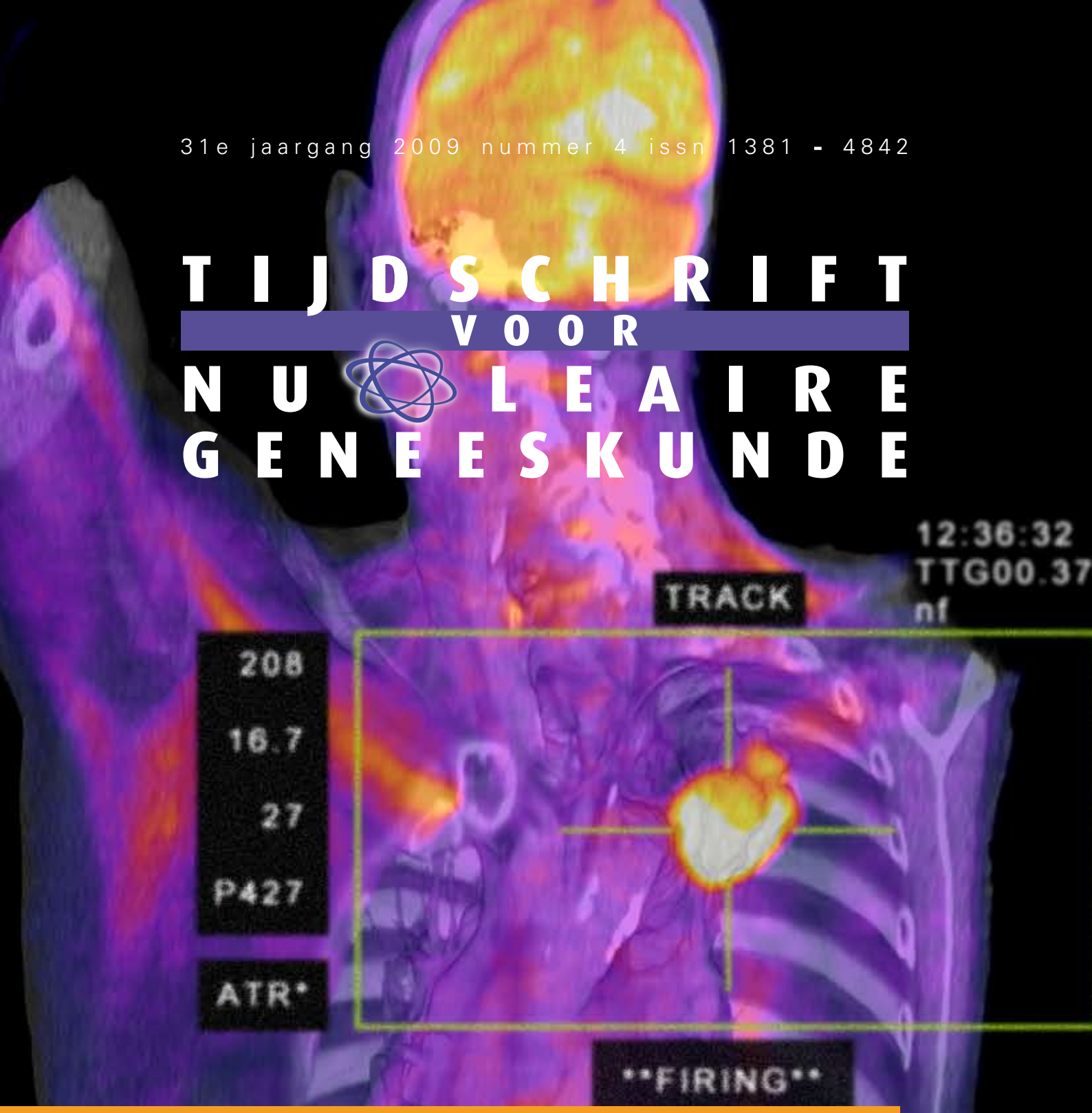
31e jaargang 2009 nummer 4 issn 1381 - 4842

TIJDSCHRIFT VOOR NUCLEAIRE GENEESKUNDE



Themanummer Radiotherapie

New developments in radiation oncology

The use of FDG PET to target tumours by radiotherapy

The role of PET in radiotherapy of head and neck cancers

COVIDIEN

Formerly Tyco Healthcare/Mallinckrodt

Octreoscan™

Your reliable diagnostic tool for diagnosis and staging of Neuro Endocrine Tumours

Experience the high impact on your clinical patient management

- When a primary has been resected, SSRS may be indicated for follow up (grade D)[1]
- For assessing secondaries, SSRS is the most sensitive modality (grade B)[1]

1) Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours, J.K. Ramage et al, UKNET work for neuroendocrine tumours, GUT 2005, 54 (Suppl IV):iv1-iv16

For specific prescribing information of your country consult the local COVIDIEN office or its representative.

MALLINCKRODT MEDICAL BV

a Covidien company

Westerduinweg 3

1755 ZG Petten, The Netherlands

Telephone +31(0) 224 567890

Fax +31(0) 224 567008

E-mail info.nuclear@covidien.com

Trade name of the medicinal product: OctreoScan™ | **Qualitative and quantitative composition:** OctreoScan™ is supplied as two vials which cannot be used separately. 1 vial 4920/A with 1.1 ml solution contains at activity reference time: (^{111}In) Indium(III)chloride 122 MBq 1 vial 4920/B contains: Pentetreotide 10 µg. | **Indications:** ^{111}In pentetreotide specifically binds to receptors for somatostatin. OctreoScan™ is indicated for use as adjunct in the diagnosis and management of receptor bearing gastro-entero-pancreatic neuroendocrine (GEP) tumours and carcinoid tumours, by aiding in their localisation. Tumours which do not bear receptors will not be visualised. | **Posology and method of administration:** The dose for planar scintigraphy is 110 MBq in one single intravenous injection. Careful administration is necessary to avoid paravasal deposition of activity. For single photon emission tomography the dose depends on the available equipment. In general, an activity dose of 110 to 220 MBq in one single intravenous injection should be sufficient. No special dosage regimen for elderly patients is required.There is limited experience on administrations in paediatric patients, but the activity to be administered in a child should be a fraction of the adult activity calculated from the bodyweight. | **Contraindications:** No specific contraindications have been identified. | **Special warnings and special precautions for use:** Because of the potential hazard of the ionizing radiation ^{111}In-pentetreotide should not be used in children under 18 years of age, unless the value of the expected clinical information is considered to outweigh the possible damage from radiation. Administration of a laxative is necessary in patients not suffering from diarrhoea, to differentiate stationary activity accumulations in lesions in, or adjacent to, the intestinal tract from moving accumulations in the bowel contents. In patients with significant renal failure administration of ^{111}In-pentetreotide is not advisable because the reduced or absent function of the principal route of excretion will lead to delivery of an increased radiation dose. Positive scintigraphy with ^{111}In-pentetreotide reflects the presence of an increased density of tissue somatostatin receptors rather than a malignant disease. Furthermore positive uptake is not specific for GEP- and carcinoid- tumours. Positive scintigraphic results require evaluation of the possibility that another disease, characterised by high local somatostatin receptor concentrations, may be present. An increase in somatostatin receptor density can also occur in the following pathological conditions: tumours arising from tissue embryologically derived from the neural crest, (paragangliomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas), tumours of the pituitary gland, endocrine neoplasms of the lungs (small-cell carcinoma), meningiomas, mamma-carcinomas, lympho-proliferative disease (Hodgkin's disease, non-Hodgkin lymphomas), and the possibility of uptake in areas of lymphocyte concentrations (subacute inflammations) must be considered. Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides. | **Interaction with other medicaments and other forms of interaction:** No drug interactions have been reported to date. | **Effects on the ability to drive and use machines:** ^{111}In-pentetreotide does not affect the ability to drive or to use machines. | **Undesirable effects:** Adverse effects attributable to the administration of OctreoScan™ are uncommon. Specific effects have not been observed. The symptoms reported are suggestive of vasovagal reactions or of anaphylactoid drug effects. **MANUFACTURED AND RELEASED BY:** Mallinckrodt Medical B.V., Westerduinweg 3, 1755 LE Petten, The Netherlands

E Pluribus Unum

Er loopt een, hoewel op het eerste gezicht wat merkwaardige, parallel tussen het wapenschrift van de Verenigde Staten van Amerika ("e pluribus unum"), het land met het machtigste leger op de aarde, en de dagelijkse strijd tegen kanker door een legertje medisch specialisten en de patiënt. Laat ik deze vreemde parallel wat verder uitwerken.
In de krijgskunde is in de laatste eeuw een ontwikkeling op gang gekomen waarbij het luchtwapen een steeds belangrijker rol is gaan spelen. In de 1e Wereldoorlog gooiden de piloten van de twee- en driedekkers met de hand een bom op de vijandelijke troepen, in de hoop die dan ook te raken. In de 2e Wereldoorlog had men geleerd van z'n missers: men gooide hele bommentapijten op het vijandelijk gebied in de hoop dat dan ook het doel wel zou zijn uitgeschakeld. Eenzelfde beeld doemt op uit de Vietnamoorlog. Maar daarna vindt er een kentering plaats in de ontwikkeling van het luchtwapen. Men wil de vijand uitschakelen, maar burgerslachtoffers, de zogenaamde 'collateral damage' wil men tot een minimum beperken. We hebben daarvan vanuit Irak en Afghanistan spectaculaire beelden gezien, gemaakt door de piloten van de gevechtsvliegtuigen. We zien nu lasergestuurde bommen die door een muur vliegen, en pas aan de binnenkant tot ontploffing komen.
Ook in ons werk zijn wij dagelijks in oorlog. Een oorlog tegen kanker. Die strijd is een zware strijd. In de eerste plaats voor de patiënt (en zijn of haar verwanten). Maar het is ook een strijd voor de betrokken specialisten. De afgelopen decennia zien we dat de behandeling van patiënten met kanker door middel van radiotherapie een stormachtige ontwikkeling doormaakt. Vaak als onderdeel van een multidisciplinaire behandeling, maar steeds meer ook alleenstaand. Het oude adagium dat chirurgie de meeste kankerpatiënten geneest, gaat nog steeds op. Maar hoe lang nog? De ontwikkeling wordt gedreven door technische ontwikkelingen enerzijds, en anderzijds de wens om het middel niet erger te doen zijn dan de kwaal. Kortom, ook in deze oorlog bestaat de wens om effectiever de vijand uit te schakelen met een minimum aan 'collateral damage'. Als ondersteunend specialisten krijgen we ook met deze ontwikkeling te maken. In dit nummer van het Tijdschrift voor Nucleaire Geneeskunde wordt er daarom dieper op ingegaan en wordt getracht een overzicht te geven van de actuele stand van zaken. Op die manier hopen we de rol van ondersteuners als radioloog en nucleair geneeskundige in de 'war on cancer' wat helderder te krijgen.
Langendijk et al. schetsen de technische ontwikkelingen van de laatste jaren binnen de radiotherapie en welke ontwikkelingen nog voor de deur staan. In de eerste plaats moet hier gedacht worden aan protontherapie; bij uitstek een methode voor een betere 'targeting'. Maar de schrijvers maken ook duidelijk dat, voor een verdere implementatie van die technieken, het van het grootste belang is om op de juiste wijze een tumor te kunnen afbeelden en te kunnen karakteriseren.
De Ruysscher et al. hebben hun sporen verdiend met betrekking tot de toepassing van ^{18}F-FDG PET bij de radiotherapeutische planning. In hun overzichtsartikel geven ze per tumortype de stand van zaken weer, telkens terugvoerend naar 2 basisvragen: 1. staat ^{18}F-FDG PET een meer accurate begrenzing van de tumor toe, en 2. verbetert ^{18}F-FDG PET de uitkomst voor de patiënt? Uit hun overzicht wordt duidelijk dat er weliswaar al veel bekend is geworden, maar dat met betrekking tot de kernvragen ook nog veel onderzoek nodig zal zijn. Een boodschap die spoort met die van de andere schrijvers.Troost et al. focusseren op het hoofdhalscarcinoom. Naast het ^{18}F-FDG PET hebben zij ook oog voor alternatieve radiofarmaca om in te zetten voor de karakterisering van tumoren. In dit kader is met name de aanwezigheid, en dus het aantonen ervan, van hypoxie van belang. Immers, hypoxie leidt tot een grotere weerstand

tegen straling en vermindert dus het effect van radiotherapie. Het aantonen van hypoxie in een tumor geeft in ieder geval de theoretische mogelijkheid om de hypoxische gebieden met een extra boost te bestralen. De toekomst zal moeten leren of dit ook werkelijkheid kan worden en of dit de gewenste effecten heeft. Vogel et al. kijken in hun bijdrage nog verder in de toekomst. Zij maken duidelijk dat om in de toekomst alle vragen van de radiotherapeut te kunnen beantwoorden CT, PET of PET-CT onvoldoende zullen zijn. Ook andere modaliteiten zullen een rol opeisen om 'het plaatje compleet te maken'. Deze visie is in lijn met een ontwikkeling waarbij we zien dat diverse modaliteiten bijna simultaan, en tegenwoordig zelfs daadwerkelijk simultaan, worden ingezet om de anatomische grenzen van een tumor te lokaliseren, en tegelijkertijd metabole processen binnen de tumor te karakteriseren. Tijdens het World Molecular Imaging Congress in Montreal, dat in september j.l. werd gehouden, werden van deze ontwikkelingen meerdere voorbeelden getoond voor het proefdiermodel. Maar naar mijn stellige overtuiging vormen de ontwikkelingen daar het voorland van de ontwikkelingen die we op termijn in de kliniek kunnen verwachten.

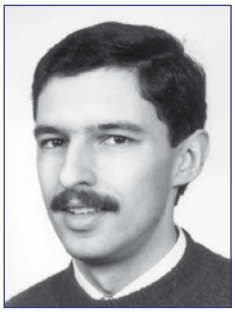
Aan het eind pleiten Vogel et al. voor een goede protocollering en validering, kortom voor standaardisering om te voorkomen dat de radiotherapeut verdwaalt in het wonderland van de (metabole) beeldvorming. Eenzelfde waarschuwing laten ook de andere schrijvers horen. Ik sluit me graag bij deze pleidooien aan. We moeten ons realiseren dat we aan het begin staan van een nieuwe ontwikkeling, maar wel een ontwikkeling die grote consequenties zal hebben voor ons vak. Ik denk dat we dus ook verder moeten kijken. We moeten ons realiseren dat een standaardisering zoals voorgesteld en de daaruit voortvloeiende nauwe samenwerking consequenties zal, ja consequenties mòet hebben voor de opleiding van nieuwe generaties nucleair geneeskundigen, radiologen en radiotherapeuten. Handhaven van de status quo is geen optie. Zelfs het nieuwe curriculum dat na 1 januari 2011 zal worden ingevoerd, dreigt dus snel te verouderen en aanpassing te behoeven van de competenties. Dat vraagt van onze beroepsgroep een 'state of mind' van continue verandering. Het enige dat niet verandert is de verandering zelf. Geen 'je maintiendrai', maar 'e pluribus unum'. Samen staan we sterk in de strijd tegen kanker.
Ook op dit gebied.

Jan Pruim
Afdeling Nucleaire Geneeskunde en Moleculaire Beeldvorming
Universitair Medisch Centrum Groningen

Voorpagina: "War on Cancer" (J. Pruim, A. Zeilstra, UMCG)

New developments in radiation oncology



Prof. dr. J.A. Langendijk **Dr. J. Widder** **Dr. ir. N.M. Sijtsema** **Dr. A.A. van't Veld**

University Medical Center Groningen, Department of Radiation Oncology, Groningen, The Netherlands

Abstract

Langendijk JA, Widder J, Sijtsema NM, Van't Veld AA. New development in radiation oncology

Radiotherapy is a rapidly developing treatment modality for patients with cancer. New radiation delivery techniques enable to achieve a better conformation of the high dose area in the target volume, which can be used for dose escalation to the tumour volume as well as to reduce the dose in critical organs. These new techniques will be described and the importance of integrating molecular imaging techniques for target volume definition in relation to the clinical introduction of these techniques will be discussed. **Tijdschr Nucl Geneesk 2009; 31(4):377-389**

Introduction

Radiotherapy plays a pivotal role in the treatment of many tumours. Currently, between 40 and 50% of all cancer patients are treated with radiotherapy, either as single modality or combined with surgery and/or systemic treatment (chemotherapy or targeting agents). In approximately half of these patients radiotherapy is given with curative intent aiming at improvement of locoregional tumour control and subsequently contributing to improved survival rates. Technical innovations over the last two decades have changed significantly the practice in radiation oncology. Nowadays, the cornerstone of modern radiotherapy treatment planning is computed tomography (CT), providing a fully three-dimensional (3D) anatomical model of the patient, which can be co-registered with other imaging modalities, such as Magnetic Resonance Imaging (MRI) and functional imaging studies, including Positron Emission Tomography (PET). Such advanced imaging now allows the radiation oncologist to more accurately identify tumour volumes and their spatial relationship with critical organs. The availability of modern 3D-treatment planning systems (TPS) allows full integration of these imaging advances into treatment delivery and has facilitated the implementation of 3D-conformal radiation therapy (3D-CRT) which is now firmly in place as the standard of practice, in particular in the curative setting (1,2). In addition, sophisticated computer-controlled linear accelerators equipped with multileaf collimator systems (MLCs) and integrated imaging systems provide beam aperture shaping and beam-intensity modulation capabilities that allow precise shaping and image-guided positioning of the radiation dose distributions (3,4). In radiotherapy, the name linear accelerator is commonly, but not entirely correct, used for the combination of a linear electron accelerator that is able to generate high energy X-rays (photons) and a gantry, an arm-like radiation beam delivery device that can rotate around the patient.

The main objective of this paper is to review the basic principles of new radiation delivery techniques to found the need of advanced imaging into the radiation treatment planning process.

2D radiotherapy

Conventional or 2D-radiotherapy refers to the use of radiation delivery to the patient via beams from one or more directions using linear accelerators, where the beams are defined on projection images. For this purpose, a conventional x-ray simulator (a specially calibrated X-ray machine) is used that generates planar radiographs on which bony landmarks can be visualized in order to design beam portals for standardized beam arrangement techniques (Figure 1). Although this technique is quick and relatively cheap, the main disadvantages include inaccuracies in translating 3D-information regarding tumour extension and definition of critical structures to 2D-planar radiographs and, subsequently, the limited possibilities to spare normal tissues without compromising the required dose to the target volume. Consequently, there is generally limited knowledge about the true radiation dosage delivered to both targets and normal tissues. Of concern is that some high-dose

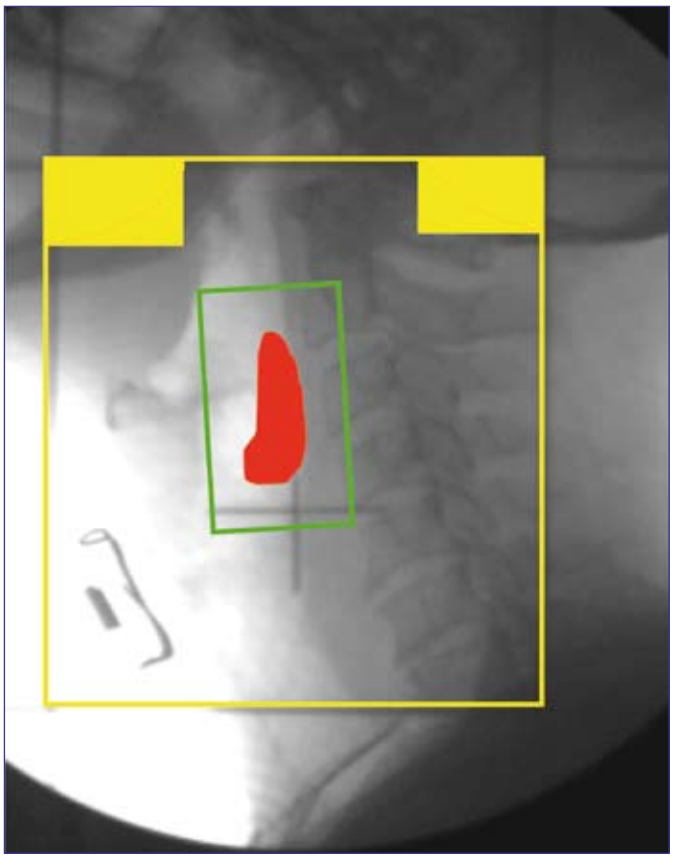


Figure 1.
Example of 2D radiotherapy with radiation beam assessment by direct simulation in piriform sinus carcinoma. RED = gross tumour volume (GTV); YELLOW = primary radiation field, including both the GTV and elective nodal areas; GREEN = boost volume including the GTV + margin.

treatments may be limited by the radiation toxicity capacity of normal tissues which lay close to the target volume. An example of this problem is seen in radiation of the prostate gland, where the sensitivity of the adjacent rectum limits further dose escalation to the prostate (5,6), which could otherwise result in higher local control rates (7). This has led to the development of a number of new radiation delivery techniques that we will describe briefly (Table 1).

3D conformal radiotherapy (3D-CRT)

In the last three decades the general practice in radiation oncology radically changed from a 2D-approach towards CT-based 3D- and even 4D-treatment planning, in particular in the curative setting. 3D-conformal radiotherapy (3D-CRT) refers to radiotherapy using CT for the delineation of target volumes and organs at risk (OARs), and to the use of an increased number of radiation beams that are shaped to conform the dose to the target volume and/or to shield normal tissues. To achieve an optimal 3D-dose distribution and to further improve the conformality of this dose distribution, conventional beam modifiers (e.g., wedges, partial transmission blocks, and/or compensating filters) are sometimes used. For 3D-CRT, but also for other more advanced radiation delivery techniques, an important prerequisite is to accurately delineate the patient's tumour, additional target volumes and organs at risk (critical normal tissues) on the planning-CT scan. In addition, an arrangement of beams will be created aiming at delivering the prescribed dose to the target (tumour) volume while keeping the dose to critical normal tissues low enough to minimize the risk of serious complications. Therefore, the first step in 3D-CRT and other advanced radiation delivery techniques is an accurate definition and delineation of the regions of interest for radiotherapy.

Target volume definition

The growing use of highly conformal radiation delivery techniques in clinics worldwide has also posed a number of problems to the radiation oncology community, such as difficulties in reporting radiation treatments uniformly and the need for a more clear definition of target volumes. To account for some of these problems, the International Commission on Radiation Units and Measurements (ICRU) produced a number of reports (8,9) addressing the issue of consistent volume and dose specification in radiotherapy. The ICRU Report 50 provided standardization of nomenclature, giving a consistent language and a methodology for image based volumetric 3D-CRT treatment planning in which different target volumes were defined.
The ICRU Report 50 defines three distinct target volumes (Figure 2): (1) the gross tumour volume (GTV), including all visible tumour as determined by physical examination and/or imaging; (2) the clinical target volume (CTV), including anatomical regions to account for uncertainties in microscopic tumour spread, e.g., microscopic invasion around the primary tumour site not detectable by imaging and/or lymph node areas with a high propensity on occult metastatic tumour foci, and finally; (3) the planning target volume (PTV), including a region to account for the net effect of all geometric variations and set up uncertainties in order to ensure that the prescribed dose is actually absorbed in the CTV. In the ICRU Report 62, a fourth volume was added, i.e. the internal target volume (ITV), which takes into account an extra margin for internal organ motion, such as due to respiratory movements in case of thoracic tumours or due to variation in rectal and bladder filling in case of pelvic tumours (see also 4D-imaging).

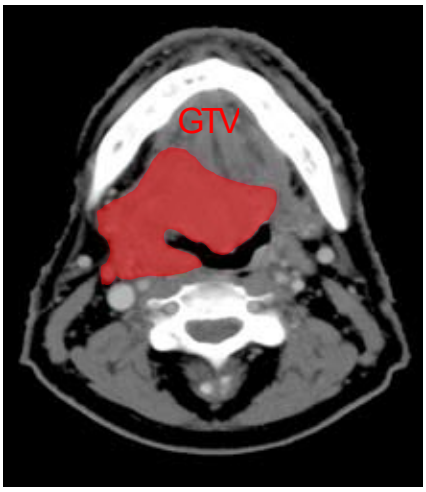
Organs at risk

Organs at risk (OARs) generally include distinct anatomical regions or structures which radiosensitivity may significantly influence treatment planning and may even hamper the delivery of the desired radiation dose to the PTV, without inducing unacceptable side effects. With the introduction of more advanced radiation delivery techniques, the prescribed dose alone can no longer be used to define the expected toxicity associated with high-dose radiation therapy (RT). However, escalated dose to the PTV results in higher doses to the adjacent normal structures, leading to an increased risk

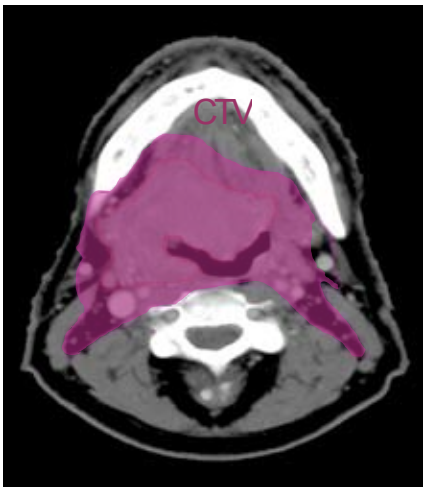
Table1. Overview of new radiation delivery techniques.

Technique	Definition	Target volume definition	Consequences for dose distribution	Typical examples of current clinical use
Conventional imaging based radiotherapy	Radiotherapy treatment based on conventional X-rays, typically in two dimensions (2D) .	Field arrangements are determined in 2D, based on anatomical structures that can be visualised on conventional X-rays (e.g., bones).	RT treatment planning is generated in one or a limited number of axial planes, allowing for relatively simple dose plans with limited possibilities to spare organs at risk.	Palliative treatments
3D-conformal radiotherapy (3D-CRT)	Radiation technique using beams with homogeneous or lineair gradient intensity from different angles and beam shaping using MLC's to conform the dose to the PTV as much as possible.	The volume that should receive a certain amount of homogeneous dose (PTV) is composed of macroscopic tumour extension (GTV), regions potentially bearing microscopic foci (CTV) and an extra margin for compensation of set up inaccuracies.	With 3D-CRT, the high dose area can be confined the the PTV much better as compared to 2D-RT.	Lung cancer and breast cancer
Intensity modulated radiotherapy (IMRT)	A radiation treatment delivery technique using beams with variable intensity. An advanced form of 3D-conformal radiotherapy usually designed with the aid of optimization algorithms during treatment planning.	The same as for 3D-CRT.	With IMRT, the high dose area can be confined even more to the PTV as compared to 3D-CRT, allowing optimal target volume dose coverage with better sparing of organs at risk.	Head and neck cancer, prostate cancer and breast cancer
Image-guided radiotherapy (IGRT)	Process of frequent 2D and/or 3D imaging, during a course of radiation treatment, used to correct for variations in the position of the patient and his/her organs and target volumes.	The same as for 3D-CRT, but because of the higher accuracy, the magins from CTV to PTV can be kept smaller.	IGRT can be delivered using 3D-CRT or IMRT. Due to the smaller margins needed from CTV to PTV, the treatment volume can be reduced, allowing for an even better sparing of organs at risk.	Prostate cancer
Adaptive radiotherapy (ART)	Radiation treatment in which dose distributions are adapted to changes in the shape and volume of target volumes and organs at risk during the course of treatment as assessed by repeated 3D-imaging.	The same as for 3D-CRT, but with adjustments made during the course of treatment.	RT treatment planning can be 3D-CRT or IMRT based. The adustments made during the course of radiation are expected to result in better target dose coverage.	Head and neck cancer
Tomotherapy	A modality of radiation treatment that combines the use of computer-controlled radiation beam collimation with an on-board computed tomography (CT) scanner to image the treatment site	The same as for 3D-CRT and IMRT, but with the possibility of making adjustments during the course of treatment.	Comparable to IMRT although the volume outside the target receiving a low dose tends to be larger	Head and neck cancer
4D-dimensional radiotherapy (4D-RT)	4D-radiotherapy which includes compensation of temporal changes in anatomy during the imaging, planning and delivery of each radiotherapy fraction, e.g., due to respiratory movements.	The same as for 3D-CRT, but with an extra target volume to account for temporal changes, i.e., internal target volume (ITV).	RT treatment planning can be 3D-CRT or IMRT based. To adjust for intrafractional movements, this technique will probably allow for better target dose coverage.	Lung cancer
Stereotactic radiotherapy (SRT) and radiosurgery (RS)	Radiotherapy treatment in which typically large doses per fraction are delivered in a very precise way (stereotactic guidance) to a small tumor area. RS refers to stereotactic radiotherapy using a single fraction.	In general, the PTV is composed of the GTV with a very small margin from GTV to PTV. In many cases, no CTV is defined.	SRT or RS allow for the administration of very high dose per fraction with minimal dose to the normal tissue.	Brain metastases and early stage (Stage I) non-small cell lung cancer.
Proton therapy (PT)	A pinpoint-accurate form of radiation therapy that uses protons instead of photons (X-rays) or electrons. The main difference compared to photons are the beam characterstics, producing a so-called Bragg-peak.	The same as for 3D-CRT, but is often combined with all kind of other emerging techniques such as IGRT, IMRT etc..	As compared to IMRT, the high dose area can be even more confined to the PTV, allowing optimal target volume dose coverage with better sparing of organs at risk.	Melanoma of the eye and pediatric tumours. Application to many current indications is expected.

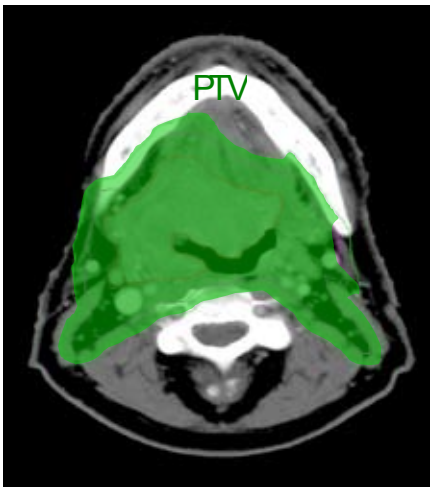
Figure 2 .
Schematic overview of GTV, CTV and PTV in a patient with squamous cell carcinoma of the base of skull. The CTV is composed of an area surrounding the GTV to account for microscopic tumour extension (in this case 1 cm) and the lymph node areas level II to IV on both sides of the neck.



