Integration of FDG-PET/CT into external beam radiation therapy planning

Technical aspects and recommendations on methodological approaches

D. Thorwarth[1]; T. Beyer[2,3]; R. Boellaard[4]; D. De Ruysscher[5]; A. Grgic[6]; J. A. Lee[7]; U. Pietrzyk[8,9]; B. Sattler[10]; A. Schaefer[6]; W. van Elmpt[5]; W. Vogel[11]; W. J. G. Oyen[12]; U. Nestle[13]

[1]University Hospital for Radiation Oncology, Section for Biomedical Physics, Eberhard-Karls University Tübingen, Germany; [2]University Hospital for Radiology, Imaging Science Institute Tübingen, Germany; [3]cmi-experts, Zürich, Switzerland; [4]University Medical Centre, Department of Nuclear Medicine & PET Research, Amsterdam, The Netherlands; [5]Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands; [6]Department of Nuclear Medicine, Saarland University Medical Center, Homburg/Saar, Germany; [7]Center of Molecular Imaging and Experimental Radiotherapy, Université Catholique de Louvain, Brussels, Belgium; [8]Institute of Neurosciences and Medicine – Medical Imaging Physics (INM-4), Research Center Jülich, Germany; [9]Faculty of Mathematics and Natural Sciences, University of Wuppertal, Germany; [10]Department of Nuclear Medicine, University Hospital Leipzig, Germany; [11]Departments of Nuclear Medicine and Radiation Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek ziekenhuis (NKI-AVL), Amsterdam; [12]Department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, The Netherlands; [13]University Hospital for Radiation Oncology Freiburg, Germany

Keywords
Radiation therapy planning, PET/CT, FDG

Summary
This work addresses the clinical adoption of FDG-PET/CT for image-guided radiation therapy planning (RTP). As such, important technical and methodological aspects of PET/CT-based RTP are reviewed and practical recommendations are given for routine patient management and clinical studies. First, recent developments in PET/CT hardware that are relevant to RTP are reviewed in the context of quality control and system calibration procedures that are mandatory for a reproducible adoption of PET/CT in RTP. Second, recommendations are provided on image acquisition and reconstruction to support the standardization of imaging protocols. A major prerequisite for routine RTP is a complete and secure data transfer to the actual planning system. Third, state-of-the-art tools for image fusion and co-registration are discussed briefly in the context of PET/CT imaging pre- and post-RTP. This includes a brief review of state-of-the-art image contouring algorithms relevant to PET/CT-guided RTP. Finally, practical aspects of clinical workflow and patient management, such as patient setup and requirements for staff training are emphasized. PET/CT-guided RTP mandates attention to logistical aspects, patient set-up and acquisition parameters as well as an in-depth appreciation of quality control and protocol standardization. Conclusion: Upon fulfilling the requirements to perform PET/CT for RTP, a new dimension of molecular imaging can be added to traditional morphological imaging. As a consequence, PET/CT imaging will support improved RTP and better patient care. This document serves as a guidance on practical and clinically validated instructions that are deemed useful to the staff involved in PET/CT-guided RTP.

Schlüsselwörter
Radiotherapieplanung, PET/CT, FDG

Correspondence to:
Daniela Thorwarth, PhD
Section for Biomedical Physics
University Hospital for Radiation Oncology
Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
Tel. +49/(0)70 71/298 60 55, Fax +49/(0)70 71/29 48 20
E-mail: Daniela.Thorwarth@med.uni-tuebingen.de

Integration der FDG-PET/CT-Bildgebung in die Planung der externen Strahlentherapie – Technische Aspekte und Empfehlungen zur methodischen Annäherung
Nuklearmedizin 2012; 51: ■■
doi:10.3413/Nukmed-0455-11-12
received: December 21, 2011
accepted in revised form: March 19, 2012
prepublished online: April 3, 2012

Zusammenfassung
Diese Arbeit geht auf die klinische Verwendung von FDG-PET/CT in der bildgestützten Radiotherapieplanung (RTP) ein. Wichtige technische und methodische Aspekte der FDG-PET/CT-basierten RTP werden erläutert, und praktische Empfehlungen für das Management von Patienten in der klinischen Routine sowie in klinischen Studien gegeben. Zunächst werden neueste Hardware-Entwicklungen der PET/CT-Bildgebung beschrieben, die für die RTP relevant sind. Die Einführung entsprechender Qualitätskontrollen und Protokolle zur Kalibrierung bildgebender Systeme ist unerlässlich für eine reproduzierbare Einbeziehung der PET/CT in die RTP. Anschließend werden Empfehlungen hinsichtlich Datenakquisition und Rekonstruktionsparametern gegeben mit dem Ziel der Standardisierung der Bildgebungsprotokolle. Eine Hauptanforderung der RTP in der klinischen Routine ist der zuverlässige Datentransfer an das Planungssystem. In einem weiteren Abschnitt dieser Arbeit werden aktuelle Methoden der Bildfusion und -registrierung diskutiert. Abschließend wird auf praktische Aspekte bezüglich klinischer Arbeitsabläufe und Patientenmanagement (z. B. Patientenlagerung und Anforderungen an die Personalschulung) eingegangen. Besonders wichtig für eine zuverlässige PET/CT-basierte RTP sind logistische Aspekte, aber auch eine reproduzierbare Lagerung der Patienten und standardisierte

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

Akquisitionsprotokolle sowie spezielle Qualitätskontrollen. Schlussfolgerung: Durch Umsetzung der genannten Anforderungen der RTP an die PET/CT, kann die Integration molekularer Bilddaten zusätzlich zur morphologischen Bildgebung erreicht werden. Die PET/CT unterstützt eine präzisere RTP und ein verbessertes Patientenmanagement. Diese Arbeit kann als praktische Empfehlung zur klinischen Verwendung von PET/CT-Bilddaten in der RTP genutzt werden.

Positron emission tomography (PET) and computed tomography (CT) imaging have been used independently for decades in diagnostic imaging to provide metabolic and anatomical image information, respectively. Unlike other imaging methods, PET and CT can be operated in close physical proximity without significant cross-talk effects and without the need to modify either component in view of conjoined operation. Thus, integrated PET/CT imaging based on the intrinsic combination of PET and CT within a single, combined gantry results in the acquisition of complementary image information within a single examination protocol without the need to reposition the patient (82).

> With the clinical adoption of combined PET/CT systems almost 15 years ago, staging and restaging of cancer patients has been improved significantly over CT- and PET-only (21).

Simultaneously, highly sophisticated radiotherapy (RT) techniques like the 3-dimensional, conformal RT (3-D-CRT), stereotactic RT (SRT) and radiosurgery, intensity modulated RT (IMRT), heavy particles RT etc. were developed in order to focus and escalate the irradiation dose on the tumour area with high precision and to spare the normal tissue (46).

Anatomical imaging forms the basis for radiation treatment planning (RTP) (23). However, conventional imaging has significant limitations for target volume delineation for RT (61). PET/CT imaging has been shown to have a significant clinical impact on the diagnosis and treatment selection of a variety of cancers (43). While ^{18}F-fluoro-desoxyglucose (FDG) reveals increased glucose metabolism (31), other compounds can be used for more specific information, for example to visualize and quantify hypoxia (e. g. ^{18}F-fluoro-misonidazole, FMISO), cell proliferation (^{18}F-3'-fluoro-3'-deoxy-L-thymidine, FLT) and other characteristics important for RTP (61).

Employing high-precision radiotherapy based upon inaccurate tumour mass delineation on morphological image volumes creates a paradox situation whereby the effort to focus the dose on an exactly delineated target is not justified. This conflict is the reason for the increasing use of molecular imaging methods for RTP (28).

