, The Netherlands. www.nvng.nl

ASNC 2011
8 - 11 September, 2011. Denver, USA. www.asnc.org

EANM Technologist PET/CT Course, basic
10 - 11 September, 2011. Vienna, Austria. www.eanm.org

EANM Cardiovascular Course, in German
17 - 18 September, 2011. Vienna, Austria. www.eanm.org

EANM Dosimetry Course, advanced
22 - 23 September, 2011. Vienna, Austria. www.eanm.org

Nuclear Cardiology/Hart House Nice
22 - 24 September, 2011. Les Templiers, France.
http://www.escardio.org/congresses/courses/EducationalProgramme

11th International Conference on Cognitive Neuroscience - ICON XI
25 - 29 September, 2011. Mallorca, Spain. www.icon11mallorca.org

EANM'11
15 - 19 October, 2011. Birmingham, Great Britain. www.eanm.org

BioVis 2011: the 1st IEEE Symposium on Biological Data Visualization
23 - 24 October, 2011. Providence, USA. www.biovis.net

EANM Paediatric Course
5 - 6 November, 2011. Vienna, Austria. www.eanm.org

Nucleaire dagen Techniek
8 - 9 November, 2011. www.nvng.nl

Cursus Medisch Management voor arts-assistenten
16 and 23 November, 2011. De Bilt, The Netherlands. www.nvng.nl

EANM/ESTRO Educational Seminar on PET in Radiation Oncology
19 - 20 November, 2011. Vienna, Austria. www.eanm.org

EANM Technologist PET/CT Course, advanced
26 - 27 November, 2011. Vienna, Austria. www.eanm.org

EANM Course on PET/CT in Oncology, advanced
1 - 3 December, 2011. Vienna, Austria. www.eanm.org

Adreswijzigingen

Regelmatig komt het voor dat wijziging in het bezorgadres voor het Tijdschrift voor Nucleaire Geneeskunde op de verkeerde plaats worden doorgegeven. Adreswijzigingen moeten altijd aan de betreffende verenigingssecretariaten worden doorgegeven. Dus voor de medisch nucleair werkers bij de NVMBR, en voor de leden van de NVNG en het Belgisch Genootschap voor Nucleaire Geneeskunde aan hun respectievelijke secretariaten.
De verenigingssecretariaten zorgen voor het doorgeven van de wijzigingen aan de Tijdschrift adresadministratie.
Alleen adreswijzigingen van betaalde abonnementen moeten met ingang van 1 januari 2011 rechtstreeks aan de abonnementenadministratie van Kloosterhof Neer B.V. worden doorgegeven: Kloosterhof Neer B.V., t.a.v. administratie TvNG, Napoleonsweg 128a | 6086 AJ Neer of per E-mail: nucleaire@kloosterhof.nl

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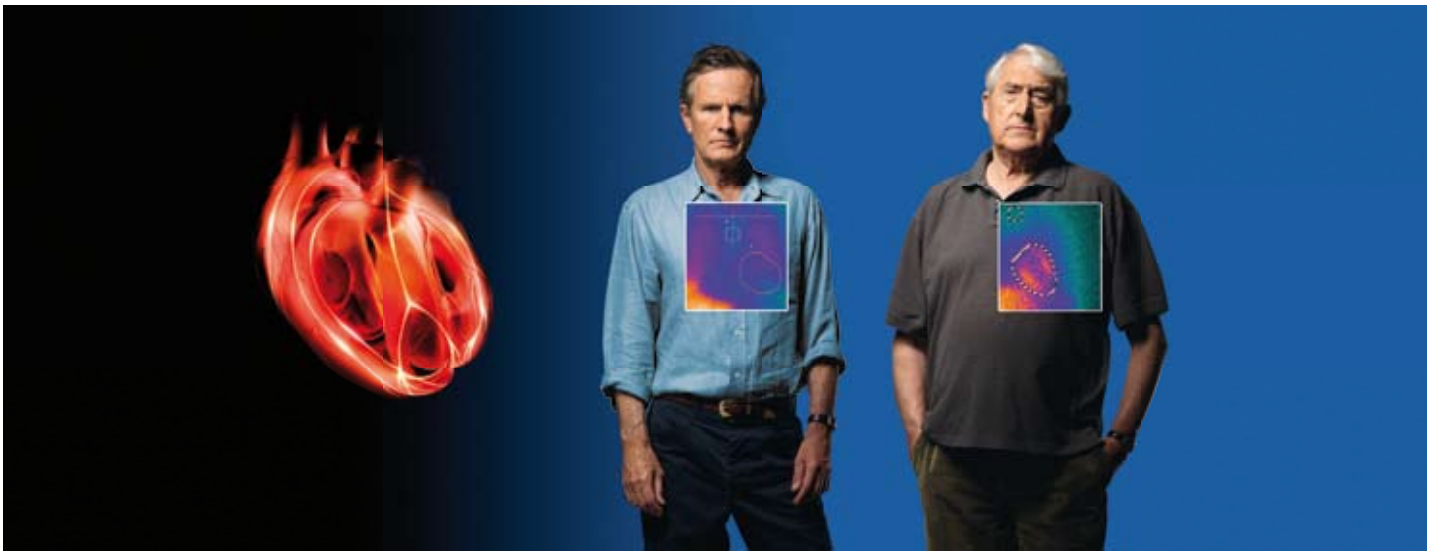