The gross tumour volume (GTV), including all visible tumour as determined by physical examination and/or imaging



The clinical target volume (CTV), including anatomical regions to account for uncertainties in microscopic tumour spread, e.g., microscopic invasion around the primary tumour site not detectable by imaging and/or lymph node areas with a high propensity on occult metastatic tumour foci



The planning target volume (PTV), including a region to account for the net effect of all geometric variations and set up uncertainties in order to ensure that the prescribed dose is actually absorbed in the CTV

of radiation-induced side effects. Modern radiation delivery techniques combined with sophisticated treatment-planning strategies have led to non-uniform partial organ irradiation of normal tissues. As a consequence, the relationship between prescribed dose to the PTV and biologic equivalent effective doses to OARs that may have existed in previous eras are no longer valid. Therefore, treatment-plan evaluation and the choice of an optimal plan have become more challenging (10). For all OARs that may be relevant for a given patient, optimal radiation treatment planning requires the definition and evaluation of constraints with regard to radiation dose and corresponding volumes that these OARs can tolerate. Physical models and other simpler dosimetric descriptors of late radiation toxicity can now play an important role in these evaluations. Many researchers have developed methods to describe late normal tissue toxicity using mathematical and/or biophysical models. For each OAR, the normal tissue complication probability (NTCP) can be calculated from the non-uniform dose distribution throughout the OAR in some sort of integrative fashion. Two of the more widely used NTCP models are the one attributed to Lyman (11) and the relative seriality model proposed by Kallman and co-workers (12,13). These mathematical models are attractive because they generally take into account the complete 3-dimensional (3D) dose distribution throughout the OAR.

Radiotherapy treatment planning

The main objective of radiotherapy treatment planning is to deliver the desired dose to the CTV by aiming at a dose to the PTV within certain sufficient limits. The dose uniformity as recommended by the ICRU is that the actual dose should fall within the limits of 7% greater and 5% less than the prescribed dose, in order to ensure reasonably low dose inhomogeneity within the PTV. If the actual dose is beyond or below these limits, it is up to the treating radiation oncologist to decide whether this is acceptable or not. In case of doses higher than the upper limit of 107% of the prescribed dose, the decision to accept this will highly depend on the exact location of this high dose area and as to whether reduction of this high dose will result in an unacceptable under dosage somewhere else in the PTV. In case of doses lower than the lower limit of 95%, the decision to accept this will be determined by the resulting dose in OARs. In some cases, the desired prescribed dose cannot be achieved without increasing the dose to OARs beyond unacceptable limits, e.g., in case the PTV is located very close to an OAR or even partly overlaps with an OAR. In these cases, more advanced radiation techniques, such as IMRT, may enable to better deliver the desired dose to the PTV, without exceeding the tolerance dose of OARs. In clinical practice, radiation oncologists make use of so-called dose volume

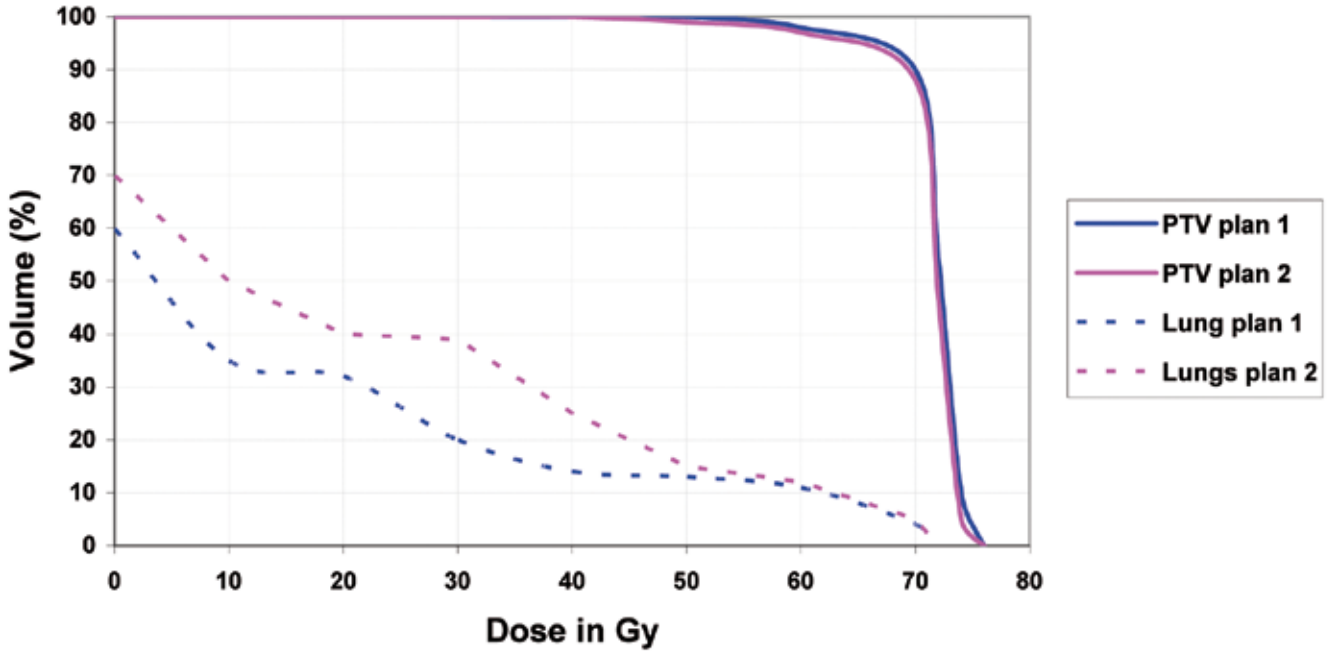


Figure 3.
Example of treatment plan comparison (plan 1 versus plan 2) in patient with lung cancer. Plan 1 is similar to plan 2 with regard to PTV coverage, while the dose to the lungs is much lower with plan 1. Based on this comparison, plan 1 provides the best therapeutic ratio.

histograms (DVH's) of target volumes and OARs. In a DVH, the relative volume of a region of interest (target volume or OAR) is expressed as a function of the dose to that volume (Figure 3). DVH's can be used to judge the feasibility of a certain radiation treatment plan and/or to compare different alternatives.

Intensity modulated radiotherapy

Intensity Modulated Radiotherapy (IMRT) enables a more precise conformal radiation dose distribution to the target area as compared to 3D-CRT by allowing to vary and control the intensity of different parts of the radiation beam (segments) within a given area and by using multiple beams. As a consequence, a much higher dose of radiation can be given to the PTV without an increase in radiation dose to OAR or, vice versa, the dose to the OAR can be reduced significantly, without hampering the dose to the PTV. IMRT utilizes beams that can be optimally weighted and multileaf collimators that can deliberately block part of the beams during treatment, varying the radiation beam intensity across the targeted field. The radiation beam shapes may be varied dozens or hundreds of times during each fraction and each segment of the beam may have a different intensity, resulting in sculpturing the radiation dose in three dimensions. The ultimate result is either better tumour control, less damage to normal tissues and fewer side effects, or both. Treatment planning and in particular treatment delivery for IMRT is more complex than for conventional 3D-CRT and requires extensive quality assurance programs to assure that the prescribed dose is actually given during each fraction.

A typical example of IMRT aiming at a similar dose to the PTV but reducing the dose to the OARs is IMRT in head and neck cancer (Figure 4). The most frequently reported side effect of radiotherapy in the head and neck area is xerostomia (14-16), which also have a negative impact on health-related quality of life (14,17). In a number of studies, there is a clear relationship between the mean dose in the parotid glands and the risk on xerostomia (18-22). With IMRT, the dose to the parotid glands can be diminished considerably as compared to 3D-CRT and a number of non-randomised and randomised studies showed that by using IMRT, the risk on xerostomia can be reduced significantly (23-25).

A typical example of IMRT aiming at dose escalation to the PTV without increasing the dose to normal tissues is IMRT in prostate cancer. Several prospective randomised studies showed that in prostate cancer, dose escalation from 70 Gy to 80 Gy results in a significant improvement of treatment outcome (26,27). However, dose escalation with conventional 3D-CRT would result in a much higher dose to the rectal wall, resulting in a higher risk of severe rectal complications. With IMRT, dose escalation can be achieved without increasing the probability of severe rectal complications.

4D-imaging in radiotherapy

As the administration of radiation takes time, ranging from about two to sometimes 20 or 30 minutes per fraction in stereotactic radiotherapy, it is inevitable that target volumes and normal tissues will move while delivering treatment;

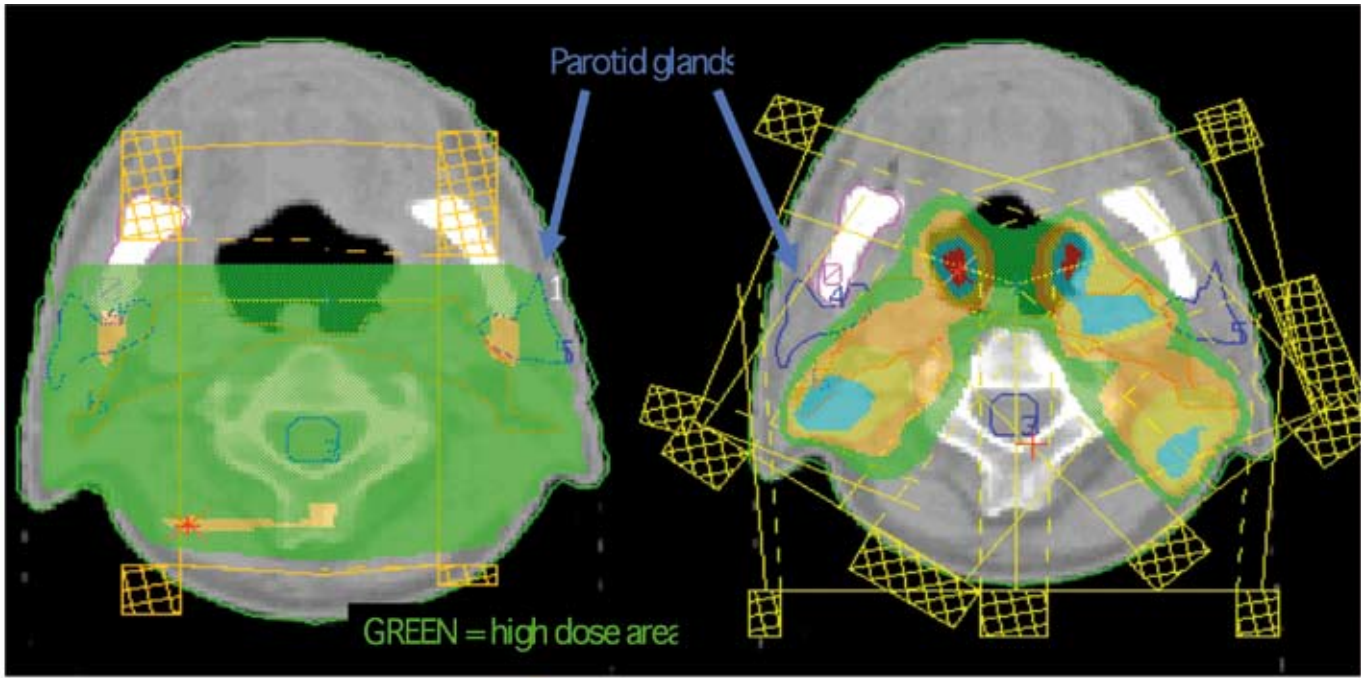


Figure 4.
Example of patient with head and neck cancer with elective neck irradiation to both sides of the neck. The left panel shows high dose region (GREEN area) achieved with conventional 3D-CRT and the right panel shows high dose region achieved with IMRT. The parotid glands can be spared significantly better with IMRT.

primarily due to respiration. The movement occurring during a single fraction is called intra-fraction motion, and this in turn is addressed by so-called 4D-imaging, where CT presently is the by far most important imaging modality. It has been shown that these movements depend on a variety of factors precluding the possibility to account for them by a simple generally applicable safety margin (28). Tumour motions not only differ in different patients due to pulmonary condition and age, but also for example according to tumour location in the lung (29). Organ motion is an issue particularly for treatment of tumours in the lung, liver, esophagus, stomach, pancreas, prostate, breast, and adrenal gland. In principle, there are three basic approaches towards the problem of irradiating a moving target. For all approaches, spatial measurement of the movement by means of quasi cinematographic imaging (e.g., 4D-CT) is a prerequisite. Thanks to powerful and fast multi-detector CT scanners it has become possible to co-register the respiration signal using various devices (pressure -, infrared -, or thermal detectors) with the tomography data and consecutively to reconstruct 3D-images at various phases in the respiratory cycle. In this way, the moving tumour becomes visible and therewith accessible for the treatment planning system. The first possible approach consists in delineating an "internal target volume (ITV)", where the whole trajectory of possible localizations of a tumour is defined as target (30,31). A variation hereof is to extract a "mid-ventilation" position of the tumour and then to calculate kind of a probability space as target volume (Figure 5) (32).

The second approach (gated radiotherapy) defines a gate within the respiration cycle where the linear accelerator will deposit radiation while being turned off at the non-gated segments of the respiratory cycle (33). In a third approach the moving target is tracked during radiation delivery, which can in principle be employed by moving the whole gantry (34) or by moving the multileaf-collimator (35). All these methods heavily depend on computer supported image acquisition and may or may not be combined with breath hold techniques or with special positioning devices such as a so called body frame. Importantly, all these approaches towards tumour and organ movement constitute individualized or personalized approaches where the situation as encountered with an individual patient is accounted for as far as possible.

Stereotactic radiotherapy

Intracranial stereotactic radiotherapy and radiosurgery

Stereotactic radiosurgery is a technique for the non-invasive sterilisation of intracranial lesions that may be inaccessible or unsuitable for surgery or where surgery carries a higher risk for adverse effects than radiation. The stereotactic method provides the basis for radiosurgery (36). More than 60 years ago, high precision radiation was combined with a concept allowing the localization of targets with millimetre precision. This consists in employing a Cartesian coordinate system and physically connecting the skull with the radiation gantry by pinning the head of the patient into a metallic frame which was then rigidly connected with the

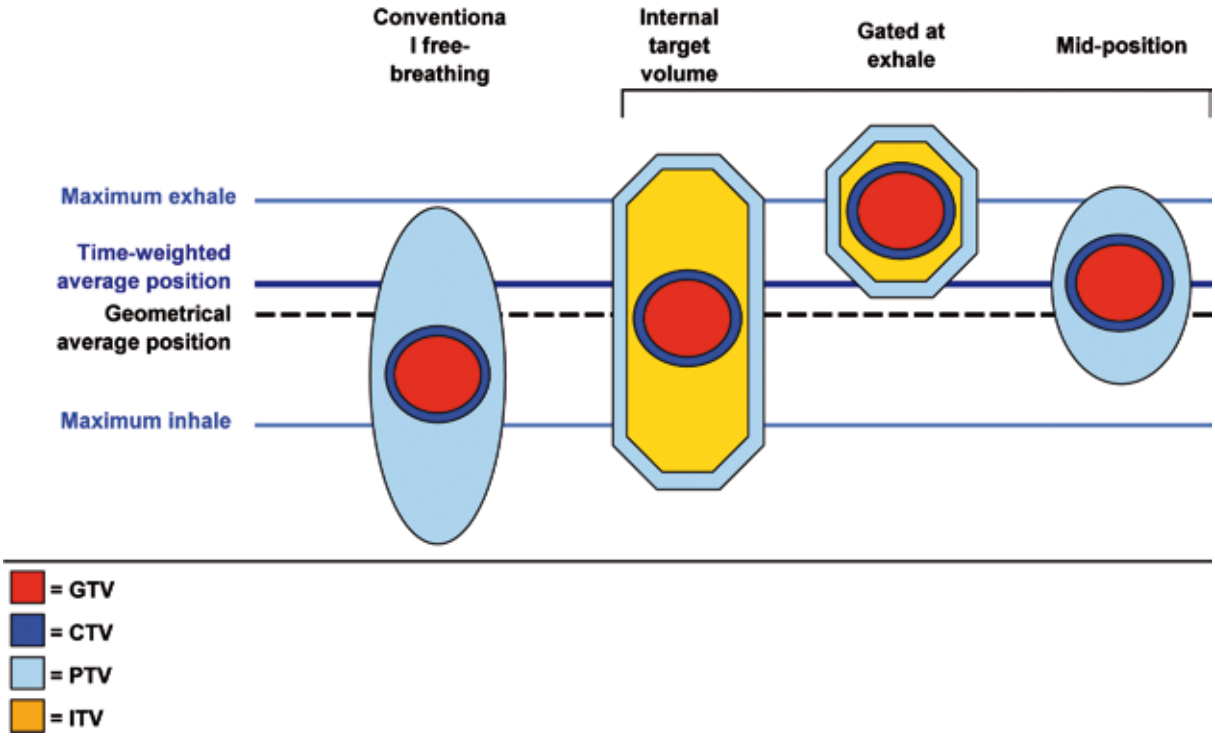


Figure 5.
Schematic overview of different treatment-planning strategies to account for respiratory motion, including: conventional free breathing; internal target volume (ITV); gating, and; mid-position.

gantry. Nowadays non-invasive stereotactic mask systems have replaced the invasive pins for most indications. The main advantage of the stereotactic technique has been the reduction of safety margins around targets (i.e., reduction of the PTV) due to positioning uncertainties to almost zero. As a consequence, the therapeutic radiation dose can be confined to target tissue with sharp dose decrease beyond targets therewith decreasing the risk for adverse affects of treatment. Stereotactic radiotherapy for intracranial lesions is now particularly used in brain metastases (Figure 6) (37) and benign lesions, such as arterio-venous malformations (37), and is increasingly used in primary brain tumours. Evidently, such an approach presupposes very exact spatial information about the target volume, in particular that of the GTV. Magnetic resonance imaging (MRI) is firmly established as the reference imaging method for the central nervous system, but recently PET imaging using novel tracers is playing an increasing role adding functional information to precise localization for various kinds of tumours (38,39). Maximal benefit for stereotactic radiosurgery depends on co-registration of spatial and functional diagnostic image information by using the same coordinate system for both. The coordinate system employed at diagnostic imaging is in turn introduced into to the treatment planning system and transferred to the radiation apparatus, which is possible nowadays at a sub millimetre level of precision. Considerably higher doses of radiation have become possible employing stereotactic technique for intracranial tumours, in turn increasing the local control rate of brain metastases and primary brain tumours.

Extracranial stereotactic radiotherapy

The same principle of using a Cartesian coordinate system for localizing the tumours as had been employed first for the immovable brain has been explored for the treatment of intrathoracic and abdominal lesions in the last decade (40). Here, targets typically move due to respiratory motion, adding one dimension of complexity compared with intracranial stereotactic radiotherapy and making extracranial stereotactic radiotherapy inevitably a 4D–endeavour (Figure 7). The problem of motion has been approached by the same principles as described in the 4D-imaging section. Only in the last couple of years, boosted by a publication of a phase I study in 2003 (41), stereotactic body radiotherapy (SBRT) is rapidly replacing conventional radiotherapy in the treatment of patients with early stage non-small cell lung cancer who are medically unfit to undergo radical surgery. In SBRT fraction doses are used that are ten times those used in conventionally fractionated radiotherapy (20 Gy instead of

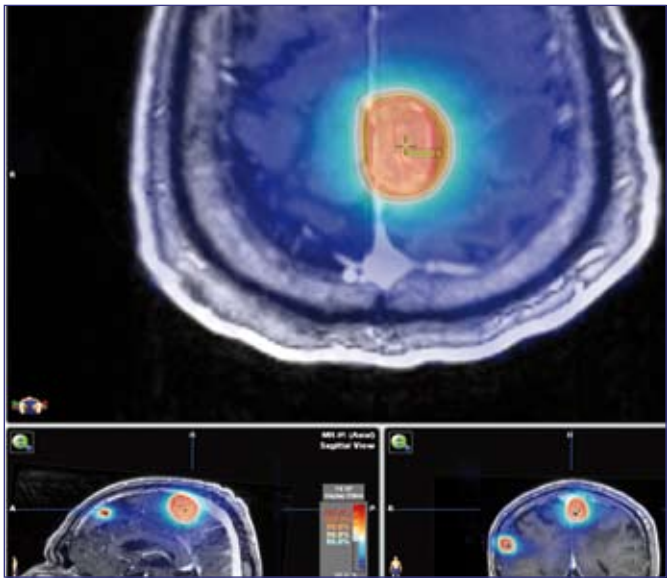


Figure 6.
Radiosurgery for brain metastases: the tumour volumes are defined upon MRI, dose calculation is performed on co-registered CT. Multiple arc treatment allows constriction of tumouricidal dose to malignant tissue.

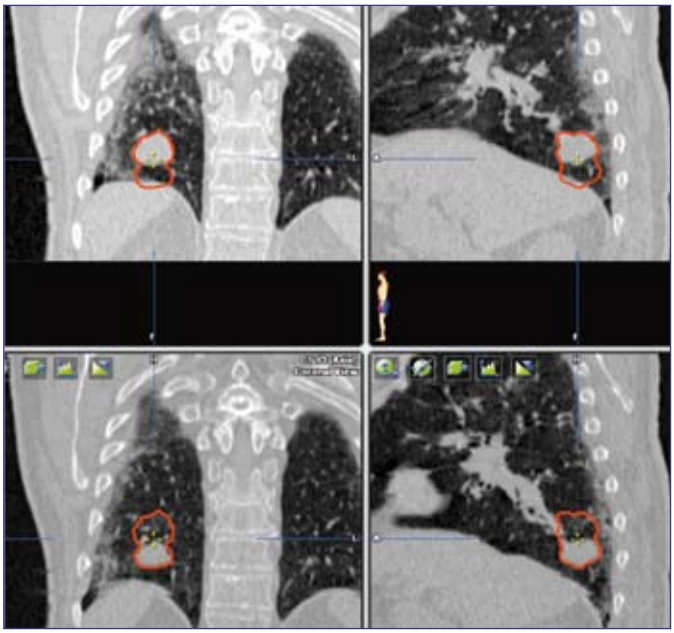


Figure 7.
4D-radiotherapy planning CT enabling tailored treatment planning. Upper panel: expiration; lower panel: inspiration.

2 Gy). The shift to SBRT is triggered by unequivocal reports favouring SBRT over conventional radiotherapy with local control rates after two years in excess of 85% (42;43). In addition to considerably higher tumour control rates, SBRT also carries a remarkably low rate of complications and adverse effects. The success gained in the treatment of primary lung cancer is also transferred to lung metastases and small volume disease in other organs such as the liver and the adrenal gland (44). There are still open questions such as the maximum tumour volume treatable with SBRT and the possibility to treat tumours located near critical structures such as the mediastinum. Although 4D-CT-based treatment planning for small lesions in the lung is usually sufficient for target delineation, in difficult cases where the tumour lies rather centrally in the lung near the hilus, additional imaging information would be able to considerably increase the certainty of target definition and therewith reduce the volume of unnecessarily irradiated normal tissues.

Image-guided radiotherapy (IGRT) and adaptive radiotherapy (ART)

In daily practice there is always an uncertainty what exactly is to be considered as target volume, e.g., as delineated on the initial CT-scan, and where this identified volume resides on any subsequent day of treatment, e.g., due to peristaltic or breathing motion and gradual change in patient geometry. Safety margins are applied to account for these uncertainties. These margins extent into normal tissues and are thus associated with excess toxicity or with limits to dose escalation and therefore tumour control (45).

Image-guided radiotherapy (IGRT) is defined as frequent imaging in the treatment room that allows treatment decisions to be made on the basis of these images (46). IGRT aims at reduction of the positional uncertainty and thus reduction of applied margins and of treated volume. Furthermore, in case of changes in patient geometry the treatment plan itself can be adapted to obtain optimal target coverage in the actual patient geometry, which is referred to as Adaptive Radiotherapy (ART)(47,48). Several techniques are available and under development for IGRT and ART. X-ray transmission images can be made either by dedicated kilovolt sources or by the megavoltage treatment beam itself. These images typically show presence or absence of radio-opaque structures, such as air cavities, bones and/or metal markers. These images can be used to correct the patient position. With well-designed correction protocols the minimum margin can be selected that is feasible within the statistical nature of the position variations (49-51). Apart form markers that are deliberately positioned in the target tissue, the position of the target volume can usually not directly be derived from these transmission images and its position must then be assumed in relation to visual structures, i.e. a margin has to be added. Soft tissue volumetric imaging can overcome this limitation. Cone beam CT imagers are nowadays often combined with treatment devices to acquire such images in treatment position. Also the other way around is implemented in a clinical apparatus, equipment of a CT with a small linear accelerator allowing helical tomotherapy as a treatment technique. Although from a radiation protection point of view the use of frequent additional CT's could be questioned, it has

been shown that Cone Beam CT guidance has a net positive impact on the integral dose: the gain caused by margin reduction is larger than the added image dose (52).
A new and promising development is the combination of a linear accelerator with a MR scanner, thus allowing superior soft tissue imaging just prior to treatment.
Common in all IGRT applications is the ongoing strive for further PTV margin reduction and treatment plan optimisation to the actual patient geometry and thus improvement of the ratio of tumour control versus prevention of normal tissue complications.

Particle therapy

As described in the former paragraphs, major progress has been made in technology development and physics of radiation therapy, all directed at achieving more effective cancer cell death while sparing normal tissue. All these radiation delivery techniques are administered using linear accelerators generating high-energy electrons and photons. These are now standard equipment in radiotherapy departments in the developed countries.
More recently, cyclotrons and synchrotrons have both been used for the generation of heavier particles for treatment, including protons and heavy ions for medical use. There are currently 9 facilities in Europe capable of generating protons for medical use, including one operating carbon ion facility in Europe, with two more under development.
The delivery of radiation with particles has important advantages compared to irradiation with the currently used photons (Figure 8)(53). Particle therapy offers the greatest conformal delivery of radiation energy, because of its unique energy absorption profile. In practice, proton beams are typically manipulated to generate a spread-out Bragg peak to yield a flat beam depth profile across the planning target volume followed by a rapid fall to zero dose, thereby producing little or no exit irradiation.
The Bragg peak associated with charged particle beams is extremely useful when attempting to treat a tumour which directly overlies vulnerable normal tissue. The advantage in the therapeutic ratio of protons compared to photons is mainly related to the physical properties and can be increased with the same principles as described earlier: (1) by reducing the dose to the critical organs while maintaining the dose to the tumour; and (2) by increasing the dose to the tumour without increasing the dose to the critical organs. Further improvement of the therapeutic ratio can be achieved by using high linear energy transfer (LET) radiations (e.g. carbon ions), combining the physical advantages of charged particles with an enhancement of the relative biological effect (RBE) which is most pronounced in the Bragg peak (54). It has been shown that the differential radiosensitivity between poorly oxygenated (more radioresistant) and well-oxygenated (more radiosensitive) cells is reduced with high-LET radiations (55;56). Therefore, tumour sites in which hypoxia is a problem might benefit most from high-LET radiations, such as in squamous cell head and neck cancer, cervical cancer and non-small cell lung cancer (57-59). Moreover, it is not inconceivable that the availability of particle therapy facilities may further increase the implementation of non-surgical and organ-preserving approaches among patients that are now treated with surgery.

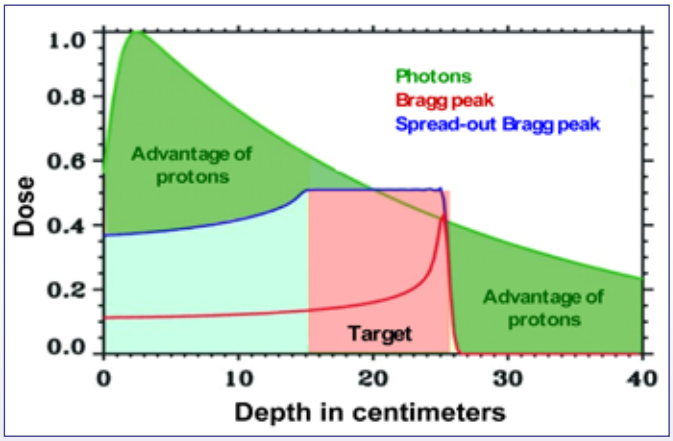


Figure 8.
Schematic view of advantages of protons over photons. The absorption of radiation into biological matter is characterized by the deposition of energy along the tracks of the path of protons in the radiation. As the energy of protons decreases, the interaction cross section enlarges. When the deposited energy dose is at its maximum, it is called the Bragg Peak. This maximum occurs shortly before the particle has lost all its energy and stops. A homogeneous dose distribution with protons can be achieved by using different energies, yielding a plateau at the target volume (spread out Bragg-peak).

The value of advanced imaging techniques in radiation oncology

The main advantage of advanced and emerging radiation delivery techniques is the increased capability to conform the high dose area to the PTV. This advantage offers on the one hand exciting new possibilities for tumour dose escalation and sparing of normal tissues, but on the other hand has posed radiation oncologists to new problems and risks. With the clinical introduction of new radiation delivery techniques, the steep dose gradient directly outside the PTV bears the risk of under dosage in case of inaccurate delineation of the target volume, in particular in case of an underestimation of the GTV. In this respect, imaging techniques that enable a more precise and accurate identification of the tumour borders will become increasingly important.
The problem of inaccuracies in target volume delineation and in particular tumour delineation is clearly illustrated by the results of numerous studies that reported on inter- and intra-observer variability in target volume delineation for virtually all tumour sites (60-65). From this point of view, the question arises as to whether the addition of other radiological as well as functional imaging techniques co-registered with planning-

CT scan will allow for a more precise delineation resulting in less inter-observer variability.
One of the tumour sites in which target volume delineation is well known to be prone to large inter-observer variability is lung cancer (66,67). The wide availability of ^{18}F-FDG PET-CT, with co-registered functional and anatomical data, has opened new exciting possibilities for target volume definition for radiation treatment purposes. ^{18}F-FDG PET-CT imaging is rapidly being implemented by radiation oncologists as a tool to improve the accuracy of tumour volume delineation in non-small cell lung cancer (NSCLC). Several authors reported on the feasibility of incorporating ^{18}F-FDG PET information into contour delineation with the aim to improve overall accuracy and to reduce inter-observer variation (66,67), showing a significant impact of ^{18}F-FDG PET-derived contours in 30-60% of the cases in reference to CT alone. The most prominent changes in the GTV have been reported in cases with atelectasis and following the incorporation of ^{18}F-FDG PET -positive nodes in otherwise CT-insignificant nodal areas. Similar results were found in esophageal cancer (68).
It should be noted that, although the addition of molecular imaging to planning-CT scan changes GTV-delineation in a considerable proportion of patients and reduces inter-observer variability, the routine introduction of PET requires further clinical validation. This can be done by means of different methods. A nice example of such a method was presented by Daisne et al. (69). In this study, the authors compared CT, MRI and ^{18}F-FDG PET delineation of the GTV in pharyngo-laryngeal squamous cell carcinoma reference to the macroscopic surgical specimen. Compared with CT- and MRI-based GTVs, ^{18}F-FDG PET-based GTVs were smaller and found to be the most accurate. However, none of these modalities managed to depict superficial tumour extension.
Validation of GTV delineation by means of comparison with pathological specimens will not be possible for all tumour sites, e.g., because of changes in the shape and volume of the pathological specimen after surgical removal. An alternative method could be to analyse the exact localization of locoregional tumour recurrences in relation to both pre-treatment CT-based and ^{18}F-FDG PET-based GTVs and in relation to the actually given radiation dose, also referred to as recurrence analysis.
An even more exciting approach to enhance the therapeutic ratio of radiation therapy by means of implementation of functional imaging techniques is the identification of radioresistant sub-volumes within the GTV, e.g., hypoxic areas, using hypoxic tracers. Modern radiation delivery techniques enable dose escalation to these radioresistant areas within the GTV. Vanderstraeten et al. reported on the results of a treatment planning study using ^{18}F-FDG PET voxel intensity-based IMRT in head and neck cancer and succeeded to create one or more sharp dose peaks inside the PTV, following the distribution of ^{18}F-FDG PET voxel intensity values while only small effects were observed on the dose distribution outside this PTV and on the dose delivered to the OARs (70). Although further improvement of such an approach could be achieved with more advanced techniques, such as protons, the clinical introduction requires additional information, e.g., with regard to the changes of radioresistant areas during the course of radiation and how to deal with these changes in daily practice.
There is no doubt that GTV delineation is affected by adding information derived from functional imaging. However, it should be noted that the clinical use of ^{18}F-FDG PET may also be hampered by some technical issues. In general, different types of contouring methods have been used, including visual interpretation (with or without source-to-background correction), or semi-automatic contouring based on different SUV-thresholds. However, these methods are neither objective nor uniform. For visual interpretation, image representation can be controlled by changing window-widths and window-levels, which is highly observer dependent, and may result in significant differences in visible tumour volumes. The SUV is, on the other hand, a semi-quantitative parameter for evaluation of the FDG uptake in tumours. However, many factors, such as patient preparation procedures, scan acquisition, image reconstruction and data analysis settings, affect the outcome of the SUV (71,72). Even though these factors have small effects individually, accumulation of many of these factors can result in considerable differences in SUV outcome.