> The ultimate goal of metabolic imaging for RTP is to add complementary information to anatomical imaging, which may be inadequate for the differentiation of necrotic from active tumour volume, for example.

FDG-PET and FDG-PET/CT can aid the delineation of metabolically active target volumes, or the gross tumour volume (GTV) (60). Several authors have shown the benefit of the addition of the molecular imaging information provided by PET into the RT treatment planning process in virtually all fields of radiation oncology (18, 30, 49, 61).

This review aims at providing a practical summary of state-of-the-art procedural and technical knowledge in terms of a "how to" guide for the up to date use of PET/CT in RT-planning in daily routine patient service and clinical studies.

PET/CT hardware

Combined PET/CT

A hardware combination of PET and CT was suggested as early as 1998 (81). Triggered by early clinical proof, PET/CT was soon commercially available and combined PET/CT system technology has advanced rapidly since then. Today, PET/CT systems for clinical use combine a whole-body, full-ring PET and a multi-slice CT within a single gantry (48).

In brief, state-of-the-art PET components are based on lutetium oxyorthosilicate(LSO)- and lutetium yttrium oxyorthosilicate(LYSO)-based scintillation detectors, and provide a transverse and axial field-of-view of 60 cm and 18–22 cm, respectively with measured isotropic image resolution of around 4.5 mm. It is important to recognize that lesion detectability in PET is not only defined by the spatial resolution of the system but also by lesion contrast. Thus, lesions that are smaller than the image resolution can still be detected in PET if the contrast between lesion and surrounding tissue is sufficiently high.

The CT components of combined PET/CT are typically multi-slice CT systems with up to 128 slices being acquired simultaneously and a maximum axial coverage of 8 cm per rotation (▶Tab. 1). Extended coaxial imaging fields are acquired by sequential acquisitions of a spiral CT scan followed by a multi-step emission scan with slightly overlapping (20–40%) bed positions. Note, an axial overlap of the PET acquisitions is required in order to ensure a uniform sensitivity profile across the axial imaging range (5). PET imaging times for a single axial bed position (15–22 cm) are on the order of 1–4 min, bringing the total emission imaging time for a torso oncology exam to anywhere between 10 min and 25 min.

Recently, several PET/CT design concepts have been presented by different vendors, all aiming at reducing footprint and bringing the PET and CT components as close together as possible (48). Despite early efforts no fully-integrated, single-detector PET/CT exists today. Thus, the centres of the fields-of-view of the CT and the PET are axially displaced by up to 110 cm. Using a joint, dedicated patient positioning system that is installed at the front of the PET/CT gantry, patients can be positioned accurately and reproducibly for coaxial imaging ranges of up to 200 cm. During the time elapsing between the acquisition of the CT and the PET data, physiologically determined alterations of the anatomy, e. g. of bladder, stomach and bowel may occur. However, combined PET/CT still offers the best possible intrapatient co-registration of complementary anatomical and functional images.

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

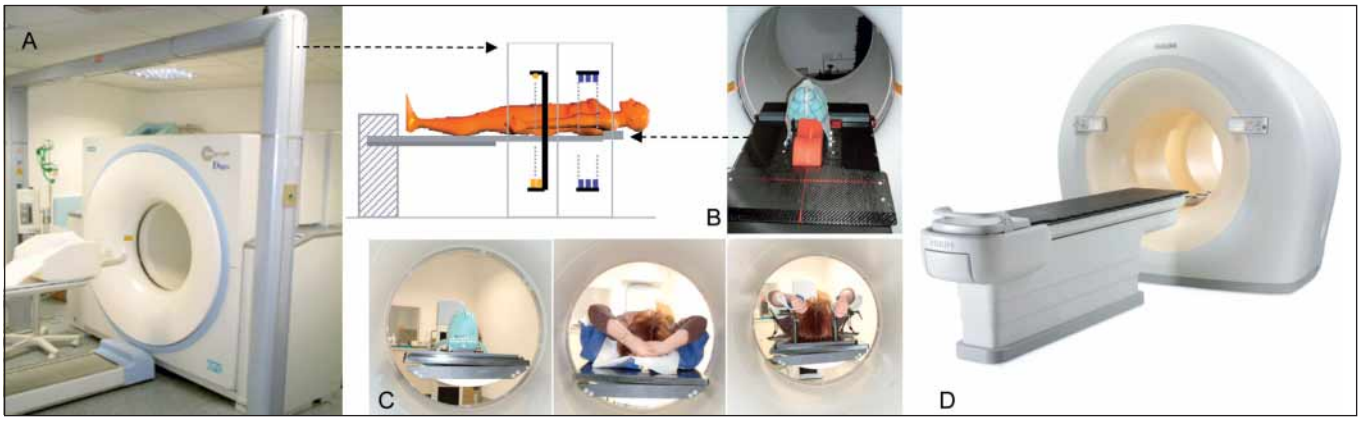

Fig. 1 PET/CT adaptations specific to radiation oncology applications
A) RT laser bridge installation in front of the combined gantry
B) patient support system with flat, carbon-fibre RT-pallet attached
C) as in B) with additional thermoplastic head restraint, vacuum lock bag and breast board (from left to right)
D) dedicated, big bore PET/CT with an 85 cm gantry opening (Philips Healthcare Systems).

PET/CT hardware and RTP

Recognizing the potential of PET/CT-guided treatment planning, a number of hardware and software innovations were adopted in commercially available PET/CT systems to meet the requirements for RTP. These included

- a flat table top attached (placed on top and secured, and with validated stability) to the PET/CT patient handling system (▶Fig. 1) to help replicate patient positoning during RT treatment,
- positioning aids and additional patient registration devices fixated to the flat RT table top (▶Fig. 1). These registration devices support adequate repositioning of patients during the imaging exam, simulation process and therapy.
- Increased gantry tunnel diameters to fit patients who are positioned with RT positioning aids into the field-of-view of the imaging system (▶Tab. 1).
- RT laser bridges or mobile RT laser installed in a reproducible manner with respect to the isocentre of the PET/CT (▶Fig. 1). These lasers cover a wider field-of-view and are more accurate that gantry-internal laser for general positioning of the patient.

Recently, major advances in PET/CT system architecture have been realized, which have a number of implications for the clinical use of PET/CT in image-guided RTP. Note, in particular, the commercial introduction of a PET/CT dedicated to RTP. In addition to hardware modifications this PET/CT links directly to the RT laser system, such that the isocentre can be adjusted and stored automatically.

Recommendations

1. Combined PET/CT systems and certified RTP hardware accessories should be used for RTP purposes.
2. A PET/CT-guided RT workflow should be defined and managed in close collaboration with the responsible radiation oncology team.

Quality control, calibration

Quality control (QC) and system calibration of the PET/CT system are prerequisites for accurate and reproducible image-guided RTP. They are performed as part of the acceptance tests by the manufacturer during the installation of a new imaging system, after maintenance service and when recommended on a regular basis (15). Control and calibration tasks involve measurements on the individual imaging components of the PET/CT as well as procedures dedicated to the dual-modality concept of the integrated hardware.

When employing PET/CT in radiation therapy planning, the available QC-guidelines for diagnostic PET/CT acquisition should be followed (15, 16), which will be briefly outlined here. Furthermore, QC and calibration of the RT-dedicated parts of the system, such as tabletop and laser positioning systems are required.

CT system

The quality control procedures for the CT system of a PET/CT follow the relevant European standards (37, 38). Quality control measurements include

- noise levels in uniform areas (air, water),
- mean CT numbers (in Hounsfield units, HU),
- uniformity,
- slice thickness,
- spatial resolution (modulation transfer function), and
- accuracy of the table positioning.