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PRESENTATION Vials containing 74 MBq/ml [^{123}I]Iobenguane at calibration date and hour. Available pack size: 37 to 740 MBq. **DIAGNOSTIC INDICATIONS** • Assessment of sympathetic innervation of the myocardium as a prognostic indicator of risk for progression of symptomatic heart failure, potentially fatal arrhythmic events, or cardiac death in patients with NYHA class II or class III heart failure and LV dysfunction. • Diagnostic scintigraphic localisation of tumours originating in tissue that embryologically stems from the neural crest. These are pheochromocytomas, paragangliomas, chemodectomas and ganglioneuromas. • Detection, staging and follow-up on therapy of neuroblastomas. • Evaluation of the uptake of iobenguane. The sensitivity to diagnostic visualisation is different for the listed pathological entities. The sensitivity is approximately 90% for the detection of pheochromocytoma and neuroblastoma, 70% in case of carcinoid and only 35% in case of medullary thyroid carcinoma (MTC). • Functional studies of the adrenal medulla (hyperplasia). **DOSAGE AND METHOD OF ADMINISTRATION** Cardiology: For adults the recommended dosage is 370MBq. Children under 6 months: 4 MBq per kg body weight (max. 40 MBq), the product must not be given to premature babies or neonates. Children between 6 months and 2 years: 4 MBq per kg body weight (min. 40 MBq). Children over 2 years: a fraction of the adult dosage should be chosen, dependent on body weight (see SPC for scheme). No special dosage scheme required for elderly patients. Oncology: For adults the recommended dosage is 80-200 MBq, higher activities may be justifiable. For children see cardiology. No special dosage scheme required for elderly patients. Administer dose by slow intravenous injection or infusion over several minutes. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. The product contains benzyl alcohol 10.4 mg/ml and must not be given to premature babies or neonates **WARNINGS AND PRECAUTIONS** Drugs known or expected to reduce the iobenguane(123-I) uptake should be stopped before administration of AdreView (usually 4 biological half-lives). At least 1 hour before the AdreView dose administer a thyroid blockading agent (Potassium Iodide Oral Solution or Lugol's Solution equivalent to 100 mg iodine or potassium perchlorate 400 mg). Ensure emergency cardiac and anti-hypertensive treatments are readily available. In theory, iobenguane uptake in the chromaffin granules may induce a hypertensive crisis due to noradrenaline secretion; the likelihood of such an occurrence is believed to be extremely low. Consider assessing pulse and blood pressure before and shortly after AdreView administration and initiate appropriate anti-hypertensive treatment if needed. This medicinal product contains benzyl alcohol. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old. **INTERACTIONS** Nifedipine (a Ca-channel blocker) is reported to prolong retention of iobenguane. Decreased uptake was observed under therapeutic regimens involving the administration of antihypertensives that deplete norepinephrine stores or reuptake (reserpine, labetalol), calcium-channel blockers (diltiazem, nifedipine, verapamil), tricyclic antidepressives that inhibit norepinephrine transporter function (amitryptiline and derivatives, imipramine and derivatives), sympathomimetic agents (present in nasal decongestants, such as phenylephrine, ephedrine, pseudoephedrine or phenylpropanolamine), cocaine and phenothiazine. These drugs should be stopped before administration of [123I]iobenguane (usually for four biological half-lives to allow complete washout). **PREGNANCY AND LACTATION** Only imperative investigation should be carried out during pregnancy when likely benefit exceeds the risk to mother and foetus. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If uncertain, radiation exposure should be kept to the minimum needed for clinical information. Consider alternative techniques. If administration to a breast feeding woman is necessary, breast-feeding should be interrupted for three days and the expressed feeds discarded. Breast-feeding can be restarted when the level in the milk will not result in a radiation dose to a child greater than 1 mSv. **UNDESIRABLE EFFECTS** In rare cases the following undesirable effects have occurred: blushes, urticaria, nausea, cold chills and other symptoms of anaphylactoid reactions. When the drug is administered too fast palpitations, dyspnoea, heat sensations, transient hypertension and abdominal cramps may occur during or immediately after administration. Within one hour these symptoms disappear. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred. **DOSIMETRY** The effective dose equivalent resulting from an administered activity amount of 200 MBq is 2.6 mSv in adults. The effective dose equivalent resulting from an administered activity amount of 370 MBq is 4.8 mSv in adults. **OVERDOSE** The effect of an overdose of iobenguane is due to the release of adrenaline. This effect is of short duration and requires supportive measures aimed at lowering the blood pressure. Prompt injection of phentolamine followed by propanolol is needed. Maintain a high urine flow to reduce the influence of radiation. **CLASSIFICATION FOR SUPPLY** Subject to medical prescription (POM).**MARKETING AUTHORISATION HOLDERS.** DE: GE Healthcare Buchler GmbH & Co. KG, 18974.00.00. DK: GE Healtcare B.V., DK R. 1013. FR: GE Healthcare SA, NL 18599. NL: GE Healthcare B.V., RVG 57689. NO: GE Healthcare B.V., MTnr. 94-191. **DATE OF REVISION OF TEXT** 9 August 2010 .

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References: 1. Jacobson AF *et al.* Myocardial Iodine-123 *Meta*-Iodobenzylguanidine Imaging and Cardiac Events in Heart Failure. Results of the Prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) Study. J Am Coll Cardiol 2010;55.

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