Conclusion

New radiation delivery techniques enable highly conformal dose distributions in the target volume, which require more accurate methods to identify and delineate GTVs. Integration of molecular imaging technology with the planning-CT scan is promising leading to a more precise definition of the GTV and identification of radioresistant sub-volumes within the GTV thus enabling increases in the therapeutic ratio of radiotherapy. However, the routine use of these imaging techniques requires further clinical validation.

Reference List

1. Purdy JA. 3-D radiation treatment planning: a new era. Front Radiat Ther Oncol. 1996;29:1-16.
2. Purdy JA. Defining our goals: volume and dose specification for 3-D conformal radiation therapy. Front Radiat Ther Oncol. 1996;29:24-30.
3. Bortfeld T. IMRT: a review and preview. Phys Med Biol. 2006;51:363-79.
4. Al Mamgani A, Heemsbergen WD, Peeters ST, Lebesque JV. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2009;73:685-91.
5. Fenoglietto P, Laliberte B, Allaw A, Ailleres N, Idri K, Hay MH, et al. Persistently better treatment planning results of intensity-modulated (IMRT) over conformal radiotherapy (3D-CRT) in prostate cancer patients with significant variation of clinical target volume and/or organs-at-risk. Radiother Oncol.

2008;88:77-87.
6. Al Mamgani A, Heemsbergen WD, Peeters ST, Lebesque JV. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2009;73:685-91.
7. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol. 2006; 24:1990-6.
8. ICRU Report 50: Prescribing, Recording, and Reporting Photon Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements. 1993:1-72.
9. ICRU Report 62: Prescribing, Recording, and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). Bethesda, MD: International Commission on Radiation Units and Measurements. 1999:1-52.
10. Ten Haken RK, Kessler ML. 3-D CRT Plan Evaluation. In: Purdy JA, Grant III WH, Palta JR, Butler EB, Perez CA, editors. 3-D Conformal and Intensity Modulated Radiation Therapy. Advanced Medical Publishing, Madison WI. 2001.
11. Lyman JT. Complication probability as assessed from dose-volume histograms. Radiat Res Suppl. 1985;8:13-9.
12. Kallman P, Agren A, Brahme A. Tumour and normal tissue responses to fractionated non-uniform dose delivery. Int J Radiat Biol. 1992;62:249-62.
13. Kallman P, Lind BK, Brahme A. An algorithm for maximizing the probability of complication-free tumour control in radiation therapy Phys Med Biol. 1992;37:871-90.
14. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol. 2008;26:3770-6.
15. Bjordal K, Kaasa S, Mastekaasa A. Quality of life in patients treated for head and neck cancer: a follow-up study 7 to 11 years after radiotherapy. Int J Radiat Oncol Biol Phys. 1994;28:847-56.
16. Jensen AB, Hansen O, Jorgensen K, Bastholt L. Influence of late side-effects upon daily life after radiotherapy for laryngeal and pharyngeal cancer. Acta Oncol. 1994;33:487-91.
17. Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;69:751-60.
18. Semenenko VA, Li XA. Lyman-Kutcher-Burman NTCP model parameters for radiation pneumonitis and xerostomia based on combined analysis of published clinical data. Phys Med Biol. 2008;53:737-55.
19. Dijkema T, Terhaard CH, Roesink JM, Braam PM, van Gils CH, Moerland MA, et al. Large cohort dose-volume response analysis of parotid gland function after radiotherapy: intensity-modulated versus conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2008;72:1101-9.
20. Jellema AP, Doornaert P, Slotman BJ, Leemans CR, Langendijk JA. Does radiation dose to the salivary glands and oral cavity predict patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with curative radiotherapy? Radiother Oncol. 2005;77:164-71.
21. Roesink JM, Schipper M, Busschers W, Raaijmakers CP, Terhaard CH. A comparison of mean parotid gland dose with measures of parotid gland function after radiotherapy for head-and-neck cancer: implications for future trials. Int J Radiat Oncol Biol Phys. 2005;63:1006-9.
22. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys. 1999;45:577-87.
23. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys. 2006;66:981-91.
24. Kam MK, Leung SF, Zee B, Chau RM, Suen JJ, Mo F, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol. 2007;25:4873-9.
25. Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys. 2009;74:1-8.
26. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol. 2006;24:1990-6.
27. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys. 2002;53:1097-105.
28. Keall P. 4-dimensional computed tomography imaging and treatment planning. Semin Radiat Oncol. 2004;14:81-90.
29. Seppenwoolde Y, De Jaeger K, Boersma LJ, Belderbos JS, Lebesque JV. Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2004;60:748-58.
30. Underberg RW, Lagerwaard FJ, Slotman BJ, Cuijpers JP, Senan S. Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer. Int J Radiat Oncol Biol Phys. 2005;63:253-60.
31. Underberg RW, Lagerwaard FJ, Slotman BJ, Cuijpers JP, Senan S. Benefit of respiration-gated stereotactic radiotherapy for stage I lung cancer: an analysis of 4DCT datasets. Int J Radiat Oncol Biol Phys. 2005;62:554-60.
32. Wolthaus JW, Sonke JJ, van Herk M, Belderbos JS, Rossi MM, Lebesque JV, et al. Comparison of different strategies to use four-dimensional computed tomography in treatment planning for lung cancer patients. Int J Radiat Oncol Biol Phys.

2008;70:1229-38.
33. Korreman SS, Juhler-Nottrup T, Boyer AL. Respiratory gated beam delivery cannot facilitate margin reduction, unless combined with respiratory correlated image guidance. Radiother Oncol. 2008;86:61-8.
34. Nuyttens JJ, Prevost JB, Praag J, Hoogeman M, Van Klaveren RJ, Levendag PC, et al. Lung tumour tracking during stereotactic radiotherapy treatment with the CyberKnife: Marker placement and early results. Acta Oncol. 2006;45:961-5.
35. Sawant A, Smith RL, Venkat RB, Santanam L, Cho B, Poulsen P, et al. Toward submillimeter accuracy in the management of intrafraction motion: the integration of real-time internal position monitoring and multileaf collimator target tracking. Int J Radiat Oncol Biol Phys. 2009;74:575-82.
36. Leksell L. Stereotactic radiosurgery. J Neurol Neurosurg Psychiatry. 1983;46:797-803.
37. Muller-Riemenschneider F, Bockelbrink A, Ernst I, Schwarzbach C, Vauth C, der Schulenburg JM, et al. Stereotactic radiosurgery for the treatment of brain metastases. Radiother Oncol. 2009;91:67-74.
38. Tian M, Zhang H, Oriuchi N, Higuchi T, Endo K. Comparison of 11C-choline PET and FDG PET for the differential diagnosis of malignant tumours. Eur J Nucl Med Mol Imaging. 2004;31:1064-72.
39. Gulyas B, Nyary I, Borbely K. FDG, MET or CHO? The quest for the optimal PET tracer for glioma imaging continues. Nat Clin Pract Neurol. 2008;4:470-1.
40. Blomgren H, Lax I, Naslund I, Svanstrom R. Stereotactic high dose fraction radiation therapy of extracranial tumours using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol. 1995;34(6):861-70.
41. Timmerman R, Papiez L, McGarry R, Likes L, DesRosiers C, Frost S, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest. 2003;124:1946-55.
42. Haasbeek CJ, Senan S, Smit EF, Paul MA, Slotman BJ, Lagerwaard FJ. Critical review of nonsurgical treatment options for stage I non-small cell lung cancer. Oncologist. 2008;13:309-19.
43. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008;70:685-92.
44. Timmerman RD, Bizekis CS, Pass HI, Fong Y, Dupuy DE, Dawson LA, et al. Local surgical, ablative, and radiation treatment of metastases. CA Cancer J Clin. 2009;59:145-70.
45. Jaffray DA. Image-guided radiation therapy: from concept to practice. Semin Radiat Oncol. 2007;17:243-4.
46. Verellen D, Ridder MD, Linthout N, Tournel K, Soete G, Storme G. Innovations in image-guided radiotherapy. Nat Rev Cancer. 2007;7:949-60.
47. Nijkamp J, Pos FJ, Nuver TT, de Jong R, Remeijer P, Sonke JJ, et al. Adaptive radiotherapy for prostate cancer using kilovoltage cone-beam computed tomography: first clinical results. Int J Radiat Oncol Biol Phys. 2008;70:75-82.
48. Schulze D, Liang J, Yan D, Zhang T. Comparison of various online IGRT strategies: The benefits of online treatment plan re-optimization. Radiother Oncol. 2009;90:367-76.
49. Stroom JC, Koper PC, Korevaar GA, van Os M, Janssen M, de Boer HC, et al. Internal organ motion in prostate cancer patients treated in prone and supine treatment position. Radiother Oncol. 1999;51:237-48.
50. Stroom JC, de Boer HC, Huizenga H, Visser AG. Inclusion of geometrical uncertainties in radiotherapy treatment planning by means of coverage probability. Int J Radiat Oncol Biol Phys. 1999;43:905-19.
51. van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. Int J Radiat Oncol Biol Phys. 2000;47:1121-35.
52. van Herk M. Different styles of image-guided radiotherapy. Semin Radiat Oncol. 2007;17:258-67.
53. Schulz-Ertner D, Jakel O, Schlegel W. Radiation therapy with charged particles. Semin Radiat Oncol. 2006;16:249-59.
54. Gerweck LE, Kozin SV. Relative biological effectiveness of proton beams in clinical therapy. Radiother Oncol. 1999;50:135-42.
55. Tobias CA, Blakely EA, Alpen EL, Castro JR, Ainsworth EJ, Curtis SB, et al. Molecular and cellular radiobiology of heavy ions. Int J Radiat Oncol Biol Phys. 1982;8:2109-20.
56. Hirayama R, Furusawa Y, Fukawa T, Ando K. Repair kinetics of DNA-DSB induced by X-rays or carbon ions under oxic and hypoxic conditions. J Radiat Res (Tokyo). 2005;46:325-32.
57. Vaupel P, Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. Cancer Metastasis Rev. 2007;26:225-39.
58. Feldmann HJ. Oxygenation of human tumours--implications for combined therapy. Lung Cancer. 2001;33:77-83.
59. Rudat V, Stadler P, Becker A, Vanselow B, Dietz A, Wannenmacher M, et al. Predictive value of the tumour oxygenation by means of pO2 histography in patients with advanced head and neck cancer. Strahlenther Onkol. 2001;177:462-8.
60. Foroudi F, Haworth A, Pangehel A, Wong J, Roxby P, Duchesne G, et al. Inter-observer variability of clinical target volume delineation for bladder cancer using CT and cone beam CT. J Med Imaging Radiat Oncol. 2009;53:100-6.
61. Yu H, Caldwell C, Mah K, Poon I, Balogh J, MacKenzie R, et al. Automated radiation targeting in head-and-neck cancer using region-based texture analysis of PET and CT images. Int J Radiat Oncol Biol Phys. 2009;75:618-25.
62. (Vorwerk H, Beckmann G, Bremer M, Degen M, Dietl B, Fietkau R, et al. The delineation of target volumes for radiotherapy of lung cancer patients. Radiother Oncol. 2009;91:455-60.
63. Dimopoulos JC, De Vos V, Berger D, Petric P, Dumas I, Kirisits C, et al. Inter-observer comparison of target delineation for MRI-assisted cervical cancer brachytherapy: application of the GYN GEC-ESTRO recommendations. Radiother Oncol. 2009;91:166-72.
64. Nakamura K, Shioyama Y, Tokumaru S, Hayashi N, Oya N, Hiraki Y, et al. Variation of clinical target volume definition among Japanese radiation oncologists in external beam radiotherapy for

prostate cancer. Jpn J Clin Oncol. 2008;38:275-80.
65. Kepka L, Bujko K, Garmol D, Palucki J, Zolciak-Siwinska A, Guzel-Szczepiorkowska Z, et al. Delineation variation of lymph node stations for treatment planning in lung cancer radiotherapy. Radiother Oncol. 2007;85:450-5.
66. van Baardwijk A, Baumert BG, Bosmans G, van Kroonenburgh M, Stroobants S, Gregoire V, et al. The current status of FDG PET in tumour volume definition in radiotherapy treatment planning. Cancer Treat Rev. 2006;32:245-60.
67. Bachaud JM, Marre D, Dygai I, Caselles O, Hamelin D, Begue M, et al. [The impact of 18F-fluorodeoxyglucose positron emission tomography on the 3D conformal radiotherapy planning in patients with non-small cell lung cancer. Cancer Radiother. 2005;9:602-9.
68. Vesprini D, Ung Y, Dinniwell R, Breen S, Cheung F, Grabarz D, et al. Improving observer variability in target delineation for gastro-oesophageal cancer--the role of (18F)fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography. Clin Oncol (R Coll Radiol). 2008;20:631-8.
69. Daisne JF, Duprez T, Weynand B, Lonneux M, Hamoir M, Reychler H, et al. Tumour volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology. 2004;233:93-100.
70. Vanderstraeten B, Duthoy W, De Gersem W, De Neve W, Thierens H. [18F]fluoro-deoxy-glucose positron emission tomography ([18F]FDG PET) voxel intensity-based intensity-modulated radiation therapy (IMRT) for head and neck cancer. Radiother Oncol. 2006;79:249-58.
71. Boellaard R, Oyen WJ, Hoekstra CJ, Hoekstra OS, Visser EP, Willemsen AT, et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. Eur J Nucl Med Mol Imaging. 2008;35:2320-33.
72. Boellaard R, Krak NC, Hoekstra OS, Lammertsma AA. Effects of noise, image resolution, and ROI definition on the accuracy of standard uptake values: a simulation study. J Nucl Med. 2004;45:1519-27.

The use of ^{18}F-FDG PET to target tumours by radiotherapy

Prof. dr. D.K.M. De Ruysscher

Dr. A. van Baardwijk

Dr. B.G. Baumert

Dr. G. Lammering

Dr. J.H. Borger

Dr. L.C.H.W. Lutgens

Drs. P.L.A. van den Ende

Dr. M.C. Öllers

Prof. dr. P. Lambin

Maastricht University Medical Centre, Department of Radiation Oncology (MAASTRO clinic), GROW Research Institute, Maastricht, The Netherlands

Abstract

De Ruysscher DKM, Van Baardwijk A, Baumert BG, Lammering G, Borger JH, Lutgens LCHW, Van den Ende PLA, Öllers MC, Lambin P. The use of ^{18}F-FDG PET to target tumours by radiotherapy

^{18}F-FDG PET plays an increasingly important role in radiotherapy, beyond staging and selection of patients. Especially for non-small cell lung cancer, ^{18}F-FDG PET has in the majority of the patients lead to the safe decrease of radiotherapy volumes, enabling radiation dose escalation and experimentally, re-distribution of radiation doses within the tumour. In limited-disease small cell lung cancer, the role of ^{18}F-FDG PET is emerging. For primary brain tumours PET based on amino acid tracers is currently the best choice, including high grade glioma. This is especially true for low grade glioma's, where most data are available for the use of ^{11}C-MET in radiotherapy treatment planning. For oesophageal cancer, the main advantage of ^{18}F-FDG PET is the detection of otherwise unrecognised lymph node metastases. In Hodgkin's disease, ^{18}F-FDG PET is essential for involved-node irradiation and leads to decreased radiation volumes whilst also decreasing geographical miss. ^{18}F-FDG PET its major role in the treatment of cervical cancer with radiotherapy lies in the detection of para-aortic nodes that can be encompassed in radiation fields. Besides for staging purposes, ^{18}F-FDG PET is not recommended for routine radiotherapy delineation purposes. It should be emphasised that using PET is only safe when strictly standardised protocols are used.

Tijdschr Nucl Geneesk 2009; 31(4):390-401

Background

Radiotherapy is a key treatment modality in the curative treatment of patients with cancer. The probability for radiotherapy to achieve tumour control is dependent on two crucial issues: dose and treatment time on one hand and precise delivery of that dose on the tumour on the other. The latter seems obvious, but is not trivial at all. Indeed, theoretically, when extreme high radiation doses (e.g. 200 Gy) could be given to the tumour only, thus sparing normal tissues, a virtually 100% probability to achieve local tumour control would emerge, without toxicity. Apart from biological and physical factors, central to achieve the ultimate therapeutic ratio is adequate delineation of the tumour. An incorrect definition of the gross tumour volume (GTV) (i.e. detectable tumour) or clinical target volume (CTV) (tumour plus a margin for microscopic extension) is a source of systematic errors, which can lead to under-treatment and reduces the probability of tumour control.

Perfect delineation of the tumour requires apart from optimal diagnostic accuracy (cancer or not) also the capability to identify sharply the anatomical borders of the tumour. Indeed, under-dosage of parts of the tumour results is a dramatic decrease in tumour control probability. Moreover, many tumours move substantially due to physiologic processes such as respiration, cardiac beats, bowel and bladder filling. As the delivery of radiotherapy typically takes 10-15 minutes, any imaging modality should take this time frame into account. Tracking or gating techniques may tackle some of these problems, but apart from their availability, many technical problems still have to be solved for many tumour locations. Repeated imaging would also deal with volume and shape changes during therapy. All this should be done in radiotherapy position, in order to avoid mismatching, image warping and other image manipulations, which all increase the chance of errors.

A weak point in current tumour delineation protocols is its manual component. Indeed, visual tumour contouring is routinely used in clinical practice. Even with carefully designed protocols, significant inter- and intra-observer variability still occurs. Automated tools are therefore needed.

PET, and certainly integrated PET-CT, has many potential advantages for radiotherapy planning. They combine anatomical and biological information in an identical position of patient as radiotherapy will be delivered, there is no time interval between PET and CT scan, the CT can be used for attenuation correction and CT densities can be used for radiation dose calculation.

Although not the aim of this article, it should be emphasized that as with any other imaging and therapeutic modality, also PET in radiotherapy should be calibrated thoroughly as well as used in strict clinical protocols. Volume assessment with PET is crucially dependent on technical factors and huge mistakes can only be avoided by sticking to well-established protocols (1).

PET with FDG as tracer in radiotherapy planning has been investigated in many cancer types, of which non-small cell lung cancer is the most widely applied in clinical practice. In other tumour types, such as head and neck cancer, neurological tumours, oesophageal carcinoma, rectal cancer, lymphoma and cervical carcinoma, radiotherapy planning using ^{18}F-FDG PET has a role to play.

For each of these tumour types, the following questions will be addressed:

1. Does PET scanning allow accurate tumour delineation? Does PET scanning change Gross Tumour Volume (GTV), Clinical Target Volume and/or the Planning Target Volume (PTV), both for the primary tumour and the local and regional lymph nodes?
2. Does PET scanning allow improvement of treatment outcome?

1. Lung cancer

1.1 Non-small cell lung cancer (NSCLC)

PET for defining tumour volumes in NSCLC (Figure 1)

Nodal target volumes

Accurate identification of nodal metastases is crucial for planning curative radiotherapy; particularly as routine elective nodal irradiation is no longer recommended in NSCLC (2). ^{18}F-FDG PET scan has a higher sensitivity, specificity and accuracy for detection of lymph node involvement and distant metastases in NSCLC than CT scan and therefore, results in a more accurate staging (3).

In several planning studies, it was shown that PET or PET-CT influences the GTV (4,5). The PET volumes were in general smaller than with CT (6,7). A prospective clinical trial using selective mediastinal radiotherapy of PET positive nodes reported isolated nodal failures in only 1 of 44 patients (8). These results were subsequently confirmed in another, similar prospective study from the Netherlands Cancer Institute (9), but not in a US retrospective series (10). The latter may be due to the absence of a clearly defined PET-delineation protocol. Although PET-defined mediastinal radiotherapy fields appears to be safe, because of a false-positive rate of approximately 30% and a false-negative rate of about 7%, depending on the patient population, ideally, pathological confirmation of PET-positive mediastinal nodes should be obtained by mediastinoscopy or endoscopic ultrasound guided fine needle aspiration (EUS-FNA).

Target volumes for the primary tumour

At present, ^{18}F-FDG PET scans offer little additional advantage

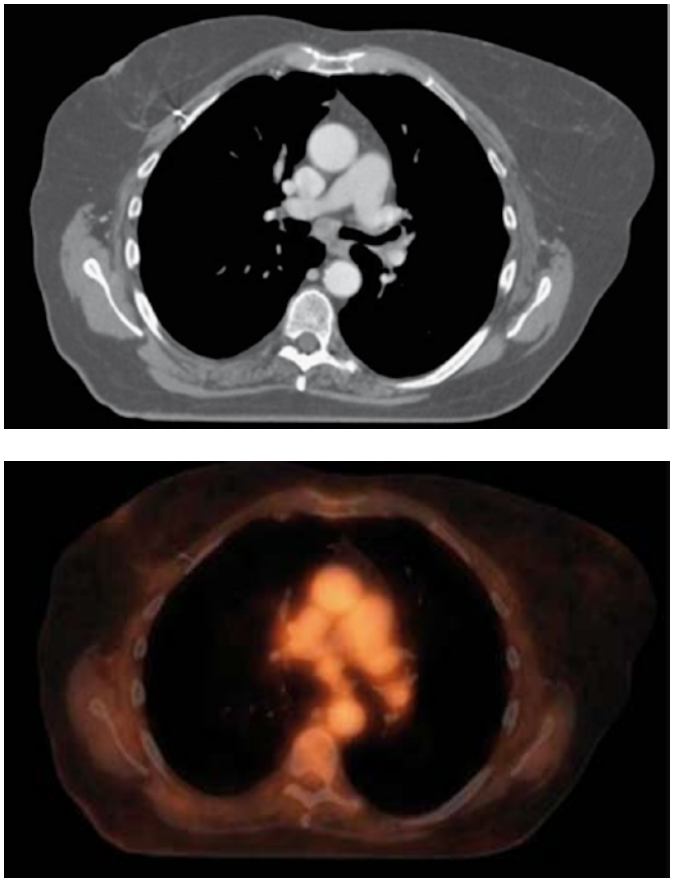


Figure 1.
Non-small cell lung cancer. Axial view of ^{18}F-FDG PET-CT with contrast. CT shows an enlarged node (level 7, diameter of 1.9 cm), while PET shows no FDG uptake in level 7. This finding influences the delineation of the nodal target volume.

over CT or MRI scans for staging of the primary tumour because of its lack of precise anatomical localization. The spatial resolution of modern CT scanners (typically about 1 mm) is far superior to that of current PET scanners (6–8 mm), so that the extra gain with fusion is expected not be large, unless PET scans can reliably address tumour delineation caused by atelectasis or intra-tumour heterogeneity. However, PET did show a remarkably good correlation with pathology and patient data (11-13).

Moreover, PET scans reduced the inter-observer variability compared to CT alone (14). Integrated PET-CT scans further improved delineation variability (15). The next step is to use the PET signal to construct automatic delineation of the tumour and to offer the radiation oncologist a solution that only needs contour editing. This method was on its turn to be less prone to variability than PET-CT (11).

As PET acquisition takes several minutes, tumour motion due to respiration or cardiac action results in PET "GTVs" that incorporate at least some effects of this motion. Respiration-gated PET acquisition techniques have been developed (16,17) and are at present evaluated in clinical studies.

Clinical Target Volume
In view of the relatively poor spatial resolution of PET scans, it does not come as a surprise that at the time of writing, no clear advantage of PET to define the microscopic extensions of the tumour were reported. The development of new methods may change this picture in the future (12).

Do PET scans change the outcome of patients with NSCLC treated with radiotherapy?
PET scans have shown to detect distant metastases in up to 30% of the patients with stage III NSCLC who were M0 with conventional staging (18,19). This clearly affects patient outcome for it spares toxic therapy in individuals who will not benefit from it.
The PET volumes were in general smaller than with CT. The incorporation of PET in radiotherapy planning has as previously shown the potential to allow radiation-dose escalation without increasing side effects, this because of the reduction of radiation fields (6,7). In a phase I/II trial, it was shown that this pre-requisite is indeed true (20). Whether this radiation dose increase will ultimately lead to higher cure rates is matter of current research.
PET scans may also allow the identification of therapy-resistant areas within the tumour that could be given a higher radiation dose and hence lead to a better outcome (21, 22).

1.2 Small cell lung cancer (SCLC)

PET scan for radiotherapy for limited disease small-cell lung cancer.
Literature is sparse on the role of PET in limited disease small-cell lung cancer (LD-SCLC). Although after CT-based radiotherapy planning, isolated nodal recurrences may be seen in over 10% of the patients, in a prospective study selective nodal irradiation based on PET scans proved to result in only 3% of isolated nodal failures (23).

Conclusions
For NSCLC, ^{18}F-FDG PET scans allow more thorough staging, thus avoiding unnecessary treatments. In most patients, it reduces radiation treatment volumes because of the avoidance of mediastinal lymph nodes that are PET negative and hence reduces toxicity with the same radiation dose or enables radiation dose escalation with the same toxicity. Data are also encouraging for small cell lung carcinoma.
More research is needed to assess the effect of PET on survival.

PET also reduces inter-observer variability for delineating tumours and opens perspective for more automated delineation parts in radiation planning, as well as innovative radiation treatment delivery.

2. Primary brain tumours

Compared with other organ systems, ^{18}F-FDG PET imaging of the brain presents unique challenges because of the high background glucose metabolism of normal gray matter structures. Highly metabolically active tissues such as the normal brain can mask detection of adjacent abnormalities and as such are not always helpful for tumour and target delineation. Furthermore, many primary brain tumours as for example, meningioma, show no uptake of FDG and cannot be imaged with ^{18}F-FDG PET. Interpretation of functional PET images can be improved by correlation with anatomic imaging. Co-registration of MRI or CT and FDG PET images is essential for accurate evaluation of brain tumours. Also, primary brain tumours consist of a group of various pathologies and carry variable prognoses. They have the tendency to recur locally and to undergo malignant degeneration in which case PET can have added value during follow-up.

2.1. Low-grade glioma

Functional imaging with modern tracers such as ^{11}C-MET (methionine) results in good visualization of low-grade gliomas. Baseline amino acid uptake on ^{18}F-FET PET in a diffuse versus circumscribed tumour pattern on MRI is a strong predictor for the outcome of patients with low-grade glioma (24). The combination of PET with conventional imaging techniques (MRI, CT) may lead to synergy in delineating these tumours in the course of radiotherapy planning. Early reports (25) found ^{11}C-MET to be superior to CT in delineating gliomas. Comparing ^{18}F-FDG PET with MRI in 14 patients with predominantly low-grade glioma, PET-volumes were larger than, equal to or smaller than MRI-derived tumour volumes in 7, 4 and 3 patients, respectively (26). PET was helpful in outlining the GTV in 3 cases only. Jacobs (27) and Kaschten (28) found ^{11}C-MET superior to ^{18}F-FDG and ^{18}F-FLT, respectively, in delineating low-grade glioma. For low grade glioma, the use of an amino acid tracer is the first choice tracer in radiotherapy treatment planning.

2.2. Pituitary adenoma

The value of ^{18}F-FDG and ^{11}C-MET in addition to MRI was investigated in a population of 57 patients comprising a variety of tumours including 10 pituitary adenomas (29, 30). PET influenced the target volume in 69% of the target volumes for stereotactic radiosurgery. In recurrent adenoma after surgery, ^{11}C-MET may distinguish between active tumour and fibrosis which is essential to define an optimal target volume for radiotherapy purposes (31).

2.3. High grade glioma (Figure 2)

Studies comparing tumour volumes based on PET (both ^{18}F-FDG and ^{11}C-MET) and other imaging modalities usually show that PET scan volumes are smaller than MRI and CT based volumes (32, 33). In a study of 57 patients treated by radiosurgery for 72 target volumes, an abnormal uptake of

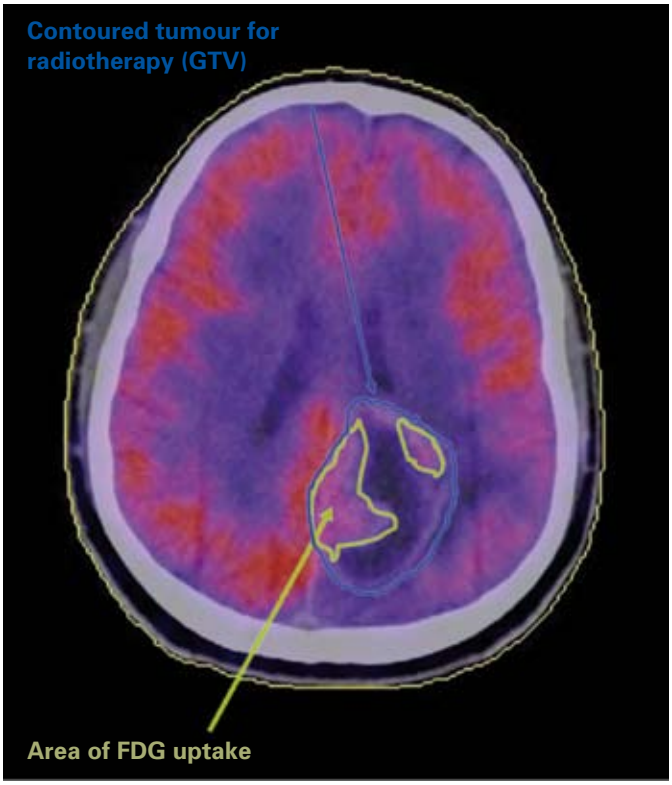


Figure 2: Glioblastoma. Axial view of ^{18}F-FDG PET-CT with contrast. The area of the post-operative tumour volume for radiotherapy is defined in blue. Yellow areas are the areas of FDG uptake. Volumes are usually within the contrast enhanced area of CT and MRI. The normal brain shows high uptake of FDG in general and makes a clear distinction between tumour and normal brain difficult.