Measurements are performed on a daily, monthly or quarterly basis, as detailed in (37, 38). All CT vendors require a daily checkup of the system by means of air measurements with varying X-ray beam parameters. CT and PET/CT systems are provided with necessary quality control and calibration phantoms for routine quality control measurements. When doing 4D PET/CT, additional quality assurance (QA) procedures for 4D-CT scan techniques are useful (36). Post-maintainance acceptance testing may require

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

Tab. 1 Basic parameters of current PET/CT systems of major manufacturers

manufacturer brand, type		Mediso	SIEMENS	PHILIPS		GE	
		Anyscan	Biograph mCT	Ingenuity TF	Gemini TF Big Bore	Discovery 690	Elite/VCT
PET detector	max. axial FOV [cm]	15.1	21.6	18		15.7	
	material (scintillator)	LYSO	LSO	LYSO		LYSO	
	crystal element size [mm]	3.9×3.9×20	4×4×20	4×4×22		4.2×6.3×25	
	resolution [mm] FWHM NEMA @ 1 cm]	4.1×4.2	4.4	4.7×4.7×4.7		4.9×4.6	
MSCT	detector lines coverage [mm]	16 rows 20	20/32/64 12/19.2/38.4	64-chanel 40	16-chanel 24	16 / 64 20 / 40	
	max. tube power [kW]	60	100	eff. 105	60	Elite: 53	85/100 (optional)
	s/rotation (360°)	0.5	0.30	0.4		Elite: 0.5	0.35
	transversal CT-FOV [cm] measured- /display FOV [cm]	50	50/78	50/70	60/70	50 (measured)/70 (displayed)	
hard-ware	patient port, bore size [cm]	70	78	70	85	71	
	axial displacement of PET and CT in gantry [cm]	56	75	110		68	
	patient handling system	bed support in tunnel	bed on rails	bed support in tunnel		dual-position bed	
	flat carbon pallet (yes/no/size)	optional	yes / 51.7 cm	yes / 53cm		yes / 48.5 cm	
	respiratory gating (retro-/ prospective, CT and/or PET) supported gating device	PET (WIP)	prospective CT, retrospective PET • bellow belts • Varian RPM	retrospective / prospective PET and CT • bellow belts • Varian RPM		retrospective / prospective PET and CT • bellow belts • Varian RPM	

phantoms that are available to service staff only. An overview of routine quality control procedures for the X-ray unit of a PET/CT system is given in (16).

PET components

Quality control of the PET components consists of three procedures:

- Check of coincidence sensitivity and detector normalization, which yields evidence whether the sensitivity for the coincidence detection of all combinations of detectors is acceptable.
- Normalization calibration, which yields the conversion factor for the activity concentration as determined by the emission measurements, and
- certification of imaging properties that describes the results of mandatory data correction (e. g., randoms, attenuation, scatter).

In summary, applying quality assurance and control procedures to PET system calibration reduces measurement variability (26, 47). In addition, the periodic measurements of the transaxial resolution, imaging scale and documentation unit are recommended (27). An overview of all routine quality control measurements for the PET is given in (16).

PET/CT alignment

The physical alignment of the CT and PET component, frequently referred to as "offset", must be known to automatically reference PET and CT data within the same spatial coordinates. This offset must be measured for the first time following the installation of the PET/CT; this is part of the acceptance procedure (15). The offset may change after the system was serviced, whereby the CT and PET components were physically set apart for access to the interior gantry; the alignment measurement must then be performed again prior to clinical routine. Obviously, the absolute offset values vary with the PET/CT and installation and must be determined individually (15, 16).

RT specific aspects

A number of quality control steps need to be performed on top of QC of the PET/CT when using the available image information for RTP. As there is no standard yet regarding this QC procedure, a minimum number of QC steps of PET/CT-related ancillary devices in RT should be followed.

The positioning and movement of the tabletop must be precisely controlled under constant load. Inaccuracies in the tabletop geometry will translate into poor patient position reproducibility on the treatment machine. Inaccurate table indexing can cause image spatial distortions and vertical

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

and longitudinal movement errors can cause inaccuracies when marking the patient skin relative to the calculated treatment isocentre.

A sample QA procedure for scanner table and rationale for the above listed tests is detailed in (51). Testing frequencies and tolerances may vary. The flat tabletop should not contain any objectionable artifact producing objects (screws).

When immobilisation devices are used in radiotherapy their exact position relative to the table top is registered for reproducibility, e. g. by using landmarks or lateral notches on the dedicated RT pallet. Detailed instructions for storage and insertion of the couch top and registration of immobilisation devices should be prepared for the PET/CT staff (19, 70).

An alignment tool or a phantom is needed to assess laser geometry and accuracy. There are several designs for scanner laser QA devices. A simple laser QA process is detailed in (51). Parts of this process should be performed daily and the full procedure should be performed monthly or more frequently depending on laser stability.

The accuracy of the lasers directly affects the ability to localize treatment volumes relative to patient skin marks and the reproducibly of patient positioning from the CT to the RT treatment machine. Accuracy and spatial orientation of the RT lasers must be comparable to treatment machine laser accuracy. Laser accuracy tolerances depend on the goals of radiation therapy and required accuracy of treatment procedures.

Recommendations

1. Regular QC and calibration of PET/CT hardware is required for PET/CT-guided RTP. Existing guidelines and recommendations should be followed.
2. In view of a lack of standard QC procedures for ancillary RT devices it is advised to agree on a set of QC measures among expert staff from nuclear medicine, radiology and radiation oncology.
3. The full range of system operations must be verified following service access of the PET/CT hardware.

Data acquisition and reconstruction

A PET/CT study can be requested for purposes of staging, response assessment, or target volume definition (21). Depending on the clinical and diagnostic question, a PET/CT study may cover different co-axial imaging ranges (▶Fig. 2). A torso scan is typically performed for staging and response assessment covering a co-axial imaging range from mid-thigh to the base of the skull (44). If a PET/CT study is performed for the sole purpose of target volume definition, then a limited co-axial imaging range is acceptable. In this case particular attention must be given to patient positioning since the patient should be imaged and treated in exactly the same position . The same acquisition protocol (e. g., positioning, imaging range, acquisition parameters and image reconstruction) should be enforced for pre- and post-therapy examinations in order to facilitate a therapy response assessment based on standardized image data.

In general, a standard PET/CT examination employing FDG for whole-body staging consists of a topogram, or scout scan, a low-dose CT acquired specifically for the purpose of attenuation correction followed by a multi-step PET emission scan and a contrast-enhanced, multi-phase CT examination (▶Fig. 2A). Note, contrast-enhanced CT images can also be used for attenuation correction (7).

Residual, local misregistration in areas of high respiratory mobility have been reported, but these occur less frequently in patients examined in quiet respiration on a PET/CT employing multi-slice CT technology with six or more CT detector rows (8). Nonetheless, respiration-induced misalignments may cause severe attenuation correction artifacts, especially near the diaphragm. This can be a problem in RTP of tumours of the thorax and upper abdomen. In order to minimize these artifacts several strategies have been proposed: tidal breathing, breathhold techniques and gated image acquisition.

Tidal breathing (▶Fig. 2B): Patients are instructed to breathe shallowly during the CT and PET acquisitions. Thus, the frequency and magnitude of artifacts due to misalignment between CT and PET can be minimized (8). This technique is feasible for the use in RT-planning, if no detailed depiction of the breathing movement and/or amplitude of tumour motion is required. Alternatively, CT data can be acquired over several breathing cycles (slow CT imaging) (▶Fig. 2B), with a CT pitch value of less than 1 (65). As a result, both, the CT and emission data are motion-blurred. Using this strategy, attenuation correction based on the CT will be more accurate, but both PET and CT suffer from image resolution loss due to patient motion. This acquisition mode is suited neither for diagnostic nor for RTP purposes and is solely suitable for attenuation correction.