FDG or ^{11}C-MET on PET was seen in 86% of the targets, leading to a change in target volume in these cases in 69% compared to MRI delineation (34). In 36% of these patients the PET based volume was fully encompassed with the MRI based volume, while in 18 cases, PET showed a target volume outside the MRI-based delineation.
Using ^{18}F-FDG PET, in 22 out of 27 patients with glioblastoma, the tumour volumes were at least 25% smaller on ^{18}F-FDG PET than on MRI (35). Occasionally there was FDG uptake outside the region with gadolinium enhancement on MRI. Another study confirmed a decrease in mean volumes on ^{18}F-FDG PET than identified on MRI (T1-weighted images with gadolinium) (32).
In contrast, an increase in gross tumour volume with the use of ^{11}C-MET in 79% of the patients compared to MRI was reported (36). This was confirmed by another study (37). A first study with patients with recurrent high grade gliomas re-irradiated using ^{11}C-MET PET based tumour delineation for radiotherapy treatment planning compared to patients planned on CT/MRI images showed an improvement in survival (38). Whether ^{11}C-MET PET defined tumour volumes for radiation planning and, as a consequence, extended radiation fields,

will have a significant influence on outcome in terms of overall survival, has to be proven in future studies.
Additionally, PET can reduce inter-observer variability in delineation of brain tumours. Van Laere et al. compared FDG and ^{11}C-MET PET for the delineation of brain tumours (39). The inter-observer agreement was 100% for ^{11}C-MET PET and 73% for ^{18}F-FDG PET. Many high-grade gliomas show intra-tumour heterogeneity and PET could be used to define tumour regions being at high risk for recurrence. Regions with abnormal tracer uptake (reported for FDG or FET are at risk for first tumour progression and could therefore be a target for dose escalation (40, 41). Areas of FET uptake on FET-PET-CT for radiotherapy planning were being observed up to 20 mm outside the area of gadolinium enhancement on MRI (41).

2.4. Meningioma

A small study of 10 patients treated with fractionated stereotactic radiotherapy showed a significant increase of the gross tumour volume when ^{11}C-MET PET for the tumour delineation was used (42). The addition of ^{11}C-MET PET was beneficial for GTV delineation in all but 3 out of 32 patients. RT planning for skull base meningiomas influenced the GTV, possibly resulting in an increase, as well as in a decrease (43). DOTATOC-PET delivered additional information concerning tumour extension in all investigated patients planned for fractionated stereotactic radiotherapy in meningioma (44). In 73% of the patients the planning tumour volume was significantly modified and in 1 patient no tumour was exactly identified on CT-MRI but was visible on PET.
Another tracer currently being tested is ^{18}F-tyrosine. This tracer is also taken up by meningioma with a tumour to cortex ratio of 2.53 +/- 0.35 (45). The ^{18}F-tyrosine anomalies completely overlapped with the MR image in 54% of the tumours, extended beyond the MRI lesion in 38% of the tumours, and were smaller in 8% of the tumours. Meningiomas of the skull base are clearly visualized using ^{18}F-tyrosine PET, even after radiotherapy.

Conclusions

^{18}F-FDG PET is mainly used in brain tumours for definition of tumour grading and prognosis and differentiation between recurrence and radio-necrosis. Tumour delineation for radiotherapy planning was not substantially influenced as physiologically, the most intense FDG uptake is seen in brain tissue. Therefore, the tracer is not very suitable for the imaging of most intracerebral malignancies.
For low and high grade grade gliomas and meningioma, ^{11}C-MET or other amino acid tracer as for example ^{18}F-tyrosine are currently the first choice tracer in radiotherapy treatment planning. First data have shown a survival advantage for patients with a high grade glioma if ^{11}C-MET PET based radiotherapy planning was used. However, further investigation is needed.

3. Oesophageal carcinoma

PET for defining tumour volumes in oesophageal carcinoma

Nodal target volume

Nodal staging using ^{18}F-FDG PET is limited by local tumour invasion.Consequently, the accuracy of staging regional node metastases decreases with an accuracy rate of 24% to 90% for PET compared with 40% to 73% for CT. The reported sensitivity and specificity of 18F-FDG PET regarding nodal staging was 24% to 72% and 82% to100%, respectively (46-48). Generally, FDG PET has a higher specificity (89% vs 67%) with a lower sensitivity (33% vs 81%) for identifying nodal metastases compared with the use of combined CT/EUS-FNA. The lower sensitivity of ^{18}F-FDG PET for detecting local lymph nodes depends on the limited spatial resolution of PET with a difficulty to discriminate the primary tumour from local, peritumoural lymph nodes.
Vrieze et al assessed lymph node involvement by CT, EUS, and ^{18}F-FDG PET in 30 patients with advanced esophageal carcinoma (49). In 47% of patients, discordance was noted between lymph nodes detected by ^{18}F-FDG PET and by CT/EUS. The authors suggested that irradiated volumes should not be reduced based on negative ^{18}F-FDG PET results, given the false negatives noted in this report. However, they also concluded that ^{18}F-FDG PET demonstrated adequate specificity to conclude that ^{18}F-FDG PET positive disease should be included in the irradiated volume. As these patients received neoadjuvant chemoradiation, no histologic confirmation of discordant findings is possible.

Target volume for the Primary Tumour

Konski et al performed CT and ^{18}F-FDG PET for radiation planning in 25 patients with esophageal carcinoma; 18 of the 25 also had EUS for comparison (50). Mean GTV as determined by CT scan was significantly longer than that determined by ^{18}F-FDG PET. EUS detected more regional adenopathy than both CT and PET. Moureau-Zabotto et al. performed ^{18}F-FDG PET and CT for simulation purposes in 34 patients with esophageal carcinoma (51). Five fiducial markers were used to precisely coregister the CT and ^{18}F-FDG PET images for planning purposes. GTV was reduced in 35% and increased in 21% of patients. Leong et al enrolled 21 esophageal carcinoma patients in a prospective trial to determine effects of PET-CT on delineation of tumour volume for radiation therapy planning (52). PET-CT detected disease in eight patients that was not detected by CT scan: four of these patients were found to have metastatic disease and four had regional nodal disease. In 16 of 21 patients who proceeded to the radiotherapy planning phase of the trial, 69% had PET-CT positive disease that would have been excluded if CT alone had been used for radiation planning.

Do PET scans change the outcome of patients with esophageal cancer treated with radiotherapy?

Well-performed ^{18}F-FDG PET improves the selection of

patients with oesophageal cancer for potentially curative surgery, especially in stages III-IV (53). This clearly affects patient outcome since it saves an extra complication and mortality risk in individuals who will not benefit form surgery. The incorporation of PET in radiotherapy planning has as previously shown the potential to allow radiation-dose escalation without increasing side-effects, this because of the reduction of radiation fields.

Conclusions

A well performed ^{18}F-FDG PET-CT is important to detect of distant metastases and hence to select patients suitable for local therapy. For the nodal target volume, ^{18}F-FDG PET has a higher specificity with a lower sensitivity compared with the use of combined CT/EUS-FNA. ^{18}F-FDG PET results in a smaller GTV in most of the patients analysed. If validated, the use of ^{18}F-FDG PET might result in a smaller target volume, which would reduce the toxicity or enables radiation dose escalation with the same toxicity.

4. Rectal cancer

PET for defining tumour volumes in rectal cancer (Figure 3)

Nodal target volume

Studies investigating the role of ^{18}F-FDG PET for the initial staging of rectal cancer suggest that PET is useful in the diagnosis of the primary tumour but it is of limited value for detecting regional lymph node metastases, with a sensitivity of only about 30% (54,55). Irradiated volumes should therefore not be reduced based on negative ^{18}F-FDG PET results. However, as the positive predictive value was approximately 90%, ^{18}F-FDG PET positive disease should be included in the irradiated volume.

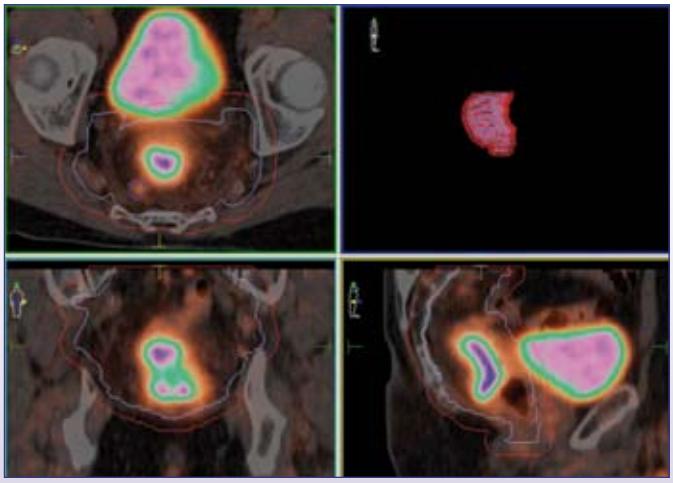


Figure 3.
Delineation of the GTV, CTV and PTV on the basis of a ^{18}F-FDG PET-CT from a patient with a mid rectal cancer. GTV is light brown, the enlarged PET-positive mesorectal lymphnode is blue, the CTV is light blue and the PTV is red.

Target volume for the primary tumour

^{18}F-FDG PET represents the imaging technique of choice to discriminate between benign or malignant tumours of presacral residual postsurgical masses in rectal cancer patients (56), although infection can lead to false positive findings. The data on the use of ^{18}F-FDG PET for radiation planning in rectal cancers is limited. Ciernik et al. evaluated the value of PET-CT on radiation planning for patients with tumours at several sites, including carcinoma of the rectum (6 patients) and carcinoma of the anus (7 patients) (57). The GTV increased in 3 of 6 patients with rectal primaries, with a mean GTV increase of 50% and a planning target volume (PTV) increase of 20%. Several groups have investigated the impact of PET-CT use on the treatment and the radiotherapy volume definitions (57,58). Significant tumourvolume changes were observed. However, even if PET can provide additional functional information, its usefulness in the treatment of rectal cancer is still questionable and needs to be evaluated in prospective trials with strict methodology. Its benefit may be of little interest in preoperative 3D conformal radiotherapy, as the total mesorectum included in the CTV will be surgically removed anyway. But, it may become important when higher doses in relevant biologic regions need to be achieved with boost techniques.

Several studies have demonstrated the substantial variability among radiation oncologists in defining the target volume using CT images. At the time of writing, it remains unclear as to weather PET based delineation accurately represents the real macroscopic tumour extension.

Clinical Target Volume

In general the current treatment regimes for rectal cancer question the additive value for the use of PET-CT in the definition of the CTV, since the total mesorectum included in the CTV will be surgically removed anyway.

Do PET scans change the outcome of patients with rectal cancer treated with radiotherapy?

The incorporation of PET in radiotherapy planning has the potential to allow radiation-dose escalation without increasing side-effects, this because of the reduction of radiation fields. Whether this radiation dose increase will ultimately lead to higher cure rates or less surgical resections with as a result less complications is matter of current research. A more individualized approach based on early treatment response might have the advantage of an response-adjusted radiotherapy treatment with as goal more complete tumour responses. This could than help to avoid unnessary surgical resections, thereby improving outcome and quality of life. Published data indicate that PET-CT has a high predictive value in the therapeutic management of rectal cancer (59,60). This could be an asset for improving patient care by reducing the effort, cost and morbidity assiciated with ineffective treatment in nonresponders. The available studies

on preoperative radiochemotherapy indicate that PET-CT is a significant predictor of therapy outcome and correlates better with pathology than morphologic imaging modalities. Since PET-CT is able to predict the final outcome, it may be used to guide treatment regimens in the near future, thereby better individualizing treatment while improving the outcome of the patients.

Conclusions

Although ^{18}F-FDG PET-CT is of limited value for detecting regional lymph node metastases, its high positive predictive value may change radiation volumes. Although the current radiotherapy treatment of rectal cancer includes the whole mesorectum, which will be surgically removed anyway, future developments may involve ^{18}F-FDG PET in patient selection suitable for non-surgical therapy as well as for more sophisticated radiation treatment delivery.

5. Lymphoma

PET for defining tumour volumes in lymphoma

^{18}F-FDG PET is superior to CT or MRI for the staging of both non-Hodgkin and Hodgkin lymphoma (61). Early assessment of FDG-uptake in the tumour during chemotherapy is highly predictive for subsequent outcome, as is residual FDG avidity after treatment (62-64). With the concept of involved-node irradiation in Hodgkin's disease (65-67), increased interest has emerged to include ^{18}F-FDG PET-scan information for defining target volumes (68). After chemotherapy, the initial ^{18}F-FDG PET helped the delineation of involved-node radiotherapy fields due to the identification of lymph nodes that were undetected on CT in 36% of the patients. Pre-chemotherapy ^{18}F-FDG PET data were thus essential for correctly implementing the involved-node radiotherapy concept.

Do PET scans change the outcome of patients with lymphoma treated with radiotherapy?

No trials have thus far been completed that address this question, but in view of the decreased radiation volumes (65) and at the same time the decreased probability of geographical miss (68), it is very likely that the inclusion of ^{18}F-FDG PET information improves the outcome of patients with Hodgkin's disease.

Conclusions

In Hodgkin's disease, ^{18}F-FDG PET is essential for involved-node irradiation and leads to decreased radiation volumes whilst also decreasing geographical miss.

6. Cervical carcinoma

PET for defining tumour volumes (Figures 4 and 5)

Target volume for primary tumour

The sensitivity of ^{18}F-FDG PET for detecting local disease ranges between 91-100%. Due to the limitations in spatial resolution PET imaging is inaccurate for assessing local tumour extension in to adjacent structures such as the parametrium. For this purpose MRI is the modality of choice (69)

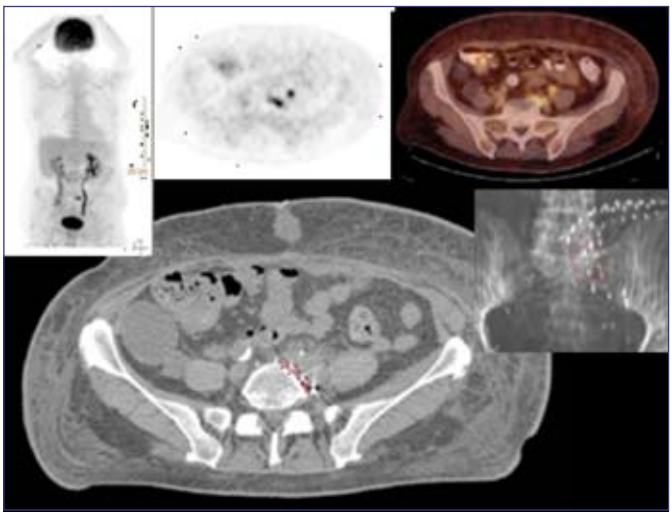


Figure 4.
Cervical cancer. Patient presenting with isolated lymphatic recurrence 15 months following initial treatment with chemo-radiation. Treatment consisted of gross tumour resection with subsequent HDR brachytherapy delivered to the tumourbed.

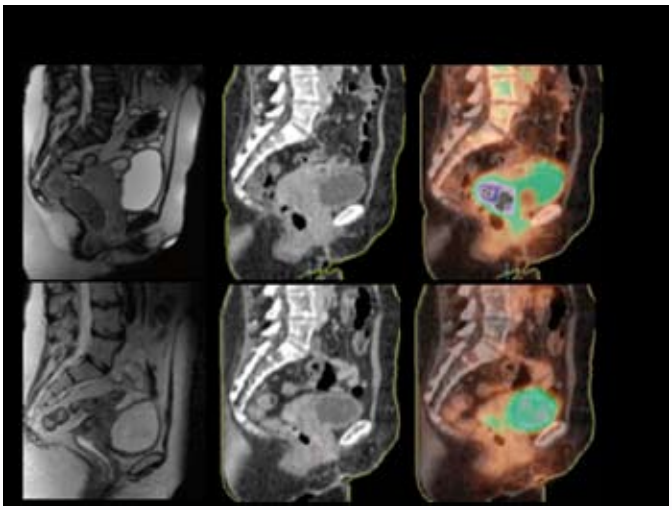


Figure 5.
Tumour response in a patient with cervix carcinoma FIGO stage IVA (extension to bladder) following 50 Gy External Beam Radiation plus Hyperthermia as determined with MRI, CT and ^{18}F FDG PET. Upper row = before, lower row = after therapy.

Nodal target volumes

Due to the small risk of lymphatic spread in early stage cervical cancer, the sensitivity of PET is low (70). In locally advanced cervical carcinoma, biological PET criteria have been demonstrated to be superior to morphologic MRI criteria for assessing retro-peritoneal metastases (71). In case of spread to the para-aortic nodes about one third of the patients may

still be cured following extended field radiotherapy. ^{18}F-FDG PET is the most accurate technique for evaluating para-aortic lymph nodes (73). Identification of gross tumour deposits will change the radiation treatment volume and/or total dose in locally advanced disease.

Do PET scans change the outcome of patients with cervical cancer treated with radiotherapy?

At present, no randomised study has been performed to answer this question. However, in view of the detection of otherwise unrecognised nodal disease in the para-aortic region that can be treated with curative intent with radiation, a significant gain can reasonably be expected.
Although no definite conclusions can yet be drawn on determining cutoff values for SUVmax, integration of SUVmax in clinical studies as an additional prognostic marker seems warranted. So far changes in metabolic response observed during treatment did not correlate with survival outcome whereas post treatment evaluation seems to be a reliable measure for treatment outcome enabling dicision taking regarding additional salvage treatment.

Conclusions

Currently ^{18}F-FDG PET is the imaging modality of first choice for assessing lymphatic spread in locally advanced disease. Its role in providing additional prognostic information with impact on primary treatment decision making need to be evaluated in prospective clinical trials.

7. Head and neck cancer

PET for defining tumour volumes

An in-depth comparison between ^{18}F-FDG PET, MRI and CT scans with the histology of resection specimen showed that ^{18}F-FDG PET may be the most accurate of the three for the detection of head and neck cancer (73). Tumour volume determined by ^{18}F-FDG PET tends to be smaller than the volume determined by the other modalities, but most closely approximates the pathological tumour volume (74). Moreover, some tumour regions that are apparent on CT or MRI may not be imaged on PET, or the reverse may occur. PET-based delineation of the primary tumour is at present not ready for routine clinical practice.

PET for defining nodal volumes

^{18}F-FDG PET often changes the nodal staging in head and neck cancer (75). However, many lymph nodes that are enlarged and considered metastatic by standard CT-based criteria are negative on ^{18}F-FDG PET scan (76). On the other hand, a small proportion of marginally enlarged nodes are positive on ^{18}F-FDG PET scan. However, as the results are largely dependent on the PET segmentation tool used, until proper validation with pathology, ^{18}F-FDG PET cannot be recommended for target volume definition of metastatic lymph nodes in routine practice.

Do PET scans change the outcome of patients with head and neck cancer treated with radiotherapy?

Besides for staging purposes, such as for carcinoma with unknown primary (77), for purely radiotherapy purposes, ^{18}F-FDG PET has not shown to be beneficial for head and neck cancer patients.

Conclusions

^{18}F-FDG PET defined tumour volumes are more closely related to pathology than those for CT and MRI, but both over- and underestimation still occur. Besides for staging purposes, ^{18}F-FDG PET is not recommended for routine radiotherapy delineation purposes.

General conclusions

^{18}F-FDG PET plays an increasingly important role in radiotherapy, beyond staging and selection of patients. Especially for non-small cell lung cancer, ^{18}F-FDG PET has led to the safe decrease of radiotherapy volumes, enabling radiation dose escalation and experimentally, re-distribution of radiation doses within the tumour. In limited-disease small cell lung cancer, the role of ^{18}F-FDG PET is emerging. For low grade glioma's, ^{11}C-MET is the first choice tracer in radiotherapy treatment planning. PET for high-grade glioma's is investigational.
For oesophageal and rectal cancer, the main advantage of ^{18}F-FDG PET is the detection of otherwise unrecognised lymph node metastases. In Hodgkin's disease, ^{18}F-FDG PET is essential for involved-node irradiation and leads to decreased radiation volumes whilst also decreasing geographical miss. ^{18}F-FDG PET its major role in the treatment of cervical cancer with radiotherapy lies in the detection of para-aortic nodes that can be encompassed in radiation fields. Besides for staging purposes, ^{18}F-FDG PET is not recommended for routine radiotherapy delineation purposes.
It should be emphasised that using PET is only safe when strictly standardised protocols are used.

References

1. Boellaard R, Oyen WJ, Hoekstra CJ, Hoekstra OS, Visser EP, Willemsen AT et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. Eur J Nucl Med Mol Imaging. 2008;35:2320-33
2. Senan S, De Ruysscher D, Giraud P, Mirimanoff R, Budach V Radiotherapy Group of European Organization for Research and Treatment of Cancer. Literature-based recommendations for treatment planning and execution for high-precision radiotherapy in lung cancer. Radiother Oncol. 2004;71:139–46
3. van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. Lancet. 2002;359:1388-93
4. Nestle U, Kremp S, Grosu AL. Practical integration of 18F-FDG PET and PET-CT in the planning of radiotherapy for non-small cell

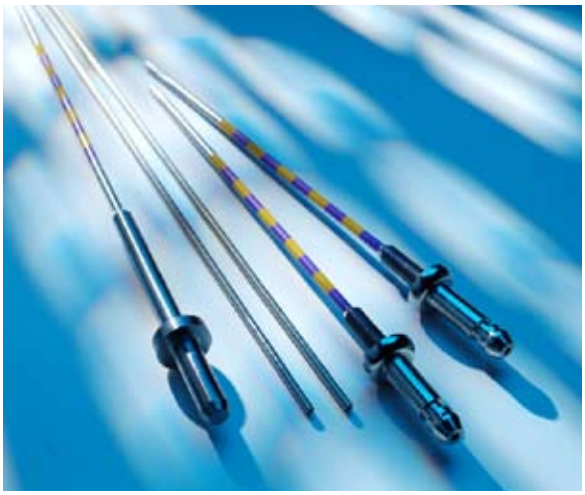
lung cancer (NSCLC): the technical basis, ICRU-target volumes, problems, perspectives. Radiother Oncol. 2006;81:209-25
5. Nestle U, Schaefer-Schuler A, Kremp S, Groeschel A, Hellwig D, Rübe C et al. Target volume definition for 18F-FDG PET-positive lymph nodes in radiotherapy of patients with non-small cell lung cancer. Eur J Nucl Med Mol Imaging. 2007;34:453-62
6. van Der Wel A, Nijsten S, Hochstenbag M, Lamers R, Boersma L, Wanders R et al. Increased therapeutic ratio by 18FDG PET-CT planning in patients with clinical CT stage N2/N3 M0 non-small cell lung cancer (NSCLC): A modelling study. Int J Radiat Oncol Biol Phys. Int J Radiation Oncol Biol Phys. 2005; 61:648-54
7. De Ruysscher D, Wanders S, Minken A, Lumens A, Schiffelers J, Stultiens C et al. Effects of radiotherapy planning with a dedicated combined PET-CT-simulator of patients with non-small cell lung cancer on dose limiting normal tissues and radiation dose-escalation: Results of a prospective study. Radiother Oncol. 2005;77:5-10
8. De Ruysscher D, Wanders S, van Haren E, Hochstenbag M, Geeraedts W, Utama I et al. Selective mediastinal node irradiation on basis of the FDG PET scan in patients with non-small cell lung cancer: A prospective clinical study. Int J Radiat Oncol Biol Phys. 2005;62:988-94
9. Belderbos JS, Heemsbergen WD, De Jaeger K, Baas P, Lebesque JV. Final results of a Phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66:126-34
10. Sura S, Greco C, Gelblum D, Yorke ED, Jackson A, Rosenzweig KE. 18F-fluorodeoxyglucose positron emission tomography-based assessment of local failure patterns in non-small-cell lung cancer treated with definitive radiotherapy. Int J Radiat Oncol Biol Phys. 2008;70:1397-1402
11. van Baardwijk A, Bosmans G, Boersma L, Buijsen J, Wanders S, Hochstenbag M et al. PET-CT-based auto-contouring in non-small-cell lung cancer correlates with pathology and reduces interobserver variability in the delineation of the primary tumour and involved nodal volumes. Int J Radiat Oncol Biol Phys. 2007;68:771-78
12. Stroom J, Blaauwgeers H, van Baardwijk A, Boersma L, Lebesque J, Theuws J et al. Feasibility of pathology-correlated lung imaging for accurate target definition of lung tumours. Int J Radiat Oncol Biol Phys. 2007;69:267-75
13. Schaefer A, Kremp S, Hellwig D, Rübe C, Kirsch CM, Nestle U. A contrast-oriented algorithm for FDG PET-based delineation of tumour volumes for the radiotherapy of lung cancer: derivation from phantom measurements and validation in patient data. Eur J Nucl Med Mol Imaging. 2008;35:1989-99
14. Mah K, Caldwell CB, Ung YC, Danjoux CE, Balogh JM, Ganguli SN et al. The impact of (18)FDG PET on target and critical organs in CT-based treatment planning of patients with poorly defined non-small-cell lung carcinoma: a prospective study. Int J Radiat Oncol Biol Phys. 2002;52:339-50
15. Steenbakkers RJ, Duppen JC, Fitton I, Deurloo KE, Zijp LJ, Comans EF et al. Reduction of observer variation using matched CT-PET for lung cancer delineation: a three-dimensional analysis. Int J Radiat Oncol Biol Phys. 2006;64:435-48
16. Nehmeh SA, Erdi YE, Rosenzweig KE, Schoder H, Larson SM, Squire OD et al. Reduction of respiratory motion artifacts in PET imaging of lung cancer by respiratory correlated dynamic PET: methodology and comparison with respiratory gated PET. J Nucl Med. 2003;44:1644–48
17. Grgic A, Nestle U, Schaefer-Schuler A, Kremp S, Kirsch CM, Hellwig D. FDG PET-Based Radiotherapy Planning in Lung Cancer: Optimum Breathing Protocol and Patient Positioning-An Intraindividual Comparison. Int J Radiat Oncol Biol Phys. 2009;73:103-11
18. Hicks RJ, Kalff V, MacManus MP, Ware RE, Hogg A, McKenzie AF et al. 18F-FDG PET provides high-impact and powerful prognostic stratification in staging newly diagnosed non–small cell lung cancer. J Nucl Med. 2001;42:1596–1604.
19. MacManus MP, Hicks RJ, Matthews JP, Hogg A, McKenzie AF, Wirth A et al. High rate of detection of unsuspected distant metastases by PET in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. Int J Radiat Oncol Biol Phys. 2001;50:287–93.
20. van Baardwijk A, Bosmans G, Boersma L, Wanders S, Dekker A, Dingemans AM et al. Individualized radical radiotherapy of non-small-cell lung cancer based on normal tissue dose constraints: a feasibility study. Int J Radiat Oncol Biol Phys. 2008;71:1394-1401
21. Aerts HJ, Bosmans G, van Baardwijk AA, Dekker AL, Oellers MC, Lambin P et al. Stability of (18)F-Deoxyglucose Uptake Locations Within Tumour During Radiotherapy for NSCLC: A Prospective Study. Int J Radiat Oncol Biol Phys. 2008;71:1402-07
22. Aerts HJ, van Baardwijk AA, Petit SF, Offermann C, Loon JV, Houben R et al. Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy (18) Fluorodeoxyglucose-PET-CT scan. Radiother Oncol. 2009;91:386-92
23. van Loon J, De Ruysscher D, Wanders R, Boersma L, Simons J, Oellers M et al. Selective nodal irradiation on basis of 18FDG PET scans in limited disease small cell lung cancer: A phase II trial. Int J Radiat Oncol Biol Phys. Accepted2009
24. Floeth FW, Sabel M, Stoffels G, Pauleit D, Hamacher K, Steiger HJ et al. Prognostic value of O-(2-18F-fluoroethyl)-L-tyrosine PET and MRI in low-grade glioma. J Nucl Med. 2007;48:519-27
25. Ogawa T, Shishido F, Kanno I, Inugami A, Fujita H, Murakami M et al. Cerebral glioma: evaluation with methionine PET. Radiology. 1993;186:45-53.
26. Nuutinen J, Sonninen P, Lehikoinen P, Sutinen E, Valavaara R, Eronen E et al. Radiotherapy treatment planning and long-term follow-up with 11Cmethionine PET in patients with low-grade astrocytoma. Int J Radiat Oncol Biol Phys. 2000;48:43-52
27. Jacobs AH, Thomas A, Kracht LW, Li H, Dittmar C, Garlip G et al. 18F-fluoro-L-thymidine and 11C-methylmethionine as markers of increased transport and proliferation in brain tumours. J Nucl Med. 2005;46:1948-58
28. Kaschten B, Stevenaert A, Sadzot B, Deprez M, Degueldre C, Del Fiore G et al. Preoperative evaluation of 54 gliomas by PET with fluorine-18-fluorodeoxyglucose and/or carbon-11-

methionine. J Nucl Med. 1998;39:778-85.
29. Levivier M, Massager N, Wikler D, Goldman S. Modern multimodal neuroimaging for radiosurgery: the example of PET scan integration. Acta Neurochir. 2004;91:1-7
30. Levivier M, Massager N, Wikler D, Lorenzoni J. Use of stereotactic PET images in dosimetry planning of radiosurgery for brain tumours: clinical experience and proposed classification. J Nucl Med. 2004;45:1146-55
31. Bergström M, Muhr C, Lundberg PO, Långström B. PET as a tool in the clinical evaluation of pituitary adenomas. J Nucl Med. 1991;32:610-5
32. Gross MW, Weber WA, Feldmann HJ, Bartenstein P, Schwaiger M, Molls M. The value of F-18-fluorodeoxyglucose PET for the 3-D radiation treatment planning of malignant gliomas. Int J Radiat Oncol Biol Phys. 1998;41:989-95
33. Grosu AL, Weber WA, Franz M, Stärk S, Piert M, Thamm R et al. Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumour volume for stereotactic fractionated radiotherapy. Int J Radiat Oncol Biol Phys. 2005;63:511-9
34. Levivier M, Massager N, Wikler D, Lorenzoni J, Ruiz S, Devriendt D et al. Use of stereotactic PET images in dosimetry planning of radiosurgery for brain tumours: clinical experience and proposed classification. J Nucl Med. 2004;45:1146-54
35. Tralins KS, Douglas JG, Stelzer KJ, Mankoff DA, Silbergeld DL, Rostomilly R et al. Volumetric analysis of 18F-FDG PET in glioblastoma multiforme: prognostic information and possible role in definition of target volumes in radiation dose escalation. Nucl Med. 2002;43:1667-73
36. Grosu AL, Piert M, Molls M. Experience of PET for target localisation in radiation oncology. Br J Radiol. 2005:28:8-32
37. Miwa K, Shinoda J, Yano H, Okumura A, Iwama T, Nakashima T et al. Discrepancy between lesion distributions on methionine PET and MR images in patients with glioblastoma multiforme: insight from a PET and MR fusion image study. J Neurol Neurosurg Psychiatry. 2004;75:1457-62
38. Grosu AL, Weber WA, Franz M, Stärk S, Piert M, Thamm R et al. Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumour volume for stereotactic fractionated radiotherapy. Int J Radiat Oncol Biol Phys. 2005;511-9
39. Van Laere K, Ceyssens S, Van Calenbergh F, de Groot T, Menten J, Flamen P et al. Direct comparison of 18F-FDG and 11C-methionine PET in suspected recurrence of glioma: sensitivity, inter-observer variability and prognostic value. Eur J Nucl Med Mol Imaging. 2005;32:39-51
40. Solberg TD, Agazaryan N, Goss BW, Dahlbom M, Lee SP. A feasibility study of 18F-luorodeoxyglucose positron emission tomography targeting and simultaneous integrated boost for intensity-modulated radiosurgery and radiotherapy. J Neurosurg 2004;101:381-89
41. Weber DC, Zilli T, Buchegger F, Casanova N, Haller G, Rouzaud M et al. 18Fluroroethyltyrosine-positron emission tomography-guided radiotherapy for high grade glioma. Radiation Oncology. 2008:3:44
42. Grosu AL, Weber WA, Astner ST, Adam M, Krause BJ, Schwaiger M et al. 11C-methionine PET improves the target volume delineation of meningiomas treated with stereotactic fractionated radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66:339-44
43. Astner ST, Dobrei-Ciuchendea M, Essler M, Bundschuh RA, Sai H, Schwaiger M et al. Effect of 11C-methionine-positron emission tomography on gross tumour volume delineation in stereotactic radiotherapy of skull base meningiomas. Int J Radiat Oncol Biol Phys. 2008;72:1161-7
44. Milker-Zabel S, Zabel-du Bois A, Henze M, Huber P, Schulz-Ertner D, Hoess A et al. Improved target volume definition for fractionated stereotactic radiotherapy in patients with intracranial meningiomas by correlation of CT, MRI, and 68Ga-DOTATOC-PET. Int J Radiat Oncol Biol Phys. 2006;65:222-7
45. Rutten I, Cabay JE, Withofs N, Lemaire C, Aerts J, Baart V et al. PET-CT of skull base meningiomas using 2-18F-fluoro-L-tyrosine: initial report. J Nucl Med. 2007;48:720-5
46. Heeren PA, Jager PL, Bongaerts F, van Dullemen H, Sluiter W, Plukker JT. Detection of distant metastases in esophageal cancer with 18F-FDG PET. J Nucl Med. 2004;45: 980-87
47. Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol. 2000:18:3202-10
48. Räsänen JV, Sihvo EI, Knuuti MJ, Minn HR, Luostarinen ME, Laippala P et al. Prospective analysis of accuracy of PET,CT and EUS in staging of adenocarcinoma of the esophagus and gastroesophageal cancer. Ann Surg Oncol. 2003;10:954-60
49. Vrieze O, Haustermans K, De Wever W, Lerut T, Van Cutsem E, Ectors N et al. Is there a role for FGD-PET in radiotherapy planning in esophageal carcinoma? Radiother Oncol. 2004;73:269-75
50. Konski A, Doss M, Milestone B, Haluszka O, Hanlon A, Freedman G et al. The integration of 18-fluoro-deoxy-glucose positron emission tomography and endoscopic ultrasound in the treatment-planning process for esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2005;61:1123-8
51. Moureau-Zabotto L, Touboul E, Lerouge D, Deniaud-Alexandre E, Grahek D, Foulquier JN et al. Impact of CT and 18F-deoxyglucose positron emission tomography image fusion for conformal radiotherapy in esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2005;63:340-5
52. Leong T, Everitt C, Yuen K, Condron S, Hui A, Ngan SY et al. A prospective study to evaluate the impact of FDG PET on CT based radiotherapy treatment planning for oesophageal cancer. Radiother Oncol. 2006;78:254-61
53. van Westreenen HL, Westerterp M, Sloof GW, Groen H, Bossuyt PM, Jager PL et al. Limited additional value of positron emission tomography in staging oesophageal cancer. Br J Surg. 2007;94:1515-20
54. Abdel-Nabi H, Doerr RJ, Lamonica DM, Cronin VR, Galantowicz PJ, Carbone GM et al. Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. Radiology. 1998;206:755-60

55. Kantorova I, Lipska L, Belohlavek O, Visokai V, Trubac M, Schneiderova M. Routine 18F-FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. J Nucl Med. 2003;44:1784-8
56. Flamen P, Stroobants S, Van Cutsem E, Dupont P, Bormans G, De Vadder N et al. Additional value of whole-body positron emission tomography with fluorine-18–2-fluoro-deoxy-D-glucose in recurrent colorectal cancer. J Clin Oncol. 1999;17:894-901
57. Ciernik IF, Dizendorf E, Baumert BG, Reiner B, Burger C, Davis JB et al. Radiation treatment planning with an integrated positron emission and computer tomography (PET-CT): A feasibility study. Int J Radiat Oncol Bio Phys. 2003;57:853-63
58. Anderson C, Koshy M, Staley C, Esiashvili N, Ghavidel S, Fowler Z et al. PET-CT fusion in radiation management of patients with anorectal tumours. Int J Radiat Oncol Biol Phys. 2007;69:155-62
59. Janssen MHM, Öllers MC, Buijsen J, van de Bogaard J, De Ruysscher D, Lambin P et al. Early metabolic and volume changes in rectal cancer undergoing radiochemotherapy but not radiotherapy alone. Int J Radiat Oncol Biol Phys. 2009 (in press)
60. Capirci C, Rubello D, Pasini F, Galeotti F, Bianchini E, Del Favero G et al. The Role of Dual-Time Combined 18-Fluorideoxyglucose Positron Emission Tomography and Computed Tomography in the Staging and Restaging Workup of Locally Advanced Rectal Cancer, Treated with Preoperative Chemoradiation Therapy and Radical Surgery. Int J Radiat Oncol Biol Phys. 2009 (in press)
61. Divgi C. Imaging: staging and evaluation of lymphoma using nuclear medicine. Semin Oncol. 2005;32:11–8
62. Zijlstra JM, Lindauer-van der Werf G, Hoekstra OS, Hooft L, Riphagen II, Huijgens PC. 18F-fluoro-deoxyglucose positron emission tomography for post-treatment evaluation of malignant lymphoma: a systematic review. Haematologica. 2006;91:522-9
63. Schot BW, Zijlstra JM, Sluiter WJ, van Imhoff GW, Pruim J, Vaalburg W et al. Early FDG PET assessment in combination with clinical risk scores determines prognosis in recurring lymphoma. Blood. 2007;109:486-91
64. Kobe C, Dietlein M, Franklin J, Markova J, Lohri A, Amthauer H et al. Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. Blood. 2008;112:3989-94
65. Yahalom J. Transformation in the use of radiation therapy of Hodgkin lymphoma: new concepts and indications lead to modern field design and are assisted by PET imaging and intensity modulated radiation therapy (IMRT). Eur J Haematol. 2005;66:90-7
66. Girinsky T, van der Maazen R, Specht L, Aleman B, Poortmans P, Lievens Y et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. Radiother Oncol. 2006;79:270-7
67. Eich HT, Müller RP, Engenhart-Cabillic R, Lukas P, Schmidberger H, Staar S et al. Involved-node radiotherapy in early-stage Hodgkin's lymphoma. Definition and guidelines of the German Hodgkin Study Group (GHSG). Strahlenther Onkol. 2008;184:406-10
68. Girinsky T, Ghalibafian M, Bonniaud G, Bayla A, Magne N, Ferreira I et al. Is FDG PET scan in patients with early stage Hodgkin lymphoma of any value in the implementation of the involved-node radiotherapy concept and dose painting? Radiother Oncol. 2007;85:178-86
69. Belhocine T, Thille A, Fridman V, Albert A, Seidel L, Nickers P et al. Contribution of whole-body 18FDG PET imaging in the management of cervical cancer. Gynecol Oncol. 2002;87:90-97
70. Wright JD, Dehdashti F, Herzog TJ, Mutch DG, Huettner PC, Rader JS et al. Preoperative lymph node staging of early-stage cervical carcinoma by 18F-fluoro-2-deoxy-D-glucose-positron emission tomography. Cancer. 2005;104:2484-91
71. Choi HJ, Roh JW, Seo SS, Lee S, Kim JY, Kim SK et al. Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. Cancer. 2006;106:914-22
72. Loft A, Berthelsen AK, Roed H, Ottosen C, Lundvall L, Knudsen J et al. The diagnostic value of PET-CT scanning in patients with cervical cancer: a prospective study. Gynecol Oncol. 2007;106:29-34
73. Nowak B, Di Martino E, Jänicke S, Cremerius U, Adam G, Zimny M et al. Diagnostic evaluation of malignant head and neck cancer by F-18-FDG PET compared to CT-MRI. Nuklearmedizin. 1999;38:312-8
74. Daisne JF, Duprez T, Weynand B, Lonneux M, Hamoir M, Reychler H et al. Tumour volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology. 2004;233:93-100
75. Paulino AC, Koshy M, Howell R, Schuster D, Davis LW. Comparison of CT and FDG PET-defined gross tumour volume in intensity-modulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2005;61:1385–92
76. Schinagl DA, Hoffmann AL, Vogel WV, van Dalen JA, Verstappen SM, Oyen WJ et al. Can FDG PET assist in radiotherapy target volume definition of metastatic lymph nodes in head-and-neck cancer? Radiother Oncol. 2009;91:95-100
77. Johansen J, Buus S, Loft A, Keiding S, Overgaard M, Hansen HS et al. Prospective study of 18FDG PET in the detection and management of patients with lymph node metastases to the neck from an unknown primary tumour. Results from the DAHANCA-13 study. Head Neck 2008;30:471-8

IDB Holland bv

From Atom to Image



YOUR PARTNER IN:

Nuclear Medicine

PET/CT

SPECT/CT

Please visit us at the
EANM 2009 congress
in Barcelona
Booth number: 26
Holland Pavilion

IDB Holland bv
Weverstraat 17
5111 PV Baarle-Nassau
The Netherlands

Tel +31 (0)13 507 9558
Fax +31 (0)13 507 9912
Email Sales@idb-holland.com
Visit www.idb-holland.com

The role of PET in radiotherapy of head and neck cancers

Radboud University Nijmegen Medical Centre,
Institute of Oncology
Departments of Radiation Oncology[1]
and Nuclear Medicine[2], Nijmegen,
The Netherlands

Drs. E.G.C. Troost[1] **Prof. Dr. W.J.G. Oyen[2]** **Prof. Dr. J.H.A.M. Kaanders[1]**

Abstract

Troost EGC, Oyen WJG, Kaanders JHAM. The role of Pet in radiotherapy of head and neck cancers

High quality imaging is a necessity in modern radiotherapy. Positron emission tomography (PET) provides functional information about the tumour, complementary to anatomical imaging by computed tomography (CT) or magnetic resonance imaging (MRI). Integrated PET-CT has found its way into the practice of radiation oncology and 18F-fluorodeoxyglucose ^{18}F-FDG PET is being introduced for radiotherapy planning. In addition to ^{18}F-FDG PET, other PET tracers are available for imaging specific biological tumour characteristics determining radiation resistance. The potential gains of PET imaging are progressively being recognized for head and neck tumours. PET information possibly augments accurate delineation aimed at treating the tumour and its extensions to a high dose while reducing the dose to surrounding healthy tissues. Furthermore, PET may facilitate patient selection for individualized treatment modification based on biological tumour characteristics visualized with different radiopharmaceuticals. Finally, the potential role of PET for adaptive image-guided radiotherapy planning and for early response monitoring during treatment is addressed.

Tijdschr Nucl Geneesk 2009; 31(4):403-410

Radiotherapy for head and neck tumours

Squamous cell carcinomas of the head and neck primarily pose a loco-regional problem requiring a multi-modality therapeutic approach. In many cases, radiotherapy has replaced surgery as prime modality, due to the preference for organ preservation. In order to enhance radiation efficacy, chemotherapy may be added in advanced tumours (1-8). In the 1990s, the field of radiation oncology changed dramatically with the wide introduction of computer optimized intensity-modulated radiation therapy (IMRT). This technique is based on the use of photon beams with optimized non-uniform fluence profiles. IMRT can achieve much better dose conformity than conventional radiotherapy techniques. With this technique, the simultaneous delivery of different dose prescriptions to various target (sub-)sites can be achieved. Certain areas within the gross tumour volume (GTV) can be boosted to higher radiation doses while the dose to radiation sensitive normal tissues adjacent to the tumour is reduced (9,10). Therefore, precise knowledge about the location and boundaries of the primary tumour and cervical lymph node metastases is a prerequisite. For this purpose, biological imaging using positron emission tomography (PET) may augment traditional imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI).

PET for highly accurate radiation treatment planning

1. Identification of tumour spread and metastases formation based on ^{18}F-FDG PET

Recently, a multidisciplinary expert panel developed recommendations on the use of ^{18}F-FDG PET in oncology practice (11). With respect to primary head and neck tumours, the panel concluded that ^{18}F-FDG PET should not be added to clinical examination and anatomical imaging routinely performed in the diagnostic work-up (11). However, these conclusions were drawn after reviewing the available literature, mainly based on stand-alone PET scanning, and thus conclusions may be revised in the coming years with the wide introduction of integrated PET-CT scanning.

Regarding the detection of cervical lymph node metastases, two recent publications revealed contradictory findings. Fletcher et al. concluded that ^{18}F-FDG PET has a higher sensitivity, specificity, positive and negative predictive value compared to CT and MRI, and therefore recommended its use in routine local staging (11). On the contrary, Kyzas et al. performed a meta-analysis reviewing 35 studies on the use of ^{18}F-FDG PET for pre-treatment evaluation of the cervical lymph nodes (12). The authors concluded that there was insufficient solid evidence to support the routine application of ^{18}F-FDG PET,

as the sensitivity and specificity only improved by 5-7% compared to conventional imaging modalities. In the subset of studies only enrolling patients without clinically apparent cervical lymph node metastases, the sensitivity was only 50% and hence not better than conventional imaging methods, specifically ultrasound with fine needle cytology. From these publications it is evident that this unresolved issue requires further study.
For the detection of distant metastases, the net benefit of using ^{18}F-FDG PET was reported to be still uncertain (11). In patients with advanced-stage disease, functional imaging may be beneficial, as the odds of them having distant metastases are greater (11). In these patients, the ^{18}F-FDG PET findings may change the curative treatment intention to a palliative one and thus impact on the fractionation scheme, total radiation dose and hence treatment-related side-effects.

2. ^{18}F-FDG PET for delineation of the radiation therapy target volume

Accurate gross tumour volume (GTV) delineation is crucial in the era of high-precision radiotherapy, taking into account the tumour's boundaries and volume. Target volume delineation is primarily based on anatomical information of the primary tumour and metastatic lymph nodes. A thorough physical examination of the head and neck region is required for assessing the tumour extensions. Anatomical imaging using CT and/or MRI provides important complimentary information by depicting distorted anatomy or regions of abnormal contrast enhancement.
Functional imaging with ^{18}F-FDG PET provides a number of potential advantages for target volume delineation. ^{18}F-FDG PET may reduce the interobserver variability in GTV delineation, reduce the size of the GTV, identify tumour areas or lymph node metastases missed by CT or MRI, and it may identify parts of the GTV potentially requiring an additional radiation dose. However, the limited spatial resolution and the lack of a standardized method for signal segmentation currently hamper the introduction of PET in routine clinical practice.

Although a reduction of the interobserver variability has been demonstrated for non-small cell lung cancer, this finding was less consistent in head and neck cancer patients (13,14). Ciernik et al. studied patients with different primary tumours including the head and neck and found GTV delineation based on ^{18}F-FDG PET-CT to substantially increase or decrease in half of the patients compared with CT alone (15). Riegel et al. found GTVs based on ^{18}F-FDG PET-CT to be larger than the corresponding CT-based volumes, and furthermore observed large inter-observer discrepancy (16). Thresholding of the ^{18}F-FDG PET signal is one important discrepancy between these two studies: the first chose a fixed threshold-level of 50% of the maximum signal intensity, whereas the latter used a discretionary window-level setting (15,16). The issue of segmenting the ^{18}F-FDG PET signal from the background will be addressed in one of the next paragraphs.

A reduction of the GTV using ^{18}F-FDG PET has been demonstrated in a landmark study including laryngeal cancer patients (17). The authors investigated the role of co-registered CT, MRI and ^{18}F-FDG PET in GTV delineation of patients undergoing laryngectomy. Compared to the reference surgical specimen, ^{18}F-FDG PET was closest to depict the true tumour volume. Interestingly, all three imaging modalities failed to identify a small fraction of the macroscopic tumour (approximately 10%) that mainly consisted of superficial mucosal extension.

It is evident that the development and validation of operator-independent PET segmentation tools is compulsory before PET-based GTVs can reliably and reproducibly be incorporated into high-precision radiotherapy planning. The most commonly applied highly operator dependent PET segmentation tool is simple visual interpretation. This approach, however, is very susceptible to the window-level settings of the images and to interpretation differences (16,18,19). Research groups have thus explored more objective methods, such as isocontouring based on a fixed standardized uptake value (SUV) or thresholds acquired through phantom experiments, i.e., a fixed threshold

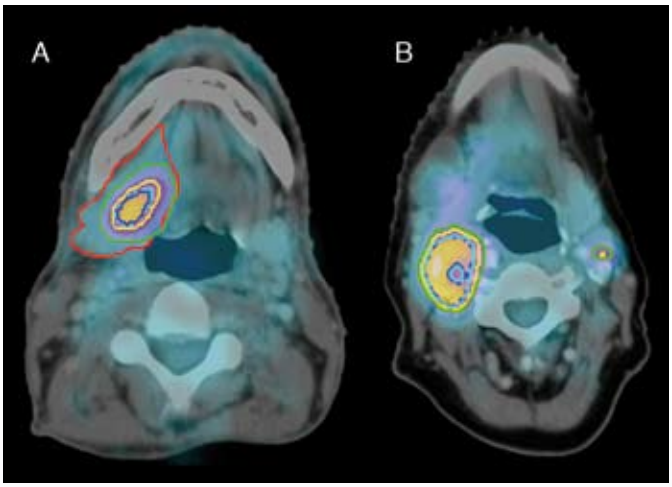


Figure 1.
***A**: Fused ^{18}F-FDG PET-CT image of a patient with a T4N2bM0 oral cavity tumour. The primary tumour was delineated on CT (red), and the PET image was segmented using the visual, operator-dependent method (light green), 40% (yellow) and 50% (blue) of the maximum standardized uptake value (SUV_{max}), and the signal-to-background ratio (skyblue).*
***B**: Fused images of a patient with a T4 oropharyngeal carcinoma showing three lymph nodes. In the left neck, a node measuring 13 mm in shortest axial diameter was visually identified (light green) and also segmented using 40% of the SUV_{max} (yellow). The large, heterogeneous lymph node in the right neck was identified by four techniques: visually, using 40% and 50% (blue) of the SUV_{max}, and by signal-to-background ratio (skyblue). A second metastasis-bearing lymph node in the right neck was not identified by ^{18}F-FDG PET as it bore a large necrotic centre.*

of the maximum tumour signal intensity (40% or 50%) (15,20, 21). Others have developed an adaptive threshold tool based on the signal-to-background ratio (SBR method), a gradient-based segmentation tool, and an iterative background-subtracted relative-threshold level method (22-25).
Schinagl et al. have recently compared five commonly applied methods of ^{18}F-FDG PET signal segmentation for primary head and neck tumours and cervical lymph node metastases (visual interpretation, 40% and 50% of the maximal SUV, fixed SUV of 2.5 and the SBR method, Fig. 1) (26, 27). The shape and volume of the resulting GTVs for both primary tumours and lymph node metastases were heavily influenced by the choice of the segmentation tool. Visual interpretation of the PET signal yielded volumes close to those of CT-based GTV delineation, whereas all automated segmentation methods resulted in significantly smaller GTVs compared to those delineated based on clinical information and CT alone (26, 27). Furthermore, in a large percentage of patients more than 20% of the ^{18}F-FDG PET-delineated GTV for the primary tumour was located outside the GTV based on clinical information and CT (26). This may be the result of tumour extension missed by clinical examination and CT, or by false-positive readings of the ^{18}F-FDG PET signal due to peritumoural inflammation. With respect to the metastatic lymph nodes, the authors additionally concluded that ^{18}F-FDG PET may facilitate dose prescription purposes in marginally enlarged lymph nodes depending on positive or negative ^{18}F-FDG PET readings (27).
From these theoretical studies it is obvious that additional validation studies are needed. Furthermore, clinical trials are required addressing the safety (side-effects) and clinical impact (locoregional control, survival) of incorporating PET information for GTV delineation.

PET may also identify parts of the GTV potentially requiring additional radiation doses. Assuming that ^{18}F-FDG uptake represents areas of high metabolic activity and thus high tumour cell density, it can be used to direct dose escalation to these tumour sub-volumes. Various theoretical planning studies have demonstrated the feasibility of this approach (28, 29). The clinical feasibility and tolerability of dose escalation to ^{18}F-FDG PET defined sub-volumes was recently explored in a phase I clinical trial (30). Forty-one head and neck cancer patients were treated with IMRT to two escalated dose levels (72.5 Gy and 77.5 Gy) using a simultaneous integrated boost (SIB) technique. With SIB, the high dose to the tumour or radioresistant sub-volume is delivered simultaneously with the lower dose to the elective areas as opposed to sequentially. The authors concluded that PET-guided dose escalation appeared to be well-tolerated at both dose levels and reported high local control rates at one year of follow-up (30).

During the course of radiotherapy, the tumour volume gradually decreases and the patient may loose weight. As a consequence, the parotid gland may shift centrally towards the high-dose region (31). As a result, a larger part of the parotid gland is potentially irradiated to a higher dose, which may result in a higher incidence and severity of xerostomia. Especially in oropharyngeal cancer patients, one may consider adjusting the GTV and ultimately the radiotherapy dose distribution accordingly. "Adaptive image-guided radiotherapy" using repetitive PET-CT scanning during the course of treatment is a promising approach to meet this end. A recent proof of principle study using repetitive ^{18}F-FDG PET scanning during the course of radiotherapy revealed that the GTVs significantly decreased and were invariably smaller than those defined on pre-therapeutic anatomical imaging (24). Although the irradiated volumes progressively decreased based on this approach, this only marginally impacted on the doses to the organs at risk, such as the parotid gland. Nevertheless, adaptive ^{18}F-FDG PET guided radiotherapy may be an attractive approach, especially for dose escalation strategies.

In conclusion, ^{18}F-FDG PET can provide important complementary information for radiotherapy planning in head and neck cancer. Based on the PET information, the GTV can potentially be reduced facilitating dose escalation to relatively small subvolumes as well as sparing of nearby normal tissues. Furthermore, the accuracy of GTV definition can be improved based on biological imaging, as ^{18}F-FDG PET may identify areas of tumour spread not recognized by anatomical imaging. However, to address the clinical value and possible shortcomings of these concepts, additional histological validation studies and especially appropriately designed clinical studies are needed.

In the meantime, two studies on clinical treatment outcome after integration of ^{18}F-FDG PET-CT data into IMRT planning have been published. A case-control-study compared 45 advanced stage pharyngeal cancer patients treated with this technique with a matched historical cohort receiving standard three-dimensional conformal radiotherapy (32). The 2-year overall survival and event-free survival rates of patients treated with IMRT were significantly better than for the control group. A similar study also reported favourable results using this approach (33).
However, caution must be taken, as it is unclear whether these encouraging results originate from improved radiation treatment techniques, from the introduction of ^{18}F-FDG PET-CT for treatment planning or from other factors. Additional limitations include the small and diverse cohort, the short follow-up period and the comparison with historical controls.

Molecular imaging for non-invasive tumour characterisation

Tumour cell hypoxia, clonogenic repopulation during the course of treatment and intrinsic radioresistance adversely affect treatment outcome and prognosis after radiation therapy (Fig. 2). Furthermore, numerous membranous tumour receptors and intracellular signalling pathways have been discovered that influence the tumour's response to irradiation. PET enables

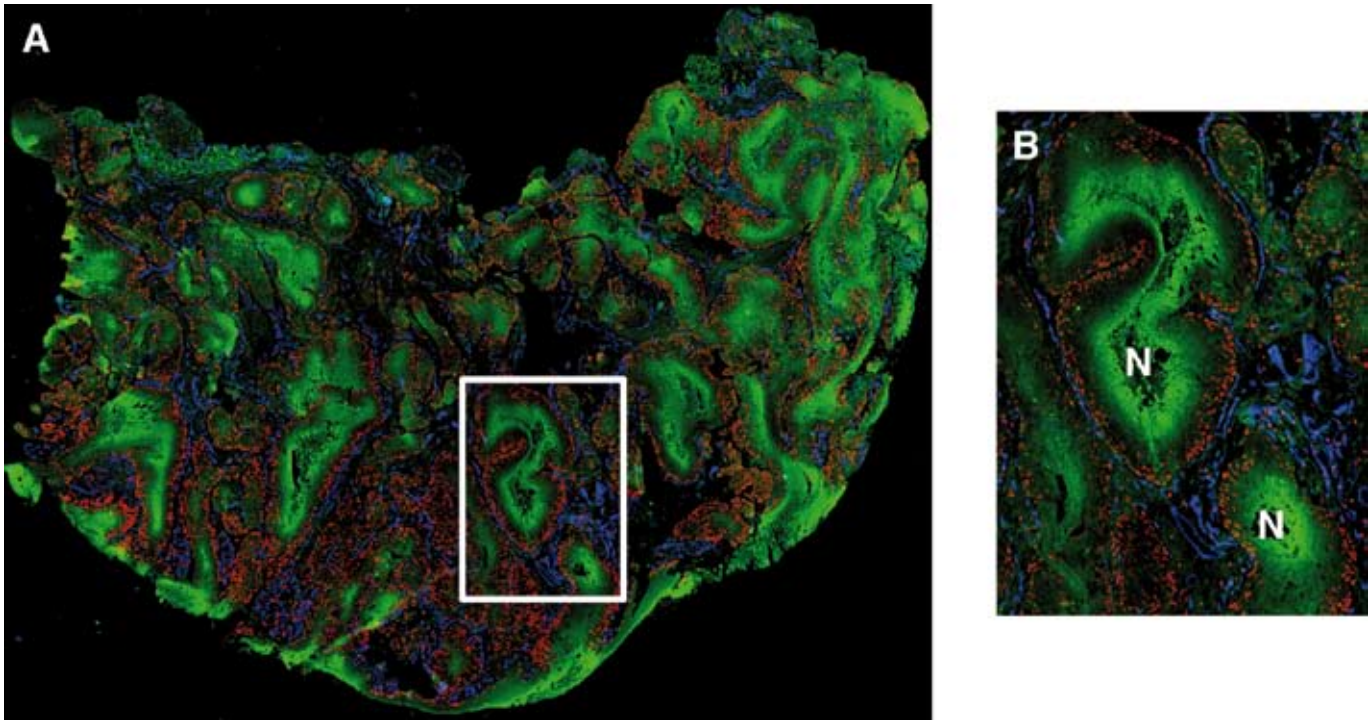


Figure 2.
***A**: Pseudo-coloured image of a biopsy obtained from a laryngeal carcinoma immunohistochemically stained for vessels (blue), tumour cell hypoxia (green) and proliferation (red). **B**: The enlarged detail illustrates the typical distribution of cells, with proliferating tumour cells lining the vasculature, hypoxia at a certain distance from the vessels (typically 150µm) and necrosis (N) at greater distance.*

non-invasive biological profiling of the tumour prior to and during radiation treatment with the potential to tailor therapy according to individual characteristics.

a. Hypoxia

Hypoxia is a common feature in squamous cell carcinomas of the head and neck (34,35). It can result from two mechanisms: impaired perfusion of the supplying vessel due to temporary vasoconstriction or endovascular obstruction (acute hypoxia) or limited diffusion capacity of oxygen due to a large distance from the supplying blood-vessel (chronic hypoxia) (36). Treatment modifications are available, but at the cost of increased morbidity (37,38). Assessment of the tumour oxygenation status is compulsory for the individualization of treatment and for the selection of patients for treatment modifications. In accessible tumours of the head and neck, this can be performed by two invasive procedures: polarographic electrode measurements or immunohistochemical staining of markers in tumour biopsies (39-41). However, there are a number of disadvantages to these procedures, e.g., inability to distinguish hypoxic from necrotic tissue, limitations regarding the spatial information and intravenous administration of exogenous markers for immunohistochemical staining. Non-invasive imaging using PET can provide information on the overall hypoxic status of a tumour and on its intra-tumoural heterogeneity, both before and during treatment. Hypoxia PET imaging can potentially provide a selection instrument for treatment modification and optimize radiotherapy planning and delivery.

The most commonly used hypoxia PETtracer, ^{18}Ffluoromisonidazole (^{18}F FMISO), has been extensively used in head and neck tumours (42-48). ^{18}F-FMISO PET was proven to have prognostic as well as predictive value in this tumour site and may thus serve as treatment selection tool (42,46,49). Apart from tumour characterization, first attempts were made to define hypoxic tumour subvolumes that are radiation resistant and thus requiring higher doses (dose escalation) (50-52). Two theoretical planning studies proved the feasibility of uniform dose escalation to the ^{18}F-FMISO PET detected hypoxic subvolume using IMRT (50, 51). In a third study, Thorwarth et al. compared IMRT planning with dose painting by numbers based on dynamic ^{18}F-FMISO PET data (52). Thereby, spatially variant doses are delivered to the tumour according to dose-escalation factors determined on the bases of the dynamic ^{18}F-FMISO PET scan. With the same level of toxicity, the theoretical tumour control probability was increased from 56% to 70% (52). Until now, clinical experience with hypoxic PET tracers other than ^{18}F FMISO is limited. ^{60}Cu(II)-diacetyl-bis(N^4-methylthiosemicarbazone) (^{60}Cu-ATSM) was the first hypoxia-related PET tracer for which the potential use of a selective boost to the hypoxic subvolume was illustrated (53). This compound is hampered by its limited specificity, especially if

imaging is performed at early time points after administration, and therefore did not find its way in larger scale clinical studies. Only a few studies have addressed the clinical value of new nitroimidazoles, such as ^{18}F-fluoroerythronitroimidazole (^{18}F-FETNIM), ^{18}F-fluoroazomycin arabinoside (^{18}F-FAZA) and ^{18}F-2-(2-nitroimidazol-1-yl)-N-(3,3,3-trifluoropropyl)-acetamide (^{18}F-EF3). In head and neck cancer patients, ^{18}F-FAZA-PET imaging was proven feasible and of sufficient quality for clinical use (54). In a subsequent study, ^{18}F-FAZA-PET was incorporated in radiation treatment planning for the detection of hypoxic sub-volumes and dose escalation purposes (55).