Breathhold techniques (▶Fig. 2B): Patients may be asked to hold their breath in mid-expiration during the entire low-dose CT, or at least for the time it takes the CT to scan the lower thorax and upper abdomen. Breath hold at end-expiration may not be feasible for severely ill patients. Alternatively, recent PET/CT technology advances (48) allow for limited axial-field-of-view acquisitions of PET/CT data in full-inspiration (53). In diagnostic use, this may help reduce motion-induced misalignment and increase the quality of the CT data of the thorax. Breathhold-techniques are of use for RTP and delivery only if the treatment can be performed under the same breathing conditions, which is e.g. the case for gated delivery (realised and controlled by the same devices as used for scanning).

Respiratory gating (▶Fig. 2C): During the acquisition of both PET and CT data the respiratory signal is monitored and used to categorize, or bin the data over the various phases of the respiratory cycle (typically into 8–16 bins). Thus, emission and transmission data can be matched for repeated phases (aka bins) of the respiratory cycle (6). Subsequently, attenuation correction and reconstruction of the emission data can be performed using the corresponding CT phase images for each respiratory bin. These so-called 4D PET/CT acquisitions can provide information on the midposition of the tumour but, more importantly, about the magnitude of tumour movement and total target volume

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

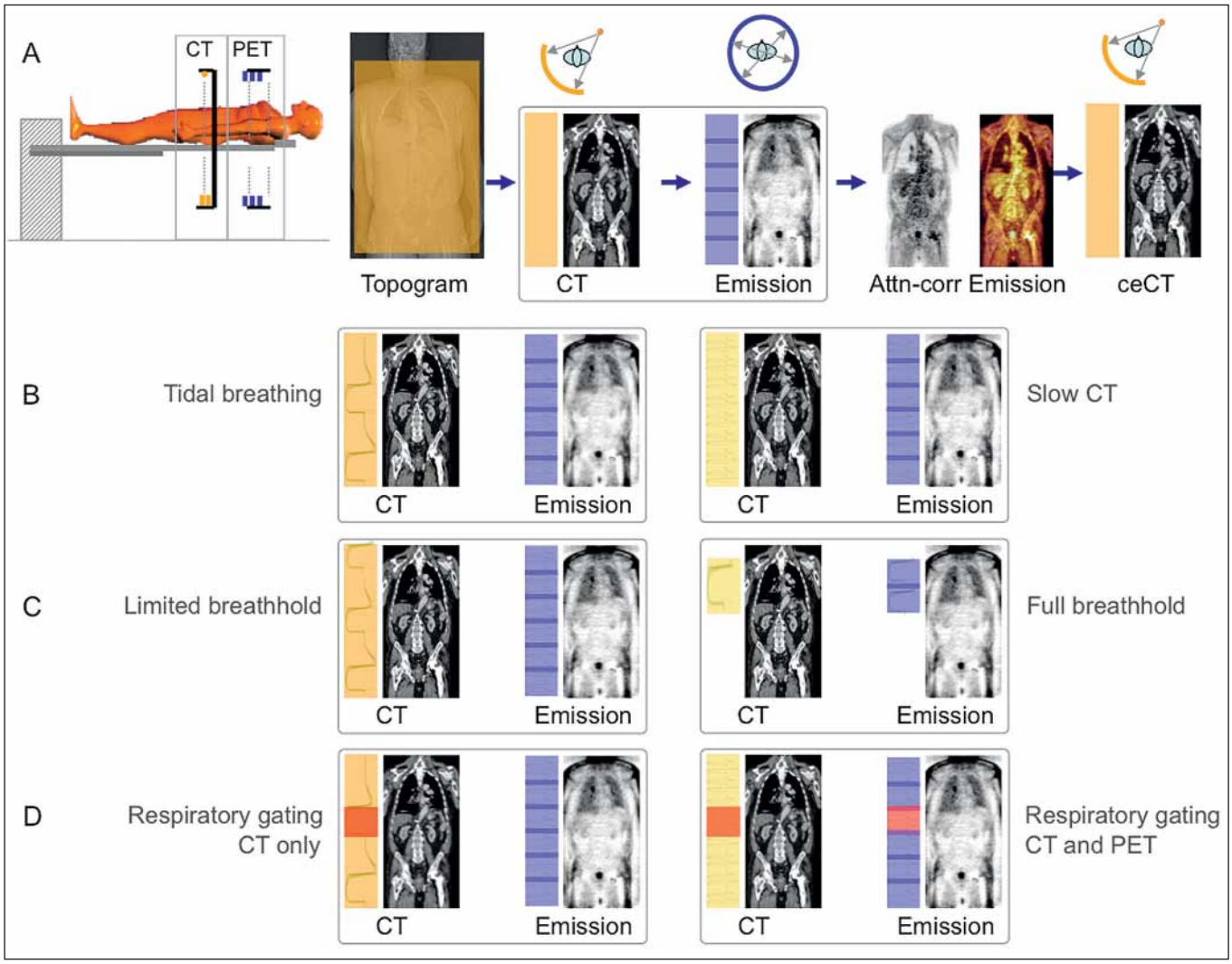

Fig. 2
A) Standard whole-body PET/CT examination protocol: a topogram followed by a spiral CT and a multi-step emission acquisition. Following image reconstruction a separate contrast-enhanced (ce) CT can be acquired.
B) CT and PET emission data can be acquired during tidal breathing, or alternatively, the CT can be acquired at a lower pitch over several breathing cycles (slow CT). This ensures a better match for the purpose of attenuation correction.
C) CT data can be acquired with limited breathhold techniques whereby patients is asked to hold their breath in normal expiration to best match the average position of the diaphragm during tidal breathing during the emission acquisition. Novel PET/CT systems are fast enough to allow for the acquisition of a limited axial field-of-view in full-inspiration breathhold for both CT and PET.
D) Respiratory gating is available and can be applied to individual bed positions for either CT-only or PET and CT.

(63, 75). The latter information can directly be used to define the extent of the radiation beam such that it would always include the tumour despite its movement. Here, the PET-data ideally complement the 4D-CT data.

The use of 4D PET data is not only helpful for gated but also for ungated RT-delivery, e. g. in approaches like individual internal target volume (ITV)-delineation and mid-ventilation amplitude calculations (4). Unfortunately, at present the implementation of 4D PET/CT is still relatively cumbersome and requires considerable efforts, quality control and optimization of work-flow processes. Furthermore, the acquisition of 4D-CT data requires increased raw data sampling due to the increased number of reconstructed CTs, and, therefore, is inherent with an increased patient exposure.

PET image reconstruction

PET/CT image reconstruction directly affects the detection and delineation of any metabolic lesion. Different diagnostic objectives may require different strategies for image quality and quantification (49, 58, 61). Furthermore, image characteristics depend strongly on the way PET/CT examinations are performed, such as patient preparation, administered amount of FDG

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

in relation to scan duration and system sensitivity, reconstruction method and settings, etc. (11, 13). Clearly, consistent and standardized procedures are a pre-requisite for the expanded use of PET/CT (12).