In summary, although several hypoxic or hypoxia-related PET-tracers are available for clinical use, their prognostic and predictive value needs to be assessed in larger clinical studies before implementation for patient selection. Furthermore, a number of unsolved issues must also be addressed, including (1) the possibility of visualizing changes in the oxygenation status caused by treatment modifications counteracting hypoxia, and (2) the limitation in spatial resolution of hypoxic PET imaging.

b. Tumour cell proliferation

Accelerated tumour cell repopulation during the course of radiotherapy adversely affects treatment outcome and prognosis in squamous cell carcinomas of the head and neck (56). 3'-deoxy-3'-^{18}F-fluorothymidine (^{18}F-FLT) is a tracer that non-invasively images DNA synthesis and therefore is more specific for actively dividing cells compared to ^{18}F-FDG (57). ^{18}F-FLT PET was validated against histopathology in a variety of solid tumours (58-60). In primary head and neck tumours, this promising compound has thus far only been applied for the detection of primary laryngeal tumours (61). Validation of ^{18}F-FLT PET in a large series of oral cavity carcinomas is ongoing at our centre. Disappointingly, ^{18}F-FLT PET is not suitable for the detection of cervical lymph node metastases in head and neck tumours due to false-positive readings in reactive lymph nodes (62).

^{18}F-FLT PET it is a promising tracer for early treatment response monitoring and adaptive radiotherapy planning. Until present, adaptive image-guided radiotherapy has been based on repetitive ^{18}F-FLT PET scanning (24). However, the ^{118}F-FLT PET signal is heavily influenced by the inflammatory response of tumour-surrounding tissues hampering segmentation of the primary tumour. The prognostic potential of repetitive ^{18}F-FLT PET imaging and its applicability for tailored treatment are subject of investigation (Fig. 3).

c. Perfusion, protein synthesis and others

Several other PET tracers for non-invasive characterization of squamous cell carcinomas of the head and neck have been studied over the last years. These include ^{15}O-labeled water for imaging perfusion and hypoxia, the amino acid analogues O-2-^{18}F-fluoroethyl-L-tyrosine and L-methyl-^{11}C-methionine for visualization of protein synthesis, and 1-^{11}C-acetate (63-68). In head and neck carcinomas, validation of these tracers visualizing tumour characteristics is required before they can be introduced into clinical practice.

d. Radiolabeled antibodies and small molecules

The use of antibodies and so-called "small molecules" directed against vital signalling pathways of the tumour cell has found its way into cancer therapy. A large randomized phase III trial on advanced stage head and neck tumours provided evidence of the enhanced radiation-efficacy when combining irradiation with cetuximab, an antibody directed against the epidermal growth factor receptor (EGFR) Bonner et al. "Radiotherapy plus

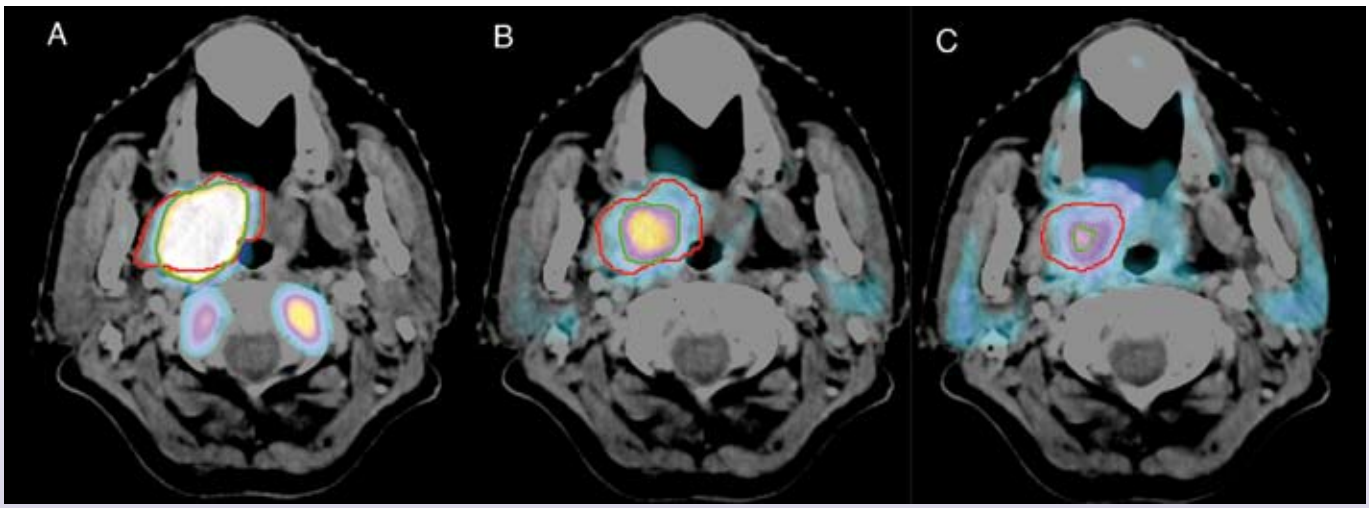


Figure 3.
*Repetitive^{18}F-FLT PET imaging in a T3N0M0 oropharyngeal tumour acquired before (**A**), after 8 (**B**) and after 18 (**C**) fractions of irradiation. Note the slow decrease in CT-delineated tumour volume (red) compared to the early changes in visually delineated PET volume (green; same window-level settings) and PET signal intensity (mean standardized uptake values: 6.0, 2.1 and 1.3, respectively).*

cetuximab for squamous-cell carcinoma of the head and neck". Unfortunately, this treatment modification again bears side-effects. Therefore, tumour characterization and individualization of treatment is necessary. Finally, non-invasive methods to assess the uptake and biodistribution of biological modifiers will be of great value to direct new targeted therapies. Radiolabeled monoclonal antibodies directed against EGFR have been validated in tumour cell lines and xenograft tumour models including squamous cell carcinomas of the head and neck (69-71). Furthermore, ^{89}Zr- and ^{64}Cu-DOTA-labeled monoclonal antibodies directed against the vascular endothelial growth factor receptor have been tested in breast and ovarian cancer tumour models (72,73).

In conclusion, PET tracers imaging specific biological tumour characteristics offer potential for tailor-made radiation therapy. However, they remain in the research arena until proper clinical validation.

Conclusions

For radiotherapy planning in head and neck cancer, ^{18}F-FDG PET may reduce the volume irradiated to high dose levels thereby facilitating normal structures sparing and dose escalation. Tailored therapy has come within reach with the introduction of several PET tracers imaging biological tumour characteristics reflecting radiation resistance mechanisms. However, clinical validation studies addressing the role of PET for treatment planning and tumour characterization are sparse. Moreover, current limitations need to be addressed, e.g., regarding PET-image segmentation, quantification and resolution.

Acknowledgements

This work was supported by EC FP6 funding (Biocare - Contract no. LSHC-CT-2004-505785) and by Junior Investigator Grant 2006-38 of the Radboud University Nijmegen Medical Centre, The Netherlands.

References

1. Adelstein DJ, Leblanc M. Does induction chemotherapy have a role in the management of locoregionally advanced squamous cell head and neck cancer? J Clin Oncol. 2006;24:2624-8
2. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350:1945-52
3. Bernier J, Vermorken JB, Koch WM. Adjuvant therapy in patients with resected poor-risk head and neck cancer. J Clin Oncol. 2006;24:2629-35
4. Brizel DM, Esclamado R. Concurrent chemoradiotherapy for locally advanced, nonmetastatic, squamous carcinoma of the head and neck: consensus, controversy, and conundrum. J Clin Oncol. 2006;24:2612-7
5. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350:1937-44
6. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349:2091-8
7. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. J Clin Oncol. 2006;24:2618-23
8. Parsons JT, Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Villaret DB, et al. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. Cancer. 2002;94:2967-80
9. Hunt MA, Zelefsky MJ, Wolden S, Chui CS, LoSasso T, Rosenzweig K, et al. Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. Int J Radiat Oncol Biol Phys. 2001;49:623-32
10. Kam MK, Chau RM, Suen J, Choi PH, Teo PM. Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation. Int J Radiat Oncol Biol Phys. 2003;56:145-57
11. Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, et al. Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med. 2008;49:480-508
12. Kyzas PA, Evangelou E, Denaxa-Kyza D, Ioannidis JP. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J Natl Canc Inst. 2008;100:712-20
13. Schinagl DA, Kaanders JH, Oyen WJ. From anatomical to biological target volumes: the role of PET in radiation treatment planning. Cancer Imaging. 2006;6:107-16
14. Steenbakkers RJ, Duppen JC, Fitton I, Deurloo KE, Zijp LJ, Comans EF, et al. Reduction of observer variation using matched CT-PET for lung cancer delineation: a three-dimensional analysis. Int J Radiat Oncol Biol Phys. 2006;64:435-48
15. Ciernik IF, Dizendorf E, Baumert BG, Reiner B, Burger C, Davis JB, et al. Radiation treatment planning with an integrated positron emission and computer tomography (PET-CT): a feasibility study. Int J Radiat Oncol Biol Phys. 2003;57:853-63
16. Riegel AC, Berson AM, Destian S, Ng T, Tena LB, Mitnick RJ, et al. Variability of gross tumour volume delineation in head-and-neck cancer using CT and PET-CT fusion. Int J Radiat Oncol Biol Phys. 2006;65:726-32
17. Daisne JF, Duprez T, Weynand B, Lonneux M, Hamoir M, Reychler H, et al. Tumour volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology. 2004;233:93-100
18. Heron DE, Andrade RS, Flickinger J, Johnson J, Agarwala SS, Wu A, et al. Hybrid PET-CT simulation for radiation treatment planning in head-and-neck cancers: a brief technical report. Int J Radiat Oncol Biol Phys. 2004;60:1419-24
19. Nishioka T, Shiga T, Shirato H, Tsukamoto E, Tsuchiya K, Kato T, et al. Image fusion between 18FDG PET and MRI-CT for radiotherapy planning of oropharyngeal and nasopharyngeal carcinomas. Int J Radiat Oncol Biol Phys. 2002;53:1051-7
20. Nestle U, Kremp S, Schaefer-Schuler A, Sebastian-Welsch C,

Hellwig D, Rube C, et al. Comparison of different methods for delineation of 18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-small cell lung cancer. J Nucl Med. 2005;46:1342-8
21. Paulino AC, Koshy M, Howell R, Schuster D, Davis LW. Comparison of CT- and FDG PET-defined gross tumour volume in intensity-modulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2005;61:1385-92
22. Daisne JF, Sibomana M, Bol A, Doumont T, Lonneux M, Gregoire V. Tri-dimensional automatic segmentation of PET volumes based on measured source-to-background ratios: influence of reconstruction algorithms. Radiother Oncol. 2003;69:247-50
23. Geets X, Lee JA, Bol A, Lonneux M, Gregoire V. A gradient-based method for segmenting FDG PET images: methodology and validation. Eur J Nucl Med Mol Imaging. 2007;34:1427-38
24. Geets X, Tomsej M, Lee JA, Duprez T, Coche E, Cosnard G, et al. Adaptive biological image-guided IMRT with anatomic and functional imaging in pharyngo-laryngeal tumours: impact on target volume delineation and dose distribution using helical tomotherapy. Radiother Oncol. 2007;85:105-15
25. van Dalen JA, Hoffmann AL, Dicken V, Vogel WV, Wiering B, Ruers TJ, et al. A novel iterative method for lesion delineation and volumetric quantification with FDG- PET. Nucl Med Commun. 2007;28:485-93
26. Schinagl DA, Vogel WV, Hoffmann AL, van Dalen JA, Oyen WJ, Kaanders JH. Comparison of five segmentation tools for 18F-fluoro-deoxy-glucose-positron emission tomography-based target volume definition in head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;69:1282-9
27. Schinagl DA, Hoffmann AL, Vogel WV, van Dalen JA, Verstappen SM, Oyen W, et al. Can FDG PET assist in radiotherapy target volume definition of metastatic lymph nodes in head-and-neck cancer? Radiat Oncol. 2009;91:95-100
28. Schwartz DL, Ford EC, Rajendran J, Yueh B, Coltrera MD, Virgin J, et al. FDG PET-CT-guided intensity modulated head and neck radiotherapy: a pilot investigation. Head Neck. 2005;27:478-87
29. Vanderstraeten B, Duthoy W, De Gersem W, De Neve W, Thierens H. 18Ffluoro-deoxy-glucose positron emission tomography (18FFDG PET) voxel intensity-based intensity-modulated radiation therapy (IMRT) for head and neck cancer. Radiother Oncol. 2006;79:249-58
30. Madani I, Duthoy W, Derie C, De Gersem W, Boterberg T, Saerens M, et al. Positron emission tomography-guided, focal-dose escalation using intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;68:126-35
31. Barker JL, Jr., Garden AS, Ang KK, O'Daniel JC, Wang H, Court LE, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. Int J Radiat Oncol Biol Phys. 2004;59:960-70
32. Rothschild S, Studer G, Seifert B, Huguenin P, Glanzmann C, Davis JB, et al. PET-CT staging followed by Intensity-Modulated Radiotherapy (IMRT) improves treatment outcome of locally advanced pharyngeal carcinoma: a matched-pair comparison. Radiat Oncol. 2007;2:22
33. Vernon MR, Maheshwari M, Schultz CJ, Michel MA, Wong SJ, Campbell BH, et al. Clinical outcomes of patients receiving integrated PET-CT-guided radiotherapy for head and neck carcinoma. Int J Radiat Oncol Biol Phys. 2008;70:678-84
34. Brizel DM, Sibley GS, Prosnitz LR, Scher RL, Dewhirst MW. Tumour hypoxia adversely affects the prognosis of carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 1997;38(2):285-9.
35. Hockel M, Schlenger K, Mitze M, Schaffer U, Vaupel P. Hypoxia and Radiation Response in Human Tumours. Sem Rad Oncol. 1996;6:3-9
36. Thomlinson RH, Gray LH. The histological structure of some human lung cancers and the possible implications for radiotherapy. Br J Cancer. 1955;9:539-49
37. Kaanders JH, Pop LA, Marres HA, Bruaset I, van den Hoogen FJ, Merkx MA, et al. ARCON: experience in 215 patients with advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2002;52:769-78
38. Overgaard J, Hansen HS, Overgaard M, Bastholt L, Berthelsen A, Specht L, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. Radiother Oncol. 1998;46:135-46
39. Bussink J, Kaanders JH, van der Kogel AJ. Tumour hypoxia at the micro-regional level: clinical relevance and predictive value of exogenous and endogenous hypoxic cell markers. Radiother Oncol. 2003;67:3-15
40. Kaanders JH, Wijffels KI, Marres HA, Ljungkvist AS, Pop LA, van den Hoogen FJ, et al. Pimonidazole binding and tumour vascularity predict for treatment outcome in head and neck cancer. Cancer Res. 2002;62:7066-74
41. Nordsmark M, Loncaster J, Chou SC, Havsteen H, Lindegaard JC, Davidson SE, et al. Invasive oxygen measurements and pimonidazole labeling in human cervix carcinoma. Int J Radiat Oncol Biol Phys. 2001;49:581-6
42. Eschmann SM, Paulsen F, Reimold M, Dittmann H, Welz S, Reischl G, et al. Prognostic impact of hypoxia imaging with 18F-misonidazole PET in non-small cell lung cancer and head and neck cancer before radiotherapy. J Nucl Med. 2005;46:253-60
43. Gagel B, Reinartz P, Dimartino E, Zimny M, Pinkawa M, Maneschi P, et al. pO(2) Polarography versus positron emission tomography 18F fluoromisonidazole, 18F-2-fluoro-2'-deoxyglucose). An appraisal of radiotherapeutically relevant hypoxia. Strahlenther Onkol. 2004;180:616-22
44. Hicks RJ, Rischin D, Fisher R, Binns D, Scott AM, Peters LJ. Utility of FMISO PET in advanced head and neck cancer treated with chemoradiation incorporating a hypoxia-targeting chemotherapy agent. Eur J Nucl Med Mol Imaging. 2005;32:1384-91.
45. Rajendran JG, Mankoff DA, O'Sullivan F, Peterson LM, Schwartz DL, Conrad EU, et al. Hypoxia and glucose metabolism in malignant tumours: evaluation by 18Ffluoromisonidazole and 18Ffluorodeoxyglucose positron emission tomography imaging. Clin Cancer Res. 2004;10:2245-52
46. Rischin D, Hicks RJ, Fisher R, Binns D, Corry J, Porceddu S, et al. Prognostic significance of 18F-misonidazole positron emission

tomography-detected tumour hypoxia in patients with advanced head and neck cancer randomly assigned to chemoradiation with or without tirapazamine: a substudy of Trans-Tasman Radiation Oncology Group Study 98.02. J Clin Oncol. 2006;24:2098-104
47. Thorwarth D, Eschmann SM, Paulsen F, Alber M. A kinetic model for dynamic 18F-Fmiso PET data to analyse tumour hypoxia. Phys Med Biol. 2005;50:2209-24
48. Thorwarth D, Eschmann SM, Holzner F, Paulsen F, Alber M. Combined uptake of 18FFDG and 18FFMISO correlates with radiation therapy outcome in head-and-neck cancer patients. Radiother Oncol. 2006;80:151-6
49. Thorwarth D, Eschmann SM, Scheiderbauer J, Paulsen F, Alber M. Kinetic analysis of dynamic 18F-fluoromisonidazole PET correlates with radiation treatment outcome in head-and-neck cancer. BMC Cancer. 2005;5:152
50. Lee NY, Mechalakos JG, Nehmeh S, Lin Z, Squire OD, Cai S, et al. Fluorine-18-labeled fluoromisonidazole positron emission and computed tomography-guided intensity-modulated radiotherapy for head and neck cancer: a feasibility study. Int J Radiat Oncol Biol Phys. 2008;70:2-13
51. Rajendran JG, Hendrickson KR, Spence AM, Muzi M, Krohn KA, Mankoff DA. Hypoxia imaging-directed radiation treatment planning. Eur J Nucl Med Mol Imaging. 2006;33:44-53
52. Thorwarth D, Eschmann SM, Paulsen F, Alber M. Hypoxia dose painting by numbers: a planning study. Int J Radiat Oncol Biol Phys. 2007;68:291-300
53. Chao KS, Bosch WR, Mutic S, Lewis JS, Dehdashti F, Mintun MA, et al. A novel approach to overcome hypoxic tumour resistance: Cu-ATSM-guided intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2001;49:1171-82
54. Souvatzoglou M, Grosu AL, Roper B, Krause BJ, Beck R, Reischl G, et al. Tumour hypoxia imaging with 18FFAZA PET in head and neck cancer patients: a pilot study. Eur J Nucl Med Mol Imaging. 2007;34:1566-75
55. Grosu AL, Souvatzoglou M, Roper B, Dobritz M, Wiedenmann N, Jacob V, et al. Hypoxia imaging with FAZA-PET and theoretical considerations with regard to dose painting for individualization of radiotherapy in patients with head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;69:541-51
56. Kim JJ, Tannock IF. Repopulation of cancer cells during therapy: an important cause of treatment failure. Nat Rev Cancer. 2005;5:516-25
57. Shields AF, Grierson JR, Dohmen BM, Machulla HJ, Stayanoff JC, Lawhorn-Crews JM, et al. Imaging proliferation in vivo with F-18FLT and positron emission tomography. Nature Medicine. 1998;4:1334-6
58. Cobben DC, Elsinga PH, Suurmeijer AJ, Vaalburg W, Maas B, Jager PL, et al. Detection and grading of soft tissue sarcomas of the extremities with 18F-3'-fluoro-3'-deoxy-L-thymidine. Clin Cancer Res. 2004;10:1685-90
59. Kenny LM, Vigushin DM, Al-Nahhas A, Osman S, Luthra SK, Shousha S, et al. Quantification of cellular proliferation in tumour and normal tissues of patients with breast cancer by 18Ffluorothymidine-positron emission tomography imaging: evaluation of analytical methods. Cancer Res. 2005;65:10104-12
60. Yap CS, Czernin J, Fishbein MC, Cameron RB, Schiepers C, Phelps ME, et al. Evaluation of thoracic tumours with 18F-fluorothymidine and 18F-fluorodeoxyglucose-positron emission tomography. Chest. 2006;129:393-401
61. Cobben DC, van der Laan BF, Maas B, Vaalburg W, Suurmeijer AJ, Hoekstra HJ, et al. 18F-FLT PET for visualization of laryngeal cancer: comparison with 18F-FDG PET. J Nucl Med. 2004;45:226-31
62. Troost EG, Vogel WV, Merkx MA, Slootweg PJ, Marres HA, Peeters WJ, et al. 18F-FLT PET does not discriminate between reactive and metastatic lymph nodes in primary head and neck cancer patients. J Nucl Med. 2007;48:726-35
63. Balogova S, Perie S, Kerrou K, Grahek D, Montravers F, Angelard B, et al. Prospective Comparison of FDG and FET PET-CT in Patients with Head and Neck Squamous Cell Carcinoma. Mol Imaging Biol. 2008;10:364-73
64. Geets X, Daisne JF, Gregoire V, Hamoir M, Lonneux M. Role of 11-C-methionine positron emission tomography for the delineation of the tumour volume in pharyngo-laryngeal squamous cell carcinoma: comparison with FDG PET and CT. Radiother Oncol. 2004;71:267-73
65. Lehtio K, Oikonen V, Gronroos T, Eskola O, Kalliokoski K, Bergman J, et al. Imaging of blood flow and hypoxia in head and neck cancer: initial evaluation with 15OH2O and 18Ffluoroerythronitroimidazole PET. J Nucl Med. 2001;42:1643-52
66. Pauleit D, Stoffels G, Schaden W, Hamacher K, Bauer D, Tellmann L, et al. PET with O-(2-18F-Fluoroethyl)-L-Tyrosine in peripheral tumours: first clinical results. J Nucl Med. 2005;46:411-6
67. Pauleit D, Zimmermann A, Stoffels G, Bauer D, Risse J, Fluss MO, et al. 18F-FET PET compared with 18F-FDG PET and CT in patients with head and neck cancer. J Nucl Med. 2006;47:256-61
68. Sun A, Sorensen J, Karlsson M, Turesson I, Langstrom B, Nilsson P, et al. 1-11C-acetate PET imaging in head and neck cancer-a comparison with 18F-FDG PET: implications for staging and radiotherapy planning. Eur J Nucl Med Mol Imaging. 2007;34:651-7
69. Aerts HJ, Dubois L, Perk L, Vermaelen P, van Dongen GA, Wouters BG, et al. Disparity between in vivo EGFR expression and 89Zr-labeled cetuximab uptake assessed with PET. J Nucl Med. 2009;50:123-31
70. Cai W, Chen K, He L, Cao Q, Koong A, Chen X. Quantitative PET of EGFR expression in xenograft-bearing mice using 64Cu-labeled cetuximab, a chimeric anti-EGFR monoclonal antibody. Eur J Nucl Med Mol Imaging. 2007;34:850-8
71. Niu G, Li Z, Xie J, Le QT, Chen X. PET of EGFR Antibody Distribution in Head and Neck Squamous Cell Carcinoma Models. J Nucl Med. 2009;50:1116-23
72. Nagengast WB, de Vries EG, Hospers GA, Mulder NH, de Jong JR, Hollema H, et al. In vivo VEGF imaging with radiolabeled bevacizumab in a human ovarian tumour xenograft. J Nucl Med. 2007;48:1313-9
73. Wang H, Cai W, Chen K, Li ZB, Kashefi A, He L, et al. A new PET tracer specific for vascular endothelial growth factor receptor 2. Eur J Nucl Med Mol Imaging. 2007;34:2001-10

iSOFT Radiology:

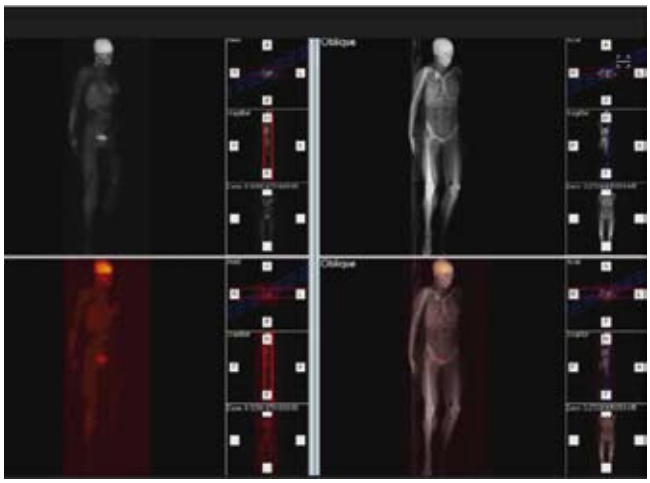
Snelheid en Kwaliteit in Nucleaire Geneeskunde

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 - de opvolger van RADI - 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.

Toekomstbestendige oplossingen
Het belangrijkste doel van het Radiologisch Informatiesysteem (RIS) is een efficiënte en patiëntveilige ondersteuning van het radiologisch werkproces. De nieuwe QualityManager-module verhindert bijvoorbeeld dat er onderzoeksaanvragen zonder gerechtvaardigde indicatie worden uitgevoerd. Met iSOFT Radiology kunt u de structuur en het procesverloop binnen de radiologische afdeling – over meerdere locaties – precies weergeven en waar nodig optimaliseren. Bij deze optimalisatie wordt u geholpen door een speciaal ontwikkelde analyzer die uw managementinformatie in beeld brengt.

Door de uitgebreide configuratiemogelijkheden van de orderformulieren worden overbodige onderzoeken voorkomen en wachttijden verkort. Deze orderformulieren zijn zodanig ingericht dat uw medewerkers zich volledig op hun kerntaak kunnen concentreren. De werkdruk daalt, met name voor de ondersteunende functies. Samen met een goed geïntegreerd PACS, ongeacht van welke leverancier, kan de radioloog vanuit een werkstation onderzoeken beoordelen en verslaan. Het PACS wordt integraal met een digitaal dicteersysteem in de workflow van iSOFT Radiology opgenomen.



Interdisciplinaire data-uitwisseling
Met de ordermodule kan het radiologisch onderzoek vanuit iedere aan het ZIS gekoppelde werkplek worden aangevraagd. Desgewenst zorgt iSOFT voor een naadloze integratie met applicaties op andere afdelingen, om een optimale interdisciplinaire data-uitwisseling te realiseren. Ook externe (huis)artsen kunnen radiologisch onderzoek aanvragen en uitslagen of beelden ontvangen. Alle betrokken partijen worden daarnaast direct geïnformeerd over gewijzigde of geannuleerde afspraken.

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
- Geïntegreerde managementinformatie.
- Digitale opdrachten-, beelden- en uitslagencommunicatie
- QualityManager
- DemoNavigator

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

Hercules op het kruispunt

Dr. W.V. Vogel[1] **Prof. dr. M. Verheij**[2] **Drs. H.J. Teertstra**[3]

[1] *Afdelingen nucleaire geneeskunde*
[2] *Radiotherapie*
[3] *Radiologie*
van het Nederlands Kanker Instituut - Antoni van Leeuwenhoek ziekenhuis (NKI-AVL), Amsterdam.

De historisch verwante vakgebieden radiotherapie, nucleaire geneeskunde en radiologie maken elk een proces van technologische ontwikkeling en modernisering door, en vinden elkaar daarbij op een nieuwe manier. De gecombineerde PET-CT scanner is daar een belangrijke aanjager voor geweest. Maar er is in feite sprake van een veel omvangrijkere evolutie. Gevolg daarvan is dat de radiotherapeut zich opnieuw moet gaan bezinnen wiens advies hij inwint bij het bepalen van een bestralingsveld.

Vrij naar het werk Hercules at the crossroads, Annibale Carracci, ongeveer 1596

Er komt steeds meer gedetailleerde informatie beschikbaar over tumoren en hun biologische gedrag, wat zowel voor de behandeling van tumortypen in het algemeen als voor individuele patiënten van groot belang is. Al deze kennis is verkregen door klinische observaties, histopathologisch onderzoek, profilering van genexpressie, en voor een belangrijk deel door beeldvormend onderzoek. Meer weten is beter: de prognose kan nauwkeuriger worden voorspeld en de keuze voor een behandeling kan beter worden onderbouwd. Inmiddels staan ook nieuwe technieken klaar om in gebruik te worden genomen, waaronder een verscheidenheid aan beeldvorming. Maar niet álle technieken kunnen zonder meer worden toegepast en zeker ook niet op álle patiënten, onder andere uit oogpunt van snelheid, financiën, logistiek, stralings- en patiëntbelasting. De belangrijkste vraag in de komende jaren zal daarom zijn welke informatie, wanneer het meest waardevol is. Elke techniek zal zich moeten bewijzen, en dat geldt ook voor alle toepassingen van PET-CT voor radiotherapie.

Zinvolle toepassing van PET-CT

Functionele beeldvorming van kwaadaardige ziekten is in de afgelopen tien jaar vooral gemeengoed geworden door de grootschalige introductie van de positron emissie tomografie (PET) techniek. Het radioactief gelabeled glucose (FDG) en de daardoor zichtbare metabole tumoreigenschappen hebben een belangrijke toepassing gevonden bij het selecteren van de juiste behandeling voor specifieke patiënten. Maar bij nadere beschouwing zijn niet alle toepassingen even sterk onderbouwd.

Vanuit de radiotherapie bezien speelt PET een grote rol bij de indicatiestelling van de behandeling. Bijvoorbeeld voor het longcarcinoom heeft de verbeterde primaire stadiëring met ^{18}F-FDG PET een grote invloed op de uiteindelijke keuze tussen chirurgie, chemoradiatie met curatieve intentie, of palliatieve chemotherapie. Bij het maligne lymfoom is respons-evaluatie met ^{18}F-FDG PET na chemotherapie bepalend bij de indicatiestelling voor aanvullende bestraling. Deze indicatiestellingen van radiotherapie zijn goed wetenschappelijk onderbouwd en geprotocolleerd, en de verwachting is dat meer toepassingen in deze lijn zullen volgen.

In toenemende mate is niet alleen belangrijk óf, maar ook hóé er wordt bestraald. Technologische ontwikkelingen zoals intensity modulated radiotherapy (IMRT) en image guided radiotherapy (IGRT) hebben een veel nauwkeuriger bestraling mogelijk gemaakt. Met een inhomogeen bestralingsveld (dose painting) kunnen delen van een tumor met een aangepaste dosis worden behandeld. Aan de definitie van het doelgebied worden daarom nieuwe eisen gesteld. ^{18}F-FDG PET kan worden ingezet voor herkenning en afgrenzing van vitale tumormassa's, bij uitstek daar waar de normale omliggende anatomie is verstoord. Omdat het resultaat van bestraling afhangt van de hoeveelheid vitale tumorcellen ter plaatse is deze informatie zeer waardevol. Maar tegelijkertijd is het ook bekend dat microscopische tumoruitbreiding met ^{18}F-FDG PET niet zichtbaar wordt en is evenmin duidelijk of intekenen op geleide van PET tot betere resultaten van de bestraling leidt.

Een bestralingsbehandeling wordt over het algemeen uitgesmeerd over een langere periode (gefractioneerde radiotherapie) om schade aan normale weefsels zoveel mogelijk te beperken. Tijdens deze behandelperiode van soms zes tot acht weken kan de tumor zodanig van vorm, positie en functie veranderen dat dit consequenties heeft voor de dosisverdeling. Het is mogelijk een bestralingsplan gaandeweg de behandeling aan te passen (adaptive radiotherapy; ART). Hiervoor is herhaalde beeldvorming noodzakelijk. Probleem hierbij kan de inflammatie zijn die de herkenning van tumor bemoeilijkt. Op dit moment is er geen onderbouwde inzet van PET tracers mogelijk voor deze toepassing.

Er zijn aanwijzingen dat het resultaat van een bestraling wordt beïnvloed door biologische kenmerken van de bestraalde weefsels, zoals de lokale perfusie, hypoxie, proliferatie, inflammatie, apoptose en necrose. Evaluatie hiervan is niet goed mogelijk met histologische biopten, althans niet voor alle tumordelen en tumorlocaties afzonderlijk, en zeker niet bij herhaling tijdens een behandeling. Hiervoor kan wel functionele beeldvorming worden gebruikt. PET tracers zijn inmiddels beschikbaar voor evaluatie van metabolisme, proliferatie, hypoxie en celdood, maar het is nog niet duidelijk of de toepassing ervan leidt tot meer curatie of langere overleving, en hoe deze tracers zich functioneel gedragen tijdens bestraling. Daarom is inzet van PET tracers voor deze indicaties op dit moment alleen te verantwoorden in studieverband.

Niet alleen PET

Alles bij elkaar, is het duidelijk dat beeldvorming met PET-CT belangrijk is maar niet het enige antwoord kan zijn op alle vragen van de radiotherapeut. Dat ligt voor een deel aan de kenmerken van het PET onderzoek zelf. De spatiële resolutie van de beelden is beperkt, waardoor scherpe afgrenzing van tumorlocaties lastig blijft. PET is voor detectie van microscopische uitbreiding of diffuus infiltratieve tumorlocaties niet goed geschikt. Opname van FDG is niet altijd representatief voor tumoractiviteit, zeker niet tijdens radiotherapie. Ook komen de beelden niet altijd overeen met de bevindingen van histopathologisch of ander onderzoek. ^{18}F-FDG PET is dus geen modaliteit met een gegarandeerde één op één vergelijkbaarheid met de werkelijkheid en met andere onderzoeken. Daarom doet zich de vraag voor of er andere technieken zijn die in bepaalde gevallen de tumor beter beschrijven, die het beloop van radiotherapie beter voorspellen, of waarvan de effectiviteit beter is te onderbouwen.

Veel functionele kenmerken van tumoren kunnen ook worden vastgesteld met beeldvormende technieken zoals dynamische CT en MRI, diffusie-MRI, MRI met gebruik van specifieke tracers zoals microscopische ijzerdeeltjes (USPIO), MR spectroscopie gericht op (de verhoudingen tussen) verschillende weefselcomponenten (MRS), echo Doppler met luchtbelletjes als contrast, en een heel scala aan alternatieve PET en SPECT tracers. Het valt buiten het bestek van dit artikel om alle mogelijke toepassingen en waarden van deze technieken voor de radiotherapie te bespreken. Het kan echter zeker wel zinvol zijn om diagnostische informatie te verkrijgen met een betere resolutie, lagere stralingsbelasting, kortere wachttijd en lagere kostprijs dan PET.

Net zoals bij PET, is van de verschillende radiologische technieken nog niet altijd even duidelijk wat hun waarde voor specifieke toepassingen in de radiotherapie is. Daarnaast is nog niet voor elke techniek de optimale uitvoering voor radiotherapie vastgesteld. Als bijvoorbeeld gecombineerde PET-CT wordt gebruikt voor bestraling van een longtumor, moet dan ook de beweging van de tumor in beeld worden gebracht door middel van een 4D-CT scan, wellicht gecombineerd met 4D PET beelden? Als MRI wordt gebruikt voor bestraling van een prostaatcarcinoom, moet dan een endorectale coil worden gebruikt, en intraveneus contrast, of spectroscopie, en voor welke patiënten heeft dat dan zin? Deze veelheid aan technieken en uitvoeringen, met ook nog verschillen tussen de centra onderling, maakt de situatie voor de radiotherapeut onoverzichtelijk. De discussie wat beter is voor radiotherapieplanning, PET of MRI, kan daarom eigenlijk nog niet worden gevoerd.

Een luxeprobleem

De beschikbaarheid van (veel) diagnostische mogelijkheden is een reëel probleem. Soms spreken de verschillende beelden niet alleen de pathologie tegen, maar ook nog elkaar. De man met twee horloges weet nooit precies hoe laat het is. Geef een radiotherapeut alleen een plannings-CT en hij weet precies waar de tumor zit, geef hem daarbij klinische evaluatie, endoscopie, biopten, echo, diagnostische CT, MRI, spectroscopie én PET-CT, en hij zal meer moeite hebben de informatie te integreren en te benutten.

Het is belangrijk het toekomstperspectief te voorkomen van de radiotherapeut "in een snoepwinkel" waar deze naar persoonlijke smaak uit een kleurig spectrum van scans kan kiezen. Een doemscenario is de radiotherapeut als Hercules op het kruispunt van mogelijkheden, waar rechts de radioloog de aantrekkingskracht van MRI bejubelt en links de nucleair geneeskundige suikerzoete PET beelden aanprijst, terwijl de voortgang wordt vertraagd doordat de behandelaar niet kan kiezen of juist alle wegen bewandelt. Deze weg zal leiden tot verschillen tussen centra, gebaseerd op enthousiasme en overtuigingskracht, in plaats van op evidence based medicine.

Behandeling met radiotherapie is uitstekend geprotocolleerd en gevalideerd, en daardoor goed vergelijkbaar tussen behandelcentra onderling. Deze eigenschap moet als een schat worden bewaakt. Dat betekent dat de beeldvormende instrumenten die worden gebruikt voor indicatiestelling, planning en monitoring van radiotherapie ook moeten worden gevalideerd, en opgenomen in landelijke protocollen die worden gedragen door de vakverenigingen van radiotherapie, radiologie en nucleaire geneeskunde.

Hoe nu verder?

De basis van een bestralingsveld blijft vooralsnog anatomische beeldvorming met CT, om de plaats van gezonde en maligne weefsels vast te stellen en de verzwakking van de bestralingsbundels te kunnen berekenen. Hieraan wordt steeds vaker MRI toegevoegd wegens de goede anatomische visualisatie. Voor functionele informatie is het nog de vraag welke beeldvormende technieken hieraan kunnen worden toegevoegd met een voldoende betrouwbare anatomische oriëntatie, met een goed reproduceerbaar signaal, met bekende correlatie met histopathologie en andere onderzoeken, tegen een goede prijs, met zo min mogelijk stralingsbelasting, voor een groep patiënten die daarvan voordeel ondervindt qua response (curatie of ziektevrije overleving) en bijwerkingen (kwaliteit van leven).

Dat betekent wetenschappelijk onderzoek. De eerste stappen hiervoor zijn inmiddels gezet, en daarvan hebt u uitstekende voorbeelden kunnen lezen in deze uitgave. De techniek van multimodality beeldvorming voor radiotherapie heeft men inmiddels goed onder de knie, en de eerste ervaringen met PET en MRI in klinische series zijn veelbelovend. Om grootschalige (landelijke) introductie van PET voor radiotherapie verder te rechtvaardigen is grootschalig onderbouwend onderzoek nodig, waarbij de nadruk ligt op onderlinge vergelijking van de beschikbare technieken en op de voordelen voor patiënten op de lange termijn. Geen afdeling kan dat alleen, en waarschijnlijk ook geen centrum alleen. Daarom moet de weg gezocht worden in samenwerking, voor multicenter onderzoek en het ontwikkelen van klinische protocollen.

De route naar gevalideerde image and biology guided radiotherapy zal lang en niet eenvoudig zijn, maar de radiotherapeut, de nucleair geneeskundige en de radioloog hebben hierbij in onze beleving wel een gemeenschappelijk belang. Hercules koos de moeilijkste weg, maar die bracht hem wel het verst.

EXPERTS IN RADIATION PROTECTION

COMECER®
SAFETY FIRST

ELFO
mobile automatic injection system

ALTHEA
automatic fractioning system

One supplier for all!

- Hot Cells for GMP production & research
- Automatic dispensing systems
- Automatic injection systems
- Validation and Qualification for GMP lab in compliance with pharmacopoeia
- Environmental monitoring systems
- Air compressing stations
- Furnishing and accessories
- Cyclotron bunker doors
- Customized projects

COMECER S.p.A.
Via Emilia Ponente 390, 48014 Castel Bolognese (RA)
Italy Tel. +39-0546656375 Fax +39-0546656353
E-mail: comecer@comecer.com

Your local contact
A.M. van Gaans T: +31 (0)30 220 5154 E-mail: comecer@vangaans.nl

www.comecer.com

Dr. I.M.C. van der Ploeg

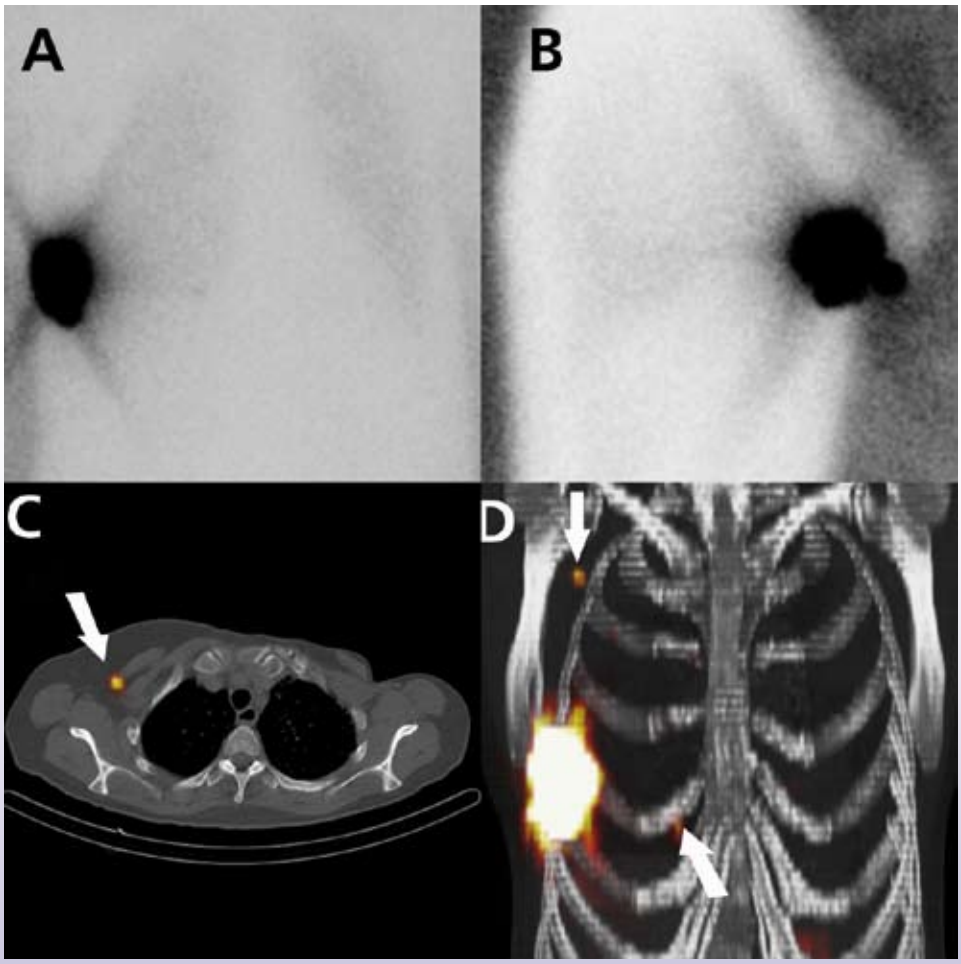
10 juni 2009
Universiteit van Amsterdam

Promotor:
Prof. dr. B.B.R. Kroon

Co-promotores:
Dr. R.A. Valdés Olmos,
Dr. O.E. Nieweg

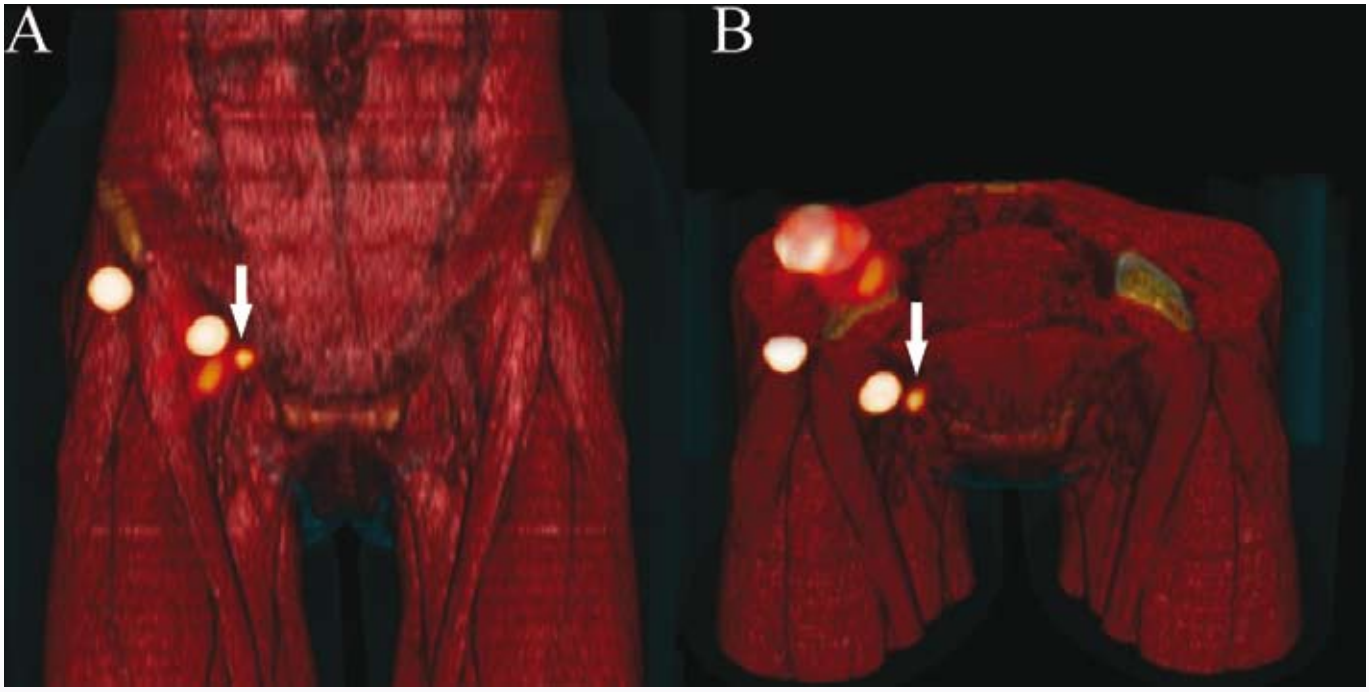
Op zoek naar de schildwachtklier

Een systematisch literatuuronderzoek van 48 studies met in totaal 14.959 schildwachtklier-negatieve mammacarcinoompatiënten die gedurende een mediane periode van 34 maanden gevolgd werden liet een mediaan, gewogen axillair lymfkliercrecidiefpercentage van 0,3% zien. Schildwachtklierbiopsie lijkt dus een veilige stadiëringsmethode voor mammacarcinoompatiënten. Het opsporen en verwijderen van schildwachtklieren buiten de oksel kan de stadiëring verbeteren, maar hier lijkt de procedure minder sensitief dan in de oksel. Mammacarcinoompatiënten bij wie lymfoscintigrafie en operatieve exploratie uitsluitend drainage naar buiten de oksel gelegen klieren laat zien kan wellicht een okselkliердissectie bespaard blijven. Na eerdere behandeling van de borst of oksel kan het lymfdrainagepatroon veranderd zijn. In een dergelijke situatie wordt vaker geen schildwachtklier waargenomen. Ook worden schildwachtklieren frequenter buiten de oksel gezien. Het verwijderen van schildwachtklieren buiten de oksel verbetert de stadiëring, maar de gevoeligheid lijkt minder goed dan voor klieren in de oksel.
Bij melanoompatiënten hebben wij geconcludeerd dat de invasiediepte vanaf het kapsel en de diameter van een schildwachtkliermetastase het best correleren met de



Figuur 1.
Een patiënt met een tumor in de rechter borst waar bij conventionele lymfoscintigrafie (A+C) geen evidente (axillaire) drainage laat zien. Een axiale SPECT-CT opname (B) laat een axillaire schildwachtklier (pijl) zien. De 3D gefuseerde SPECT-CT opname (D) laat daarnaast nog een parasternale schildwachtklier (opwaartse pijl) zien net onder de vierde rib.

aanwezigheid van additionele lymfkliermetastasen. De overleving wordt het best voorspeld door de invasiediepte van de metastase. Het lijkt juist een complementerende dissectie achterwege te laten bij patiënten met een schildwachtkliermetastase met een invasiediepte tot 0,4 mm. De uitgebreidheid van een complementerende liesklierdissectie bij schildwachtklier-positieve melanoompatiënten kan worden bepaald aan de hand van de ligging van de schildwachtklieren en tweede-echelon klieren. De tweede Multicenter Selective Lymphadenectomy Trial zal uitwijzen wat het nut is van een aanvullende klierdissectie in geval van een tumorpositieve schildwachtklier. Verwijzing van patiënten voor deze studie wordt op prijs gesteld.
De hybride SPECT-CT heeft de potentie om fusie van beeldvormingstechnieken mogelijk te maken in de dagelijkse praktijk. SPECT-CT is van aanvullende waarde bij lymphatic mapping bij mammacarcinoom- en melanoompatiënten. SPECT-CT laat de anatomische positie van schildwachtklieren nauwkeuriger zien dan conventionele scintigrammen. SPECT-CT maakt meer schildwachtklieren zichtbaar dan conventionele lymfoscintigrafie en kan ook een klier zichtbaar maken als de conventionele afbeeldingen geen drainage laten zien. Deze voordelen kunnen leiden tot een meer passende chirurgische benadering van de patiënt. SPECT-CT is aangewezen bij patiënten bij wie het conventionele lymfoscintigram geen schildwachtklieren laat zien of het drainagepatroon onduidelijk is. Het verdient aanbeveling om de oksel te exploreren met behulp van patentblauw en de gammastralendetectieprobe bij patiënten bij wie ook SPECT-CT geen schildwachtklier laat zien.



Figuur 2.
Een patiënt met een melanoom laag op de rug. Een anterieure 3D SPECT-CT opname (A) en een caudale SPECT-CT opname (B) laten twee schildwachtklieren en een tweede-echelon klier (neerwaartse pijl) in de lies zien. De meest laterale schildwachtklier in de latero-craniale zone is lateraal gelegen van de spina iliaca anterior, een bijzondere locatie.

Modernisering van de opleiding nucleaire geneeskunde; komt er nog wat van?

Prof. dr. B.L.F van Eck-Smit
Secretaris onderwijs en wetenschap NVNG

Modernisering: waarom?

Er zijn 2 belangrijke redenen om de opleiding nucleaire geneeskunde tegen het licht te houden en aan te passen aan de eisen van de huidige tijd. Ten eerste heeft de overheid enkele jaren geleden het initiatief genomen om in de medische opleidingen het competentiegericht leren te introduceren. Dat wil zeggen dat het accent van de opleiding van het vergaren van zoveel mogelijk vakkennis en handvaardigheid is verschoven naar het vormen van de professional in 7 competentiegebieden; medisch handelen, communiceren, samenwerken, organiseren, kennis & wetenschap, maatschappelijk handelen en professionaliteit. Inmiddels hebben veel van onze zusterspecialismen het opleidingscurriculum grondig hervormd en is er een begin gemaakt met de implementatie ervan. Een tweede en minstens zo belangrijke reden is de ontwikkeling van het vakgebied nucleaire geneeskunde. De intrede van Multi-Modale (MM) beeldvorming en het belang van moleculaire informatie bij de behandeling van ziekte heeft ons specialisme een enorme verbreding gegeven. Voor deze verbreding is in het huidige curriculum te weinig ruimte. Een levend bewijs hiervoor is het initiatief van een aantal nucleair geneeskundigen om na het afronden van hun opleiding aan een aanvullende opleiding radiologie te beginnen. Op deze wijze geven zij zelf en ieder op een eigen wijze invulling aan hun vorming tot expert op het gebied van MM beeldvorming. Dat dit geen optimale situatie is, spreekt voor zich. Hoog tijd dus om de opleiding nucleaire geneeskunde aan te passen aan de stand van de techniek en de huidige plaats van moleculaire en MM beeldvorming in de geneeskunde.

Modernisering: wat gaat er veranderen?

De inhoud

Binnen de opleiding krijgt training in radiologische technieken en MM beeldvorming een belangrijkere rol. Hiertoe wordt de opleiding, mits het ministerie van VWS het toestaat, verlengd van een 4-jarige opleiding naar een 5-jarige opleiding. Hiervan is 9 maanden gereserveerd voor klinische vorming en 12 maanden voor opleiding in radiologische technieken en MM beeldvorming. De klinische vorming wordt een vooropleiding, zoals dat ook het geval is bij andere specialismen die een periode van algemene klinische vorming in de opleiding kennen. Verder zal de aios ook een periode van maximaal 6 maanden in een andere opleidingskliniek doorbrengen om zo de verschillen in patiëntenpopulaties en bedrijfsvoering te kunnen ervaren. Tot slot is er voor de aios de mogelijkheid om een verdiepingsstage van minimaal 3 en maximaal 6 maanden te volgen in het laatste jaar van de opleiding. Deze stage is bedoeld voor het ontwikkelen van een aandachtsgebied en kan deels ook aan extra klinische vorming besteed worden. Het niveau-3 examen blijft ongewijzigd maar moet wel behaald worden in het eerste deel van de opleiding en geldt dan ook als voorwaarde om de opleiding te mogen voortzetten.

De vorm

Trefwoorden bij de nieuwe vorm van opleiden zijn "competentiegericht" en "actief". Aandacht voor de vorming van de aios op andere gebieden dan alleen vakkennis is de basis van het nieuwe opleiden. Naast de competenties die voor alle medisch specialisten gelden en zijn vastgelegd in 28 basiscompetenties (4 in ieder van de 7 competentiegebieden) zijn er ook competenties geformuleerd die specifiek zijn voor de nucleair geneeskundige. Deze verzameling van competenties wordt opgenomen in het nieuwe specifieke besluit "Besluit Nucleaire geneeskunde". Dit Besluit is een reglement waarin specifieker dan in het "Kaderbesluit CCMS" beschreven staat wat de rechten en plichten zijn van de opleidingsinrichting, de opleiders c.q. opleidingsgroep en de aios. Het Kaderbesluit is een overkoepelend reglement dat voor ieder specialisme geldt. De specifieke besluiten zijn de invulling ervan voor het betreffende specialisme.

Het tweede trefwoord "actief", heeft betrekking op de manier waarop van de aios verwacht wordt zijn/haar opleiding te volgen en vorm te geven. Opleiden tot zelfstandigheid en met eigen verantwoordelijkheid. Van het opleidingsteam wordt verwacht dat de aios de ruimte krijgt om zijn opleiding binnen de regels en de mogelijkheden zelf vorm te geven. Natuurlijk ontslaat dit het opleidingsteam niet van de verplichting om de aios intensief te begeleiden en zelfs meer gestructureerd dan voorheen de ontwikkelingen in kaart te brengen en te toetsen.

Het toetsen

Het toetsen moet een tweede natuur van opleidingsgroep en aios worden. Om de ontwikkeling van de competenties van de aios goed in beeld te brengen is het van belang dat er gestructureerd naar deze competenties gekeken wordt. Veelal zijn deze competenties uitsluitend te toetsen door observatie. Niets nieuws, zult u wellicht denken. Een opleider/supervisor

heeft altijd al in de gaten gehad of een aios kon samenwerken met MNW's en collega's of dat hij een hork of een ster was in communiceren naar patiënten en verwijzers. Dat klopt, maar waar het om gaat is dat er bewust en gestructureerd naar deze competenties gekeken wordt om bij te kunnen sturen waar nodig en vrijheden te geven waar mogelijk. Voorbeeld: als supervisor merkt u dat de aios bij patiëntenbesprekingen de vragen uit de zaal niet goed kan beantwoorden. Ligt dit aan gebrek aan kennis, aan communicatieve vaardigheid of aan slechte organisatie (voorbereiding van de patiëntenbespreking)? De betreffende supervisor kon in het verleden volstaan met zich te ergeren, zijn ongenoegen bij de opleider kenbaar te maken of de aios duidelijk te maken dat er nog veel aan schort. In het nieuwe opleiden moet specifiek naar de afzonderlijke competenties gekeken worden en moet dit ook worden vastgelegd in een zogenaamde "korte praktijk beoordeling" (KPB). Terugkoppeling met de aios maakt hiervan deel uit en in totaal mag het toetsen en terugkoppelen in de vorm van een KPB niet meer dan 5-10 minuten in beslag nemen. Dit kan zelfs gebeuren tijdens het teruglopen van de bespreking naar de afdeling. Het kan ook zo zijn dat de supervisor merkt dat de aios zich uitstekend redt en de aanwezigheid van de supervisor feitelijk overbodig is. In dat geval kan de opleider de aios autoriseren in het vervolg deze patiëntenbespreking, met bijvoorbeeld uitsluitend een korte voorbespreking, zelfstandig uit te voeren. Dit zal in het portfolio van de aios moeten worden vastgelegd.
Het moderne opleiden kent nog veel meer toetsvormen, allen geschikt voor een beperkt aantal competenties. Hoe en hoe vaak de verschillende competenties getoetst dienen te worden is in het opleidingsplan beschreven.
Naast deze nieuwe vormen van toetsen blijven natuurlijk ook kennistoetsen belangrijk. Ideaal zou een voortgangstoets zijn. Dit is een toets die voor iedere aios, ongeacht het opleidingsniveau, hetzelfde is en de hele nucleaire geneeskunde beslaat. In de loop van de opleiding dient het aantal juiste antwoorden steeds groter te worden om van voortgang te kunnen spreken. Helaas is het aantal aios in ons vakgebied te klein om een betrouwbare voortgangstoets te kunnen ontwerpen. Wij zullen ons daarom blijven beperken tot deeltoetsen ter afsluiting (binnen 6 maanden) van het cursorisch onderwijs.

Modernisering; wanneer gaat het gebeuren?

Zeer onlangs is ons nieuwe opleidingsplan door het Centraal College Medisch Specialisten (CCMS) goedgekeurd op voorwaarde dat het ministerie van VWS een verlenging naar 5 jaar toestaat. Uit ons nieuwe opleidingsplan is een nieuw "Besluit Nucleaire geneeskunde" door de juristen van de CCMS opgesteld en ter aanvulling/verbetering aan de NVNG aangeboden. Het Concilium van de NVNG heeft zich gebogen over een definitieve formulering van het Besluit.
Parallel hieraan lopen er gesprekken met VWS over de verlenging van de opleiding naar 5 jaar. VWS is tot nu toe wel gevoelig voor onze onderbouwing van het verzoek maar heeft nog enkele zeer goede argumenten nodig om de extra kosten te kunnen verantwoorden. Het is de verwachting dat deze extra informatie begin november bij VWS kan worden aangeleverd. De NVNG is hierbij mede afhankelijk van informatie die door het Capaciteitsorgaan moet worden aangeleverd. Het Capaciteitsorgaan raamt in opdracht van de overheid de behoefte aan medisch specialisten op korte en langere termijn.
De planning is dat het nieuwe opleidingscurriculum per 1 januari 2011 zal ingaan.

Wat betekent dit voor aios die op 1 januari al in opleiding zijn?

Zij zullen worden opgeleid volgens het opleidingsschema dat gold bij aanvang van hun opleiding. Hopelijk kan er financiering worden verkregen voor een facultatieve aanvullende opleiding MM beeldvorming.

Hoe worden opleidingscentra voorbereid op de implementatie van het nieuwe opleiden?

In 2010 zullen er voor opleidingscentra en aios bijeenkomsten worden georganiseerd om het nieuwe opleidingsplan te presenteren, toe te lichten en de introductie in de praktijk voor te bereiden.

Tot slot: Wat moet er gebeuren om erkend MM beeldvormer te worden?

Wat de status van de radiologische en MM beeldvorming in onze opleiding zal zijn moet in overleg met de Nederlandse Vereniging voor Radiologie worden vastgesteld. In Europees verband tekent zich een landschap af waarin een opleiding van twee jaar in het zusterspecialisme zal moeten kunnen leiden tot autorisatie voor het uitvoeren van MM beeldvorming. Een van die jaren wordt nu dus al in onze opleiding ingevoegd.

Kortom, het gaat er binnenkort echt van komen, maar alles valt of staat met het uiteindelijke besluit van VWS. Als dat negatief uitvalt, dan…..