Today, iterative reconstruction algorithms have become the standard on all PET/CT systems and are the preferred reconstruction methods because of their superior image quality when compared to filtered back projection ((▶Fig. 3). Iteratively reconstructed images are characterized by the number of iterations and subsets, relaxation factor, matrix size, voxel size, image zoom, image smoothing and smoothing filter size or kernel (full width half maximum, FWHM). In general, iterative reconstruction methods employing a sufficient number of iterations and subsets (product larger than 40) to ensure sufficient amount of convergence are preferred, whereby reconstruction shall be fully 3D without Fourier rebinning. PET images should be reconstructed with and without attenuation correction to allow inspection and assessment of attenuation correction artifacts due to contrast agents, metal implants and patient motion (10, 77, 78). In order to ensure correct interpretation of attenuation artefacts in the use of PET/CT in RT-planning, the diagnostic information derived from non-attenuation corrected datasets should be communicated to the radiation oncologist. In case of quantitative use all corrections needed for quantification must be applied such as e.g. dead time, correction for detector sensitivities (normalization), decay correction, scatter correction, attenuation correction etc. In the case of combined PET/CT, a correct co-registration is particularly important as the CT data are used for attenuation correction of the PET data (41) and erroneous co-registration can lead to artifacts in the attenuation corrected PET data.

When using FDG PET/CT for staging, image acquisition and reconstruction should be performed in such a way that lesion detectability is enhanced while avoiding increase of false positive findings. Although clinical evidence is not yet fully available, use of time-of-flight (TOF) (48) and resolution recovery during reconstruction will enhance image quality and, therefore, is likely to improve the diagnostic quality of the PET images (34, 69). However, PET/CT users and readers need to get familiar with the higher resolution images that this new reconstruction method provides. At this stage, until further clinical evidence is available, image resolution recovery is not yet recommended for RTP purposes.

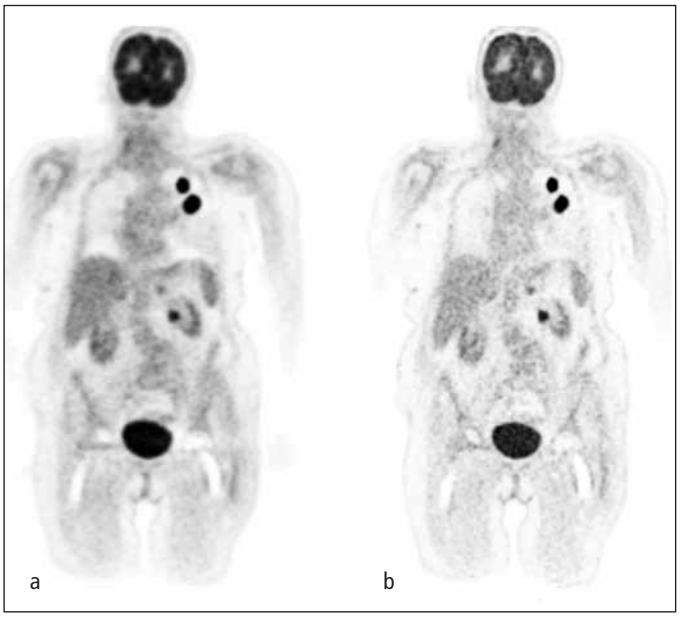

Fig. 3 Improvement of PET/CT image quality over time as a result of new technology development. Coronal image planes of a whole-body ^{18}F-FDG PET study performed on a state of the art PET/CT system, reconstructed using regular iterative reconstruction (a) and TOF + PSF iterative reconstruction (b). Courtesy of M. Lambrechts and S. Stroobants, UZA, Antwerp, Belgium.

When using FDG PET for quantification and/or quantitative response assessment it is recommended to follow the guidelines of the German Society for Nuclar Medicine (DGN) (44) and/or the European Association for Nuclear Medicine (EANM) for quantitative PET/CT studies (13). Here, specifications for standardized uptake value (SUV) recovery coefficients, measured under specific conditions and with a specific phantom are given in order to achieve harmonized image quantification.

The accuracy and precision of FDG PET based (automated) target definition is a function of both image quality and the segmentation method used (22, 61, 71, 78, 80, 89). Low noise levels in combination with a high spatial resolution are frequently considered optimal for tumour segmentation, while some users prefer substantial filtering applied during image reconstruction.

Despite the rigorous protocol harmonization efforts by the EANM (12), some residual differences in image characteristics between various PET/CT systems remain, which may have an impact on volume definition and precision rather than on quantification (24). Therefore, optimal reconstruction methods and settings for a specific task followed by a calibration of the segmentation method for a specific situation are preferred (85).

Recommendations

1. Image reconstruction should be standardised for PET/CTs used for RT-planning on an institutional or study level.
2. Hardware and software updates must be reported to the cooperating RT-responsibles, as they may affect volume delineation.
3. Retrospective image resolution recovery through deconvolution is non-standard and currently being evaluated. It cannot be recommended at this point in the context of PET/CT-guided RTP.
4. For standard planning purposes, 3D (non-respiratory gated) PET/CT imaging following limited breathhold or tidal breathing protocols is sufficient. 4D-PET/CT acquisitions may be useful to complement 4D-CT information on the magnitude of tumour motion, which may be used for optimized treatment planning purposes.
5. Users should be aware of potential artifacts in the attenuation-corrected PET due to CT truncation, the presence of CT contrast agents and metal implants as

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

well as intra-scan patient motion. Relevant artifacts should be reported by the nuclear medicine specialist in order to avoid false contouring.

Data transfer/TPS

Image interpretation, diagnosis and image-guided treatment planning are typically performed on dedicated workstations separate from the PET/CT console, so as to not to interfere with the routine acquisition workflow. In order to assure adequate image processing (incl. diagnosis, quantification and target volume (TV) delineation) certain standards of image data handling, storage and transfer need to be adhered to.

Today, any image data transfer in clinical environments is based on Digital Imaging and Communication in Medicine (DICOM) standards. Data sets of anatomical and biological image information are typically stored as DICOM objects. DICOM standards and object definitions exist for most imaging modalities including the data (54, 56) of

- CT,
- PET,
- single photon emission computed tomography (SPECT),
- ultrasound (US) and
- magnetic resonance imaging (MRI).

DICOM-conformance statements of the manufacturers of imaging and treatment systems provide detail information on the send and receive options of the DICOM nodes involved; this relates to the imaging side as well as to the treatment planning system. Data can be transferred between nodes and workstations on physical media (e. g. CD-ROM, DVD) or via internet protocol (IP) network (55, 57). In case of a direct network transfer the systems must be configured with the transmission control protocol/internet protocol (TCP/IP)-hostname (address), application entity title (AET) and the TCP/IP-port number of each other to allow for data to be sent or received respectively. For security of the data and data transfer, all data should be communicated only within a restricted, firewall-protected local area network (LAN). If data need to be communicated across firewalls, virtual private network (VPN) tunnels or dedicated IP-ports and an appropriate data encryption/decryption should be used. The protection of patient specific data is subject to regulatory issues that can vary significantly from country to country.

Treatment planning systems (TPS) are used to define a treatment plan based on a preassigned target volume or following the delineation of the TV on the TPS. Alternatively, a state-of-the-art nuclear medicine image processing workstation can be used to define a PET-based proposal for the GTV-delineation. The tumour volume may be represented differently depending on the choice of the radiopharmaceutical for PET/CT imaging (61).

The proposed GTV is stored as an RT-DICOM structure describing the target as a volume-of-interest (VOI). RT structures are stored together with the original images in DICOM format, which were used to define the GTV. DICOM RT structures are described in Supplement 11 to Part 3 of the DICOM-Standard (57). Similar to the image DICOM data, the RT structure set can be transferred via a network connection or on physical media (55).

The data transfer between the nuclear medicine imaging and RTP modalities can also be facilitated through a Picture Archiving and Communication System (PACS). However, PACS systems are designed for diagnostic use and frequently do not support DICOM RT-IODs. In addition, RT and nuclear medicine departments frequently operate on separate image or data archives that typically are not PACS-systems.