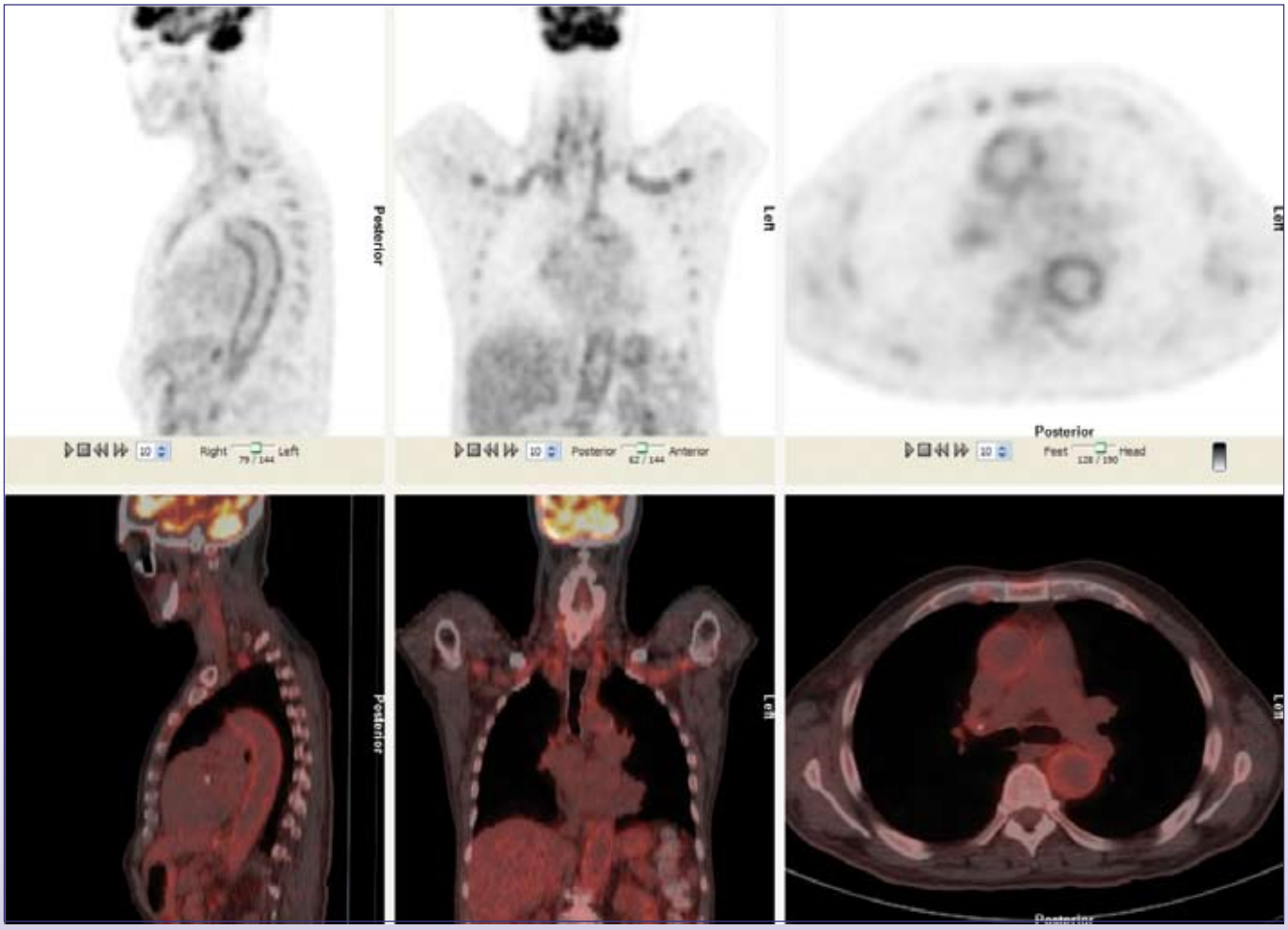
Laten we daar maar even niet vanuit gaan.

Arteritis temporalis op PET-CT

Dr. R.J. Bennink, Dr. J.V. van Thienen, Drs. J.A. Adam

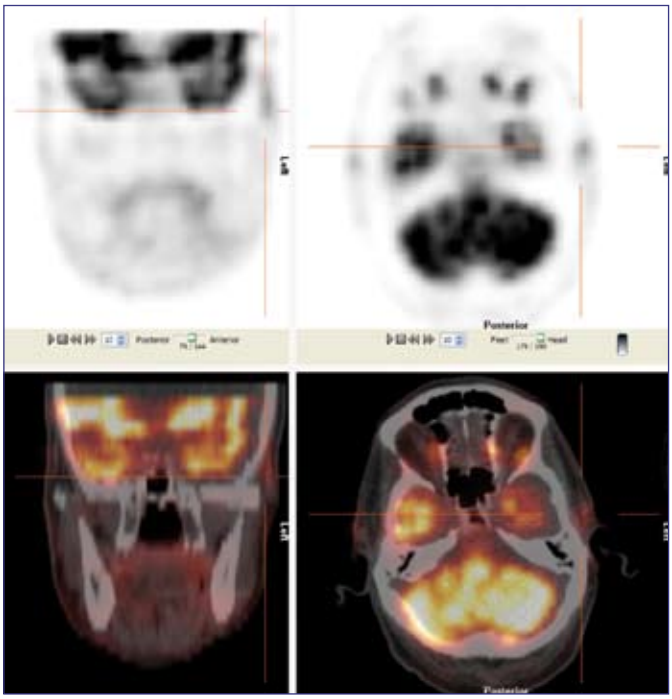
Een 76-jarige man van Marokkaanse afkomst, bekend met een pT2bNxM0 prostaatcarcinoom werd door de uroloog verwezen naar de afdeling interne geneeskunde wegens algemene malaise, koorts en gewichtsverlies welke niet direct verklaard konden worden door de oncologische problematiek. Bij scintigrafie werden geen aanwijzingen gevonden voor skeletmetastasering.
Patiënt vermeldt sinds een half jaar gewichtsverlies (14 kg) en koorts te hebben. De koorts heeft geen duidelijk patroon. De temperatuur kan oplopen tot 39ºC. De eetlust is hierbij sterk verminderd, er is geen sprake van slik- of passageklachten. Wel heeft hij nachtzweten. Hiernaast heeft patiënt diffuse hoofdpijnklachten die hij zelf wijdt aan een klap op het hoofd met een raam.

Bij klinisch onderzoek wordt een vermoeide, zieke man gezien. Hoofd/hals: geen bijzonderheden. Geen zwelling van de aa. temporales. Hart, longen en abdomen: geen bijzonderheden. Er is een verhoogde BSE en leukocytose. Een mantoux-test en interferon-gamma release assay zijn positief. Op conventionele beeldvorming wordt behoudens een licht vergrote subcarinale lymfklier geen substraat voor TBC gevonden. Er werd een PET-CT aangevraagd om een pathologische lymfklier te identificeren welke bereikbaar is voor definitieve PA diagnose.
Op de PET-CT(low-dose) wordt diffuus verhoogde FDG stapeling in de grote arteriële vaten gezien (Fig 1), waarbij eveneens stapeling zichtbaar is in beide aa. temporales (Fig 2). De subcarinale klier is FDG negatief. In de prostaat



Figuur 1.
PET-CT(low-dose) 60 min na toediening van 192 MBq ^{18}F-FDG i.v. Op de voor attenuatie gecorrigeerde sagittale, coronale en transversale PET slices is duidelijke FDG stapeling zichtbaar in de aorta en aftakkingen zoals de a. brachialis en carotis.

wordt een kleine subcapsulaire laesie gezien met verhoogde FDG stapeling. Elders in het lichaam worden geen vergrote of pathologisch FDG-stapelende lymfklieren gezien. Aan het skelet behoudens degeneratieve veranderingen geen afwijkingen.
Reuscelarteritis of arteritis temporalis is de meest voorkomende vorm van systemische vasculitis bij de mens boven de 50 jaar. Klachten zoals hoofdpijn, kaak claudicatio, proximale myalgie, gewichtsverlies, en koorts zijn suggestief voor de aandoening. Biochemische parameters van ontsteking kunnen aan de diagnose bijdragen, maar zijn niet pathognomonisch. Uiteindelijk is biopsie van de a. temporalis de gouden standaard voor diagnose, hoewel deze negatief kan zijn als gevolg van skip lesions.
Er zijn toenemende aanwijzingen dat ^{18}F-FDG PET-CT een rol kan spelen bij de diagnose van vasculitis zoals M. Takayasu maar ook bij reuscelarteritis. Reuscelarteritis is een granulomateuse vasculitis van grote en middelgrote arteries het meest voorkomend in vaten die aftakken van de arcus aortae. In 15% van de gevallen kan de gehele aorta inclusief de belangrijkste aftakkingen aangedaan zijn. De sensitiviteit van ^{18}F-FDG PET voor reuscelarteritis varieert tussen 56% en 100%, de specificiteit tussen 77% en 98% (naargelang inclusiecriteria, actieve ontsteking en intercurrerende behandeling). Visualisatie van de a. temporalis zelf blijkt soms moeilijk als gevolg van de hoge FDG stapeling in de hersenen. (1, 2)
Omdat TBC niet uitgesloten kon worden werd de patiënt in eerste instantie behandeld met quadrupel therapie (Isoniazide, Rifampicine, Pyrazinamide en Ethambutol). Een a. temporalisbiopsie heeft arteritis temporalis bevestigd. De patiënt werd aanvullend behandeld met hoge dosis prednison. Bij poliklinische controle verging het de patiënt allengs beter, zijn eetlust nam toe, het gewicht is gestegen. De BSE was significant gedaald, waardoor de behandeling met prednison afgebouwd kon worden. Voor zijn prostaatcarcinoom wordt de patiënt in opzet curatief behandeld met radiotherapie en 3 jaar aanvullend hormonale therapie.



Figuur 2.
PET-CT(low-dose) 60 min na toediening van 192 MBq ^{18}F-FDG i.v. Op de voor attenuatie gecorrigeerde coronale en transversale PET slices is duidelijke FDG stapeling zichtbaar in de a. temporalis, links meer uitgesproken dan rechts.

Referenties:

1. Walter M.A. 18F-FDG PET in large vessel vasculitis. Radiol Clin North Am. 2007;45:735-44
2. Akin E. PET-CT findings in large vessel vasculitis presenting as FUO, a case report. Clin Rheumatol. 2009;28:737-738

Het Nederlands Kanker Instituut - Antoni van Leeuwenhoek ziekenhuis (NKI-AVL), Amsterdam

Dr. W.V. Vogel
Nucleaire Geneeskundige

Geschiedenis

Al vanaf 1974 wordt in het NKI-AVL nucleaire geneeskunde bedreven. In eerste instantie werd de afdeling verzorgd door Herbert Marcuse en Jan van der Schoot. Sinds 1978 is Kees Hoefnagel vast nucleair geneeskundige, in 1989 kwam Renato Valdés-Olmos daar bij, en vanaf 2007 ook Wouter Vogel. Daarnaast bestaat er een goede samenwerking met de nucleair geneeskundigen van het nabijgelegen Lucas Andreas ziekenhuis; Ferida Sivro en Philippe Baars.

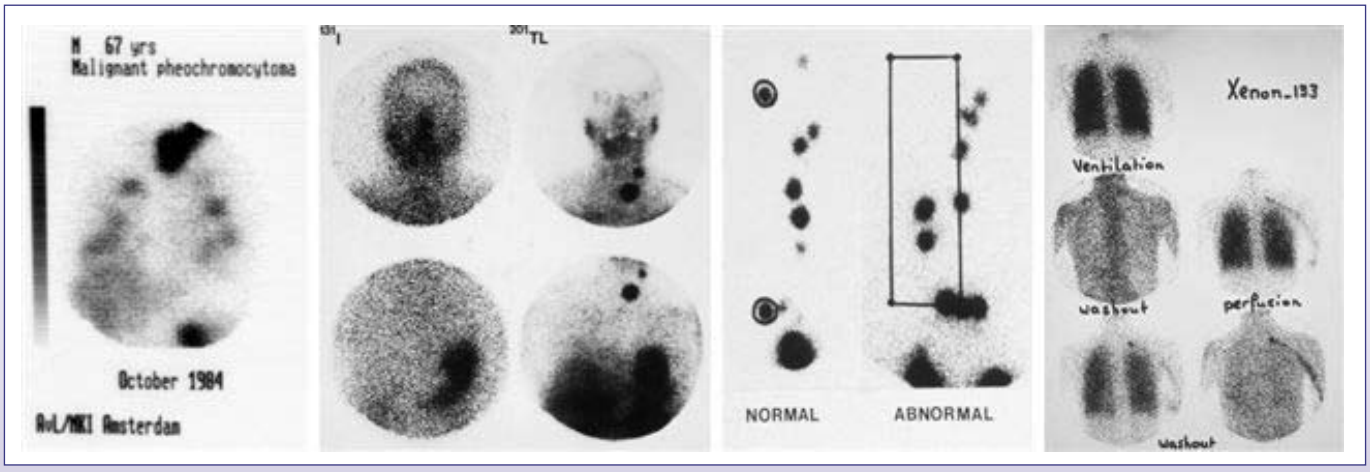
Figuur 1. Drie generaties nucleair geneeskundigen bij de opening van de nieuwe afdeling in juni 2008. Vlnr: Renato Valdés-Olmos, Jan van der Schoot, Kees Hoefnagel en Wouter Vogel.

Vanaf het begin, inclusief de mooie jaren van polaroid films en rectolineaire scanners, werd de afdeling gekenmerkt door snelle technologische ontwikkelingen en wetenschap. Zo werd al in 1978 de eerste computer voor digitale beeldverwerking van Nederland geplaatst (een MDS Modumed) en in 1982 een grootveld dubbelkops SPECT camera (Siemens Rota). In 2002 had het NKI-AVL een primeur in Nederland met de mobiele PET scanner, en in 2006 werd de eerste PET-CT met time-of-flight van Europa in gebruik genomen. Met deze apparatuur werden ook mooie nieuwe tracers en indicaties toegepast en gevalideerd (zie figuur 2).

Het oncologisch aandachtsgebied

Het NKI-AVL heeft als tertiair oncologisch centrum haar focus volledig op mensen met kanker. Deze specialisatie maakt een grootschalige aanpak van diagnostiek en behandeling mogelijk. Het ziekenhuis krijgt grote aantallen patiënten met de meest voorkomende typen kanker, waardoor er goede mogelijkheden zijn voor onderzoek en onderwijs. Door de centrumfunctie voor meer zeldzame typen kanker ontstaat ook daarvoor specifieke kennis, en kan voor deze ziekten toch op relatief grote schaal wetenschappelijk onderzoek worden gedaan.

Ook binnen de nucleaire geneeskunde wint specialisatie aan belang. Vanwege het aandachtsgebied van ons ziekenhuis hebben wij ervoor gekozen geen verrichtingen aan te bieden



Figuur 2. Historische onderzoeken in het NKI-AVL
Vlnr: (1) MIBG therapie in 1984. (2) De eerste Thallium-scintigrafie voor een jodium-negatief recidief schildklier carcinoom in 1981. (3) Parasternale lymfeklier scintigrafie in 1974. (4) Ventilatie én perfusie met de experimentele Xenon-133 generator in 1978, proefpersoon Kees Hoefnagel.

op het gebied van cardiologie of neurologie. Hierdoor kan onze aandacht volledig uitgaan naar de oncologie en het daarbij behorende wetenschappelijk onderzoek. Alles bij elkaar heeft dit in de loop der jaren geleid tot een ietwat bijzondere afdeling nucleaire geneeskunde.

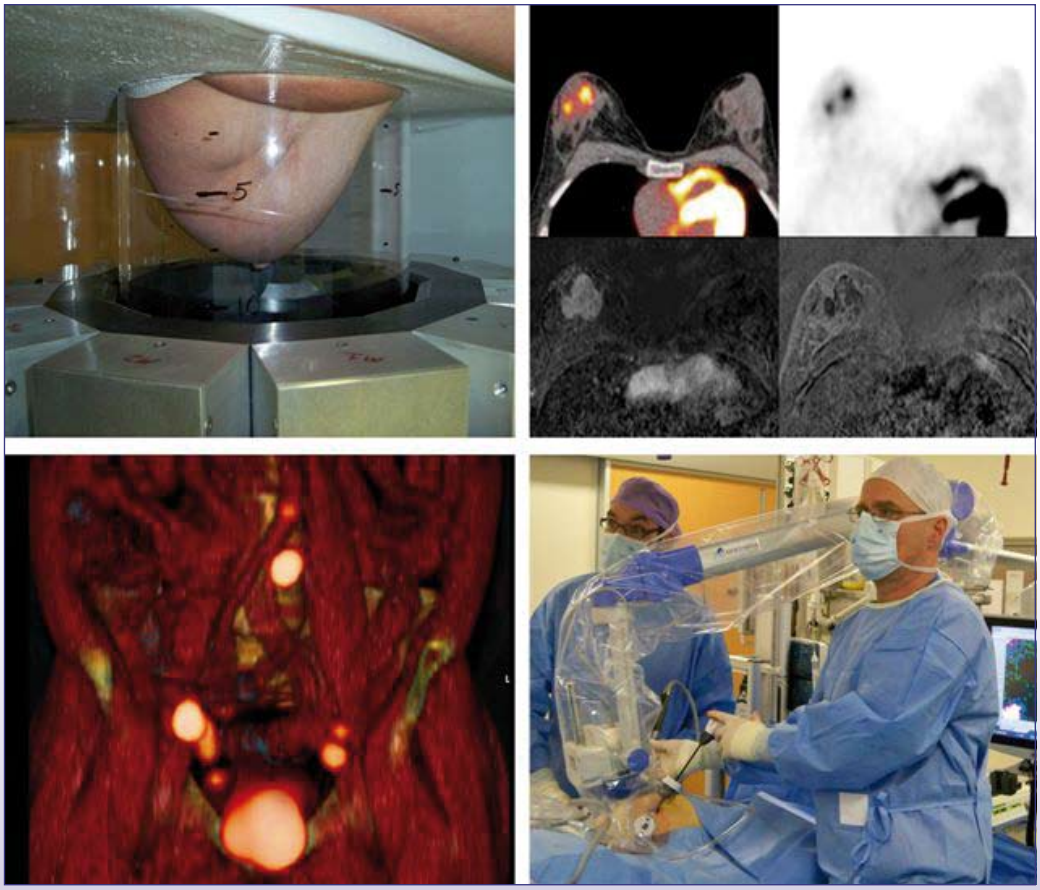
Aanpassing aan oncologie

De specifieke problemen en vraagstellingen in de oncologie hebben in de loop der jaren geleid tot allerhande aanpassingen en investeringen in apparatuur. Zo zijn onze twee SPECT-CT scanners voorzien van Mullekom collimatoren om diepgelegen sentinel nodes van abdominale organen (prostaat, blaas, nier) zonder artefacten te kunnen afbeelden in hun anatomisch kader. We hebben een mini-gammacamera voor intra-operatieve scintigrafie, inclusief mogelijkheden voor laparoscopische lokalisatie. De PET-CT heeft de beschikking over een vlakke tafel, planning lasers en gating apparatuur voor gecombineerde radiotherapie planning. Daarnaast beschikt de PET-CT over een positioneringsysteem voor het afbeelden van mamma tumoren in dezelfde oriëntatie als de MRI, voor beeldfusie en anatomische correlatie. Recent is ook een prototype van een mini-PET scanner voor specifieke beeldvorming van primair mammacarcinoom in gebruik genomen.

Van oudsher zijn de nucleaire aandachtsgebieden in het NKI-AVL de radionucliden therapie en de sentinel node-procedure. De laatste jaren zijn daar multimodality beeldvorming, response monitoring en nieuwe tracers bijgekomen. In 2008 betrokken wij een volledig vernieuwde afdeling, die ook plaats biedt aan twee afzonderlijke hotlab-ruimten met GMP kwalificatie voor ontwikkeling en synthese van nieuwe tracers voor PET, SPECT en therapie. Onze nieuwste aanwinst op het gebied van labeling is de ^{68}Gallium-generator, waarmee we tumordiagnostiek met peptiden en PET kunnen gaan uitvoeren.

Samenwerking

In het NKI-AVL wordt iedere patiënt in het diagnostisch traject multidisciplinair besproken. Daarvoor is een groot aantal specifieke oncologische werkgroepen opgezet, waar ook nieuwe technieken en indicaties kunnen worden toegelicht en geprotocolliseerd.
De werkgroepen dienen ook als tumorspecifiek onderwijs en



Figuur 3. Innovatieve apparatuur in het NKI-AVL. (Boven, links) Experimentele mamma PET detector ring, (rechts) FDG PET-CT mamma carcinoom in correlatie met MRI. (Onder, links) SPECT-CT lokalisatie van sentinel nodes van prostaat carcinoom, met (rechts) intra-operatieve imaging met een mini-gammacamera tijdens laparoscopische verwijdering.

ondersteunen de inclusie in wetenschappelijke trials. Deze filosofie is ook doorgezet in de nucleaire geneeskunde. Veel scans, bijvoorbeeld alle PET scans en onderzoeken met nieuwe tracers, worden dagelijks gezamenlijk beoordeeld. De afdeling organiseert specifieke werkgroepen in een eigen demonstratieruimte, onder andere voor longsneldiagnostiek, sentinel node-diagnostiek en het schildklier carcinoom. Daarnaast werken op onze afdeling twee promovendi aan analyse en verbetering van de geleverde zorg. Door de specialisatie en het opleidingsklimaat is het NKI-AVL erkend als opleidingskliniek voor nucleair geneeskundigen, voor een oncologische stage.

De menselijke kant

Bij iedere patiënt met kanker uit de ziekte zich op een unieke wijze, en iedere patiënt gaat op zijn eigen manier met zijn ziekte om. In ons ziekenhuis staan daarom communicatie en persoonlijke aandacht centraal. Voor anamnese, onderzoek en toediening van radioactieve stoffen worden alle patiënten gezien door een nucleair geneeskundige, of door een medisch nucleair werker met een aandachtsgebied in de oncologie. Deze aanpak heeft geleid tot een team van communicatief vaardige en betrokken medewerkers, waar wij trots op zijn.

Met alle nieuwe ruimte en apparatuur heeft onze afdeling vele mogelijkheden voor de toekomst, die wij niet allemaal zouden kunnen benutten zonder uitbreiding met een vierde nucleair geneeskundige met specifieke aandacht voor de oncologie en wetenschap. Deze eigenschappen hebben wij gevonden in collega Ernst Postema, die ons team in 2010 zal komen versterken.

Wij hopen dat u bij de recente wetenschappelijke vergadering van de NVNG de kans hebt gehad onze nieuwe afdeling te bezoeken, en dat u hebt genoten van de wetenschappelijke bijdragen. Tot slot willen wij voor de geïnteresseerden nog eens onder de aandacht brengen dat voor nucleair geneeskundigen in opleiding het volgen van een stage "nucleair geneeskundige oncologie" in het NKI-AVL tot de mogelijkheden behoort, mits ruim van tevoren geregeld.

Figuur 4. Personeel.

Bureau NVNG

Secretariaat: Locatie B42,
Postbus 8213,
3503 RE Utrecht
Telefoon: (030) 291 99 39
Fax: +31(030) 291 99 58
Email: info@nvng.nl
Internet: www.nvng.nl

Nieuwe leden

Ir. L. van den Berg
Werkadres:
Meander MC, Locatie Lichtenberg
Afdeling Klinische Fysica
Postbus 1502
3800 BM AMERSFOORT
Telefoon: 033-8504994
E-mail: l.vanden.berg@meandermc.nl

Drs.ir. G.J. Colenbrander
Werkadres:
Spaarne Ziekenhuis
Afdeling Klinische Fysica
Spaarnepoort 1
2134 TM HOOFDDORP
Telefoon: 023-8908743
E-mail: g.colenbrander@rijnland.nl

Nieuwe donateur per 1 januari 2010

AGFA Healthcare
Contactpersoon: dhr. E. Gielen
Adres:
Polakweg 10-11
2288 GG RIJSWIJK
Telefoon: 070-4131230
E-mail: erik.gielen@agfa.com

Adreswijzigingen

Drs. J.G. van der Laan
Nieuw werkadres:
Wilhelminaziekenhuis Assen
Afdeling Nucleaire Geneeskunde
Postbus 30001
9400 RA ASSEN

Beëindiging lidmaatschap

H.H.J. Baretta-Kooi
M. Heeringa-Karreman
H.M.L. Jansen
J.H.M.A. Krens
J.D. Paar

Nederlandse Vereniging Medische Beeldvorming en Radiotherapie (NVMBR)

Catharijnesingel 73
3511 GM Utrecht
Telefoon: +31(0)30-2318842
Fax: +31(0)30-2321362
E-mail: info@nvmbr.nl
Internet: www.nvmbr.nl

Hoofdbestuur

Dagelijks Bestuur
Voorzitter: Fred Felderhof,
Penningmeester: Wim Dankaart
Secretaris: Hendrik Harders

Overige bestuursleden

Herma Hemelt-Vaanholt (Echografie), Cocky Heemskerk (Radiologie), Guus Veenendaal (Radiotherapie), Suzanne Lansbergen (Nucleaire Geneeskunde), Jo Duvivier (Kwaliteit), Dirk Zweers (Straling), Peter Kappert (MRI)

Verenigingsfunctionarissen

Govert Bos, Eveline Geers, Sija Geers-van Gemeren, Mia van Hoeven, Ilse Lingg, Meiske van der Ploeg, Linda van Ree, Marloes Zeeman

Nascholing nucleaire geneeskunde 2010

Thema: hersenen 8 april en 21 september. Locatie Jaarbeurs Utrecht

Thema: productie radionuclide 16 maart en 7 oktober. Locatie Jaarbeurs Utrecht

NVMBR 60 jaar; Jubileumcongres 27 en 28 mei. Locatie MECC Maastricht

Tijdschrift voor Nucleaire Geneeskunde
ISSN 1381-4842, nr. 4 december 2009

Uitgever

KLOOSTERHOF
ACQUISITIE SERVICES - UITGEVERIJ

Kloosterhof acquisitie services - uitgeverij
Napoleonsweg 128a
6086 AJ Neer
T 0475 59 71 51
F 0475 59 71 53
E info@kloosterhof.nl
I www.kloosterhof.nl

Hoofdredacteur
mw. dr. L.F. de Geus-Oei
E redactie@sbng.nl

Redactie
mw. B. Bosveld
mw. drs. F. Celik
dr. J.A. van Dalen
dr. E. van de Garde
mw. prof. dr. I. Goethals
mw. prof. dr. ir. M. de Jong
mw. dr. ir. L.J.M. Rijks
dr. R.H.J.A. Slart
J. de Swart
mw. J. Tjoa
dr. P. van Urk
drs. F.A. van der Weel

Redactieraad
Prof.dr. F.J. Beekman
Prof.dr. O.C. Boerman
Prof.dr. E.F.I. Comans
Prof.dr. R.A.J.O. Dierckx
Prof.dr. A.A.M.S. van Dongen
Prof.dr. B.L.F. van Eck-Smit
Prof. dr. P.H. Elsinga
Prof.dr.ir. M.de Jong
Prof.dr. O.S. Hoekstra
Prof.dr. E.P. Krenning
Prof.dr. A.A. Lammertsma
Prof.dr. L. Mortelmans
Prof.dr. W.J.G. Oyen
Prof.dr. A.M.J. Paans
Prof. dr. P.P. van Rijk
Prof.dr. G.J.J. Teule
Dr. R.A. Valdés Olmos

Bureauredactie
Yvonne van Pol-Houben
T 0475 60 09 44
E nucleaire@kloosterhof.nl

Advertentie-exploitatie
Kloosterhof acquisitie services – uitgeverij
Sandra Geraedts
T 0475 59 74 21
E sandra@kloosterhof.nl

Vormgeving
Kloosterhof Vormgeving
Marie-José Verstappen
E marie-josé@kloosterhof.nl

Abonnementen
Leden en donateurs van de aangesloten beroepsverenigingen ontvangen het Tijdschrift voor Nucleaire Geneeskunde kosteloos. Voor anderen geldt een abonnementsprijs van € 45,00 per jaar; studenten betalen € 29,00 per jaar (incl. BTW en verzendkosten). Opgave en informatie over abonnementen en losse nummers (€ 13,50) bij Kloosterhof acquisitie services - uitgeverij,
telefoon 0475 59 71 51.

Verschijningsdata, jaargang 31
Nummer 4 18 december 2009

Verschijningsdata, jaargang 32
Nummer 1 26 maart 2010
Nummer 2 25 juni 2010
Nummer 3 24 september 2010
Nummer 4 24 december 2010

Aanleveren kopij, jaargang 32
Nummer 1 1 januari 2010
Nummer 2 1 maart 2010
Nummer 3 1 juni 2010
Nummer 4 1 oktober 2010

Cursus- en Congresagenda

2010

BiOS 2010
23 – 28 January, 2010. San Francisco, USA. www.spie.org

Animal Imaging Workshop by AMIE
3 – 5 February, 2010. Rotterdam, The Netherlands. www.molmed.nl

Wereldkankerdag 2010: Kennis van kanker, zorg voor patiënten
4 February, 2010. Nijmegen, The Netherlands. www.congressconsultants.com

EANM/ESTRO Educational Seminar on PET in Radiation Oncology
6 – 7 February, 2010. Brussels, Belgium. www.eanm.org

Hot topics in Molecular Imaging – TOPIM 2010
7 – 12 February, 2010. Bardonecchia, Italy. www.e-smi.eu

Creatiave Counting in Nuclear Medicine
9 February, 2010. London, Great Britain. www.ipem.ac.uk

Uses of PET in Radiotherapy
10 February, 2010. London, Great Britain. www.ipem.ac.uk

XIV Reunión de Cardiología Nuclear
17 – 19 February, 2010. Granada, Spain. www.semn.es

Cardiovascular Course
20 – 21 February, 2010. Vienna, Austria. www.eanm.org

Clinical PET/CT Course, basic
13 – 14 March, 2010. Vienna, Austria. www.eanm.org

Molecular Imaging in Radiation Oncology (MIRO)
18 - 20 March, 2010. Brussels, Belgium. www.estro-events.org

Technologist PET/CT Course, basic
20 – 21 March, 2010. Vienna, Austria. www.eanm.org

IRIST
7 - 10 April, 2010. Groningen, The Netherlands

15th European Symposium on Radiopharmacy and Radiopharmaceuticals
8 – 11 April, 2010. Edinburgh, Scotland. www.esrr10.eanm.org

German Society of Nuclear Medicine - Annual Congress
21 - 24 April, 2010. Leipzig, Germany. www.nuklearmedizin.de

ANZSNM 40th Annual Scientific Meeting 2010
23 - 26 April, 2010. Auckland, New Zealand. www.anzsnm2010.co.nz

Cardiac Imaging Symposium
24 April, 2010. Affligem, Belgium. www.cardiacimaging.be

Adreswijzigingen

Regelmatig komt het voor dat wijziging in het bezorgadres voor het Tijdschrift voor Nucleaire Geneeskunde op de verkeerde plaats worden doorgegeven. Adreswijziging moeten altijd aan de betreffende verenigingssecretariaten worden door gegeven. 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 door geven van de wijzigingen aan de Tijdschrift adresadministratie.
Alleen adreswijzigingen van betaalde abonnementen moeten rechtstreeks aan de penningmeester van de Stg. ter Bevordering van de Nucleaire Geneeskunde gemeld worden:
SBNG, tav. Penningmeester | Nieuwe Parklaan 112 | 2587 BW Den Haag of per E-mail: penningmeester@sbng.nl

Met vriendelijke groet, Koos Blokland

A step forward...
towards quality of life |

QUADRAMET®

Samarium [^{153}Sm] Lexidronam injection

METASTATIC BONE PAIN

distributed by IBA

www.cisbio.com
www.iba-worldwide.com

cisbio

iba Molecular

GE Healthcare

GE Healthcare
Postbus 746
5600 AS EINDHOVEN
tel.: 040 299 1000
fax: 040 299 1299

Radiofarmaca Apotheken

Uw service. Onze zorg.

GE imagination at work

Radiofarmaca Apotheken in Nederland:
Eindhoven
tel: 040 247 8451
Leiderdorp
tel: 071 582 8921
Zwolle
tel: 038 455 3900