If the RTP is used as a substitute of the NM viewing station, then basic display and quantification features need to be verified and standardized. This includes the correct calculation of the SUV from the available DICOM header information. Furthermore, the orientation of the image volumes as well as the accurate spatial alignment and extent need to be verified on the TPS. However, no standards exist for this procedure. Therefore, in clinical routine, a visual assessment of correct file transfer is required for all data, i. e., a check for correct orientation as well as for a complete number of images being transferred. Most of the TPS report an error in case of malfunctioning data transfer; however, the total numbers of image planes sent and received needs to be verified by the user.

In addition to the actual image data transfer, communication of the relevant diagnostic information to the experts involved in RTP must also be ensured. It is recommended that all diagnostic findings from the PET/CT are communicated amongst the nuclear medicine, radiology and radiation oncology specialists prior to defining the treatment plan based on the PET/CT data and complementary diagnostic information. Since most radiation oncologists are no PET/CT experts diagnostic information on faintly accumulating pathologic structures, such as lymph nodes as well as expert advice on any misleading image artifact should be clearly communicated (3).

Recommendations

1. Set-up and verify DICOM path between image acquisition console and RTP workstation with the help of a certified IT or system administrator.
2. Verify the alignment of PET/CT data prior to using them for RTP.
3. Implement routine to visually (manually) check number of image planes/slices when transferring data from PET/CT to the RTP system.
4. Establish routine workflow for communication of diagnostic findings and pre-defined tumour volumes between PET/CT and radiation oncology departments. Foster co-operation between radiologists, nuclear medicine specialists and radiation oncologists during diagnosis and TV delineation.

Image fusion/registration

Image co-registration is an essential part of image-guided RTP. It helps properly align and display anatomical and metabolic image information for identification of active tumour volume, target volumes and other surrounding structures. Co-registration, by itself, describes a process of data alignment by calculating the transformation that maps or transforms voxels of one image set (e. g., test, moving or float-

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

ing image) to the voxels of another image (e. g., reference image). The position of the associated voxel from the test image is assigned to the reference image (33). In the context of RTP the CT is typically the reference image and the PET is the image to be co-registered. Following accurate co-registration image fusion describes the process or results of applying the above transformation in order to view both images in the same frame of reference. Image fusion mandates pre-aligned data sets in order to be clinically useful.

Software fusion in RTP

In addition to accurate attenuation correction, new approaches of biologically adapted RTP necessite a highly accurate spatial correlation of molecular and morphological information regarding tumour activity and size for detailed assessment of early treatment response. In addition, such correlated image information can help assess potential treatment failure matching to prior radiation dose distribution. Therefore, reproducible and validated image co-registration is essential for biologically adapted radiotherapy concepts (79). However, co-registration is only given at single time points by combined CT; integration of longitudinal image information (e. g., multiple examinations before, during and after RT) necessities additional software-based registration approaches. Moreover, in most RT departments, RTP is not performed on the CT data acquired with PET/CT but on a dedicated "planning CT" data. Hence, to employ the additional PET information for treatment planning, software-based fusion to the planning CT is required.

Prior to using PET image data for RTP they may have to be co-registered to the planning CT that is used for dosimetry planning purposes (2), unless the combined PET/CT study is acquired in such a way that it replaces separate CT and PET studies. Since CT images have a higher spatial resolution than PET, the CT image planes are used as the reference frame, which the PET images are aligned to (1). This helps to maintain resolution and contrast of the CT data, which form the reference image and are used as a basis for RT dose calculation.

Co-registration algorithms and considerations for software fusion

In general, software-based image co-registration may be either linear (rigid) or non-linear (non-rigid, non-affine) (68). With rigid transformations the spatial relationship between anatomical structures and landmarks remains completely unchanged. Since, however, the reference and moving data sets usually have different pixel sizes, image matrices and number of images and slice-to-slice distance, the transformation does include an interpolation step, which assures that structures can be compared at the same scale, sampling density and pixel size. Unfortunately, this leads to a loss of contrast unless computationally more demanding algorithms, such as cubic interpolation methods are applied. Linear co-registration algorithms are widely used in brain imaging, as the brain inside the skull can be safely regarded as a rigid body.

In whole-body PET/CT, the assumption of a rigid body transformation cannot always be justified anymore. The CT acquisition takes about a minute, while the PET emission data are acquired for up to 30 minutes, depending on the actual imaging protocol. During the acquisition respiratory motion, muscle relaxation and physiological intraabdominal movements are unavoidable. Here, non-rigid, non-affine co-registration techniques may be of help, with a number of different approaches developed for diverse applications. However, due to the risk of spatial distortion, deviation of the shape and size of tumours that are not visible on CT, and change of uptake intensity due to spreading of voxel data (61), to date, no method of non-rigid registration can safely be recommended for the use in RT-planning outside of clinical studies today (29).

Currently only the use of linear co-registration algorithms can be recommended for image-guided RTP, since these algorithms maintain geometrical relationships between the structures, which are transformed. Nonetheless, feature- and volume-based algorithms can also be used for PET/CT-guided RTP. These algorithms aim at aligning corresponding anatomic landmarks, organ surfaces or other features, frequently with help of a-priori fiducial markers (74).

Volume-based image co-registration algorithms maximize measures of similarity (e. g., cost function) between images (74). Especially, methods implementing mutual information (MI) have been proven robust, stable and successful in different clinical scenarios and should be used in RTP (30,73). While improvement of image alignment with the use of non-rigid algorithms is possible, limited clinical validation restricts their use for RTP for now. It is conceivable, that the deformation of image data caused by co-registration using non-rigid algorithms may result in spatial distortion of PET images or deviation of tumour shape, especially in cases, where CT does not unequivocally depict the tumours. In addition, in patients with lung lesions this type of co-egistration may change the metabolic tumour volume if full inspiratory thoracic CT volumes are co-registered to quiet breathing PET data, and thus may change the GTV. Therefore, non-rigid co-registration algorithms cannot be recommended at this stage for RTP purposes (61).

Regardless of the imaging data used (i. e., separate PET or PET/CT) correct co-registration of the PET data with the CT data used for RT planning must be verified. Critical evaluation of the alignment quality is important in RTP, since the difference in spatial localization of tumour may lead to false estimation of GTV, and, subsequently, to incorrect treatment.

Despite the potential problems associated with expert identification of landmarks the evaluation of quality of alignment is best done by visual comparison of anatomical landmarks, which are clearly depicted by both imaging modalities (reference and moving image). In thoracic areas these are (apart from tumour): carina of the trachea, top of the lungs, spine, sternum and the thoracic wall. In the head and neck region thorough patient positioning and use of masks for PET and CT examination are mandatory to enable a better quality of alignment (8). In the abdomen, bony structures may be of use, whereas,

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

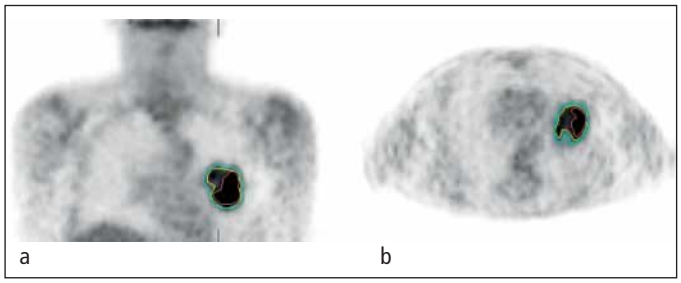

Fig. 4 Example of differences between PET-based TV delineated by different thresholding methods in a patient with lung tumour: red: relative thresholding (40% of maximum uptake; delineated volume = 47 ml); blue: absolute thresholding (2.5 SUV; delineated volume = 105 ml); yellow: adaptive thresholding according to (71) (delineated volume = 77 ml)
a) coronal slice; **b)** transversal slice

intraabdominal structures cannot be regarded safe reference points because of the changes in the physiological filling during the course of the examination.

Currently, operator independent, robust and accurate standard of reference and measures of alignment are an area of active research (90). However, depending on the imaging modalities utilized qualitative assessment of the accuracy of co-registration using imaging overlay can be performed. A straightforward method to visually validate the accuracy of co-registration is to use linked cross hair cursors.

Recommendations

1. Image fusion for RTP demands accurately aligned image volumes.
2. For the purpose of RTP based on PET or PET/CT and CT images only linear co-registration algorithms should be employed.
3. The accuracy of co-registration must be checked prior to proceeding with the treatment or planning process on the aligned data sets.

Image contouring

When employing PET image information for tumour volume delineation, the choice of the optimum delineation method is a challenge (45). Nonetheless, tumour delineation is never performed exclusively on PET alone. It is always a comprehensive interpretation of history, physical examination, endoscopy, and morphological imaging modalities, such as CT and MRI. Automatic methods for PET-based target delineation were shown to add important information for a reliable GTV definition, thus, significantly reducing the inter-observer-variability of GTV-contouring (17, 83).

From a technical perspective, PET-based tumour volume delineation is essentially an image segmentation issue whereby the image must be decomposed into non-overlapping meaningful regions or, mathematically, the voxels of the image must be grouped into a set of distinct classes. Image segmentation can be seen as a classification problem where each pixel is given a label. In the case of PET images, for example, two possible classes or regions can be defined as tumour and surrounding healthy tissues. More complex problems can be considered, involving sub-regions within the tumour (e. g., necrotic or hypoxic regions) and the healthy tissues (e. g., muscle, air cavity). Numerous segmentation algorithms, each with their own underlying model or assumptions exist today (67).

The compatibility of these assumptions with the properties of the images to be segmented is a key concern. For example, PET images are characterized by relatively low spatial resolution and signal-to-noise ratio (SNR). The SNR accounts for the statistical uncertainty of the perceived uptake in each image voxel whereas the spatial resolution accounts for the correlations between neighboring voxels. Visually, a low spatial resolution distorts the geometry of the imaged objects and leads to blurred images, with a pronounced partial volume effect (PVE) for small structures (76). The low spatial resolution of PET images and, to a lesser extent, their low SNR are considered major impediments towards accurate reproducible delineation, thus, intrinsically limiting the accuracy of many segmentation methods (45). Most studies today have investigated the use of segmentation methods that are simple to implement, such as manual delineation as well as threshold-based automatic or semi-automatic contouring.

However, geometrical distortions make manual delineation of target volumes difficult. Blurred gradients at the boundary of two regions mislead the human observer and may cause significant over- or underestimation of the true target volume. Co-registered images, such as those from PET/CT systems, may help (17, 83), but can also bias the delineation, due to patient-induced local and global misalignments, or disagreements between the two modalities regarding the extent of the tumour tissue.

Threshold-based segmentation aims at separating a region with high uptake from a background with a lower uptake. Because it is both intuitive to understand as well as easy to implement, threshold-based delineation is very popular (22, 35, 52, 59, 60, 66, 71). Nevertheless, the application of different thresholding methods may lead to large differences in delineated PET-volumes (59) as demonstrated in ▶Figure 4.

Technically, thresholding relies on the implicit assumption that the uptake of each voxel is a good indicator of its class or region. Such an assumption ignores the inter-voxel correlations that stem from the low resolution. Taking resolution into account proves to be difficult (40, 42, 76) and significantly complicates the delineation process. This approach shows that the optimal threshold should be iteratively determined after background subtraction (84), and that thresholding is affected significantly by the spatial resolution (22, 84). Segmentation algorithms beyond simple thresholding exist as well; they are based on gradient information (25), on partial volume effect correction or deblurring (25), on statistical or fuzzy clustering (32), or on a combination of all the above approaches. These algorithms are, however, frequently more complex and, thus, more difficult to implement (25, 32).

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

The routine implementation of a segmentation method mandates prior validation with phantom data at least. For obvious logistical reasons, delineation methods are often validated with a limited amount of data. Most studies in the literature are indeed motivated by specific needs in a given situation (80). This means that the re-implementation of the same method under different conditions, such as in another centre, using another PET system, or another radiotracer necessitates a recalibration and a new validation.

Today, the scientific community is just starting to become aware that accurate delineation with intrinsically blurred PET images is a particularly challenging problem (40, 42, 45, 76). The large diversity of methods described in the literature and the absence of consensus further reflects this difficulty. The next step will obviously aim at a standardization of acquisition and reconstruction protocols across PET systems and PET centres (12, 52). Given the complexity of the issues at hand, it is likely that one single approach may not be able to reliably delineate all tumour lesions, and that an optimal strategy may require input from both automatic algorithms and human intelligence.

Recommendations

1. Any segmentation algorithm chosen for RTP in the institutional setting or in the context of a clinical study should provide algorithmic robustness and should be parameterized to the spatial resolution of the PET system in use.
2. An in-situ validation of the delineation method with phantom data should be performed. Any use of a particular delineation method (e. g., with a different tracer, a different tumour type or location) requires appropriate validation.
3. In clinical routine, a delineation method needs to be selected and agreed upon among the imaging experts and radiation oncologists. This is to limit inter-observer variability within the same institution.
4. Contouring should be performed jointly by two experts from radiotherapy and nuclear medicine. This team of experts needs to be aligned on the same contouring method. The same experts should contour all data from a given patient.

Patient setup, staff training

Adequately trained PET/CT operating staff is essential for logistical efficiency, quality assurance, and safety of the procedures. This requires expertise and efforts from imaging and radiation oncology personnel. Any PET/CT-based RTP should involve technical and medical staff from the imaging department as well as from the radiation oncology department. All staff need to be aware of the combined requirements for patient set-up, tomography and imaging protocols in order to avoid errors and conflicts. Standard PET/CT patient preparation (e. g. hydration, fasting) remains unchanged compared to PET/CT imaging for staging purposes. However, the availability of standardised or personalised positioning aids (e. g. thermoplastic masks) needs to be ensured upon patient referral. In addition, a well-instructed and prepared patient is mandatory for efficient PET/CT-guided RTP.

Patient set-up

Adequate patient positioning is required in diagnostic imaging, therapy planning and therapy delivery alike. This applies to positioning of body parts inside the field-of-view, as well as outside the field-of-view to ensure reproducibility. Careful and comprehensive patient instructions prior to the examination and the use of external patient positioning aids are needed to help minimize patient motion during the imaging session. Intra-exam patient motion in PET/CT is known to affect the co-registration accuracy of functional and anatomical information, which, in turn, may lead to a false lesion definition, and may bias the metabolic uptake as measured on attenuation-corrected PET (10, 87).

Various patient positioning aids have been discussed for clinical PET/CT imaging (9, 14). In contrast, for external beam radiotherapy, the optimal patient position is dictated by treatment delivery requirements. The applied support structures must be of low physical density so as to add little, if any, attenuation of the CT transmission and PET emission signals. It is known that additional, dedicated patient fixation materials improve anato-metabolic image alignment and overall diagnostic quality significantly over examinations with patients being positioned on head pillow and/or blankets only (9, 14).

The central body may be stabilised with sufficient accuracy for radiotherapy using a vacuum mattress, typically made of a soft plastic cushion filled with very small Styrofoam beads (62), and can be applied for diagnostic PET imaging as well (14). Here, patients are positioned head first and supine and with their arms elevated. By extracting the air from the cushion and holding the mattress tight, the entire patient, or a specific anatomical region of interest (e. g., head/neck, pelvis) is fixed and supported comfortably. The extensions of the vacuum device can be elevated at the level of the trunk to prevent lateral movement of the patient.

Vacuum mattresses have a very low physical density of around –950 HU, and do not deteriorate PET image quality following CT-based attenuation correction. Care should be taken, however, when using even low-attenuating positioning devices that extent beyond the measured transverse field-of-view of the CT since unaccounted attenuation may bias the attenuation-corrected emission activity distribution (50). Alternative patient positioning devices in RT include standardised arm and knee support systems (▶Fig. 1). Similarly to the mattress, these must be accounted for during the CT transmission scan in PET/CT.

The head and neck area can be immobilised for radiotherapy using personalised thermoplastic masks, with a day-to-day repositioning error of just a few millimeters (86). It has been shown that these immobilisation systems can also be applied on PET and PET/CT systems, and that resulting fused image sets have a registration error < 3 mm and are suitable for multimodality PET/CT radiation treatment planning (88). The adoption of dedicated patient positioning devices requires experienced operators to achieve accurate repositioning results. ▶Figure 5 shows that untrained PET/CT operating staff do not achieve the same accuracy in patient positioning for radiotherapy planning purposes. Therefore, supervision or collaboration with radiation oncology staff is mandatory.

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

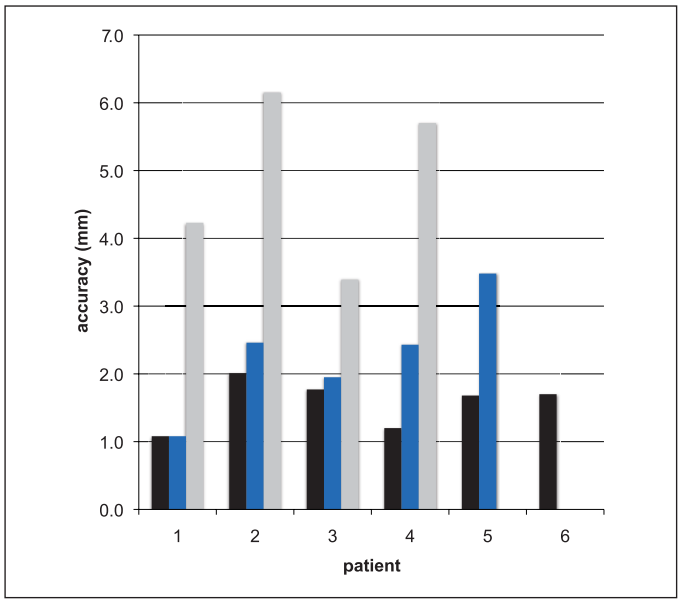

Fig. 5 Co-registration accuracy (mm) of PET and CT images during patient set-up depends on the experience of the personnel. Patient positioning by PET technologists alone shows a significant misalignment (■). When nuclear medicine technologists were supervised by experienced radiotherapy staff co-registration errors were reduced (■). Collaborative efforts in patient positioning provide the best and most reproducible accuracy (■).

Radiation exposure

Seierstad et al. estimate that 40% of the exposure to the staff engaged in clinical PET/CT routine originates from exposure during patient set-up procedures (72). This fraction increases with the complexity of the patient set-up, for example by spending more time at the patient when using more complex positioning aids (39). Pakbiers et al. have shown that patient positioning itself accounts for the largest relative contribution to the effective dose of technologists in the entire chain of activities of PET/CT patient management (64). Additional contributions to staff exposure come from setting up patients with IV lines for CT contrast administration and for repositioning patients during combined examinations (7).

It is important to note that relative contributions to staff exposure and absolute staff exposure must not deter from comprehensive patient preparation but be monitored responsibly. Excessive staff exposure can be avoided in high-throughput PET/CT imaging scenarios and set-up scenarios involving RT patients by several ways. For example, patient instructions should be given prior to the injection of the activity. Patient positioning aids should not be custom-built from the injected patient during the uptake period or following a nuclear medicine examination. RT trained staff should be involved during patient setup to shorten the time to position and fixate the patient either with a thermoplastic mask or with a vacuum mattress, thus minimizing the time needed in very close proximity to the injected patient. Using a motorized air pump to extract the air from the mattress reduces the time to fixate the patient. Additional dose reduction schemes are available with automated activity injectors (20) and new PET/CT technology that requires less activity to be injected thanks to higher sensitivity PET technology (48). PET operating personnel can play an important role in creating radiation exposure awareness of engaged radiotherapy staff.

Recommendation

1. Adequate staff training for patient positioning with the use of dedicated RT positioning devices is essential for PET/CT-guided RTP.
2. Joint efforts by PET/CT imaging staff and RT technologists are required to yield optimum exam quality and to reduce staff exposure.
3. Relatively increased staff exposure rates should not deter from careful patient positioning.

Conclusion

State-of-the-art multimodality RTP using integrated PET/CT systems require extensive and stringent logistics, preparation of patients and hardware, QC, QA and standardization. Most importantly intensive communication between specialists and technicians from all disciplines involved should be routine practice. Upon fulfilling the requirements to perform PET/CT for RTP, the new dimension of molecular imaging can be added to the traditional anatomy-based technology. This opens the window of opportunity for improved RTP, better clinical studies and ultimately enhanced patient care.

Acknowledgement

This manuscript obtained official endorsement by the EANM.

Further endorsement was obtained from the German Working Group „nuclear medicine and radiotherapy“ of the German scientific societies for nuclear medicine and radiation oncology.

DT is supported by the European Social Fund and by the Ministry of Science, Research and the Arts Baden-Württemberg.

Conflict of interest

The authors DT, RB, DDR, AG, JL, UP, BS, AS, WvE, WV, WO, UN declare, that there is no conflict of interest. TB is the founder of cmi-experts GmbH and reports no conflict of interest and financial implication with this contribution.

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

References

1. Balter JM, Cao Y. Advanced technologies in image-guided radiation therapy. Semin Radiat Oncol 2007; 17: 293–297.
2. Balter JM, Kessler ML. Imaging and alignment for image-guided radiation therapy. J Clin Oncol 2007; 25: 931–937.
3. Bayne M, Hicks RJ, Everitt S et al. Reproducibility of „intelligent" contouring of gross tumour volume in non-small-cell lung cancer on PET/CT images using a standardized visual method. Int J Radiat Oncol Biol Phys 2010; 77: 1151–1157.
4. Beddar AS, Briere TM, Balter P et al. 4D-CT imaging with synchronized intravenous contrast injection to improve delineation of liver tumours for treatment planning. Radiother Oncol 2008; 87: 445–448.
5. Bendriem B, Townsend DW (eds). The Theory and Practice of 3D PET. Developments in Nuclear Medicine (Vol 32). Kluwer Academic Publishers 1998.
6. Bettinardi V, Picchio M, Di Muzio N et al. Detection and compensation of organ/lesion motion using 4D-PET/CT respiratory gated acquisition techniques. Radiother Oncol 2010; 96: 311–316.
7. Beyer T, Antoch G, Müller S et al. Acquisition protocol considerations for combined PET/CT imaging. J Nucl Med 2004; 45 (Suppl 1): 25S-35S.
8. Beyer T, Bockisch A, Kuhl H et al. Whole-body ^{18}F-FDG PET/CT in the presence of truncation artifacts. J Nucl Med 2006; 47: 91–99.
9. Beyer T, Tellmann L, Nickel I et al. On the use of positioning aids to reduce misregistration in the head and neck in whole-body PET/CT studies. J Nucl Med 2005; 46: 596–602.
10. Bockisch A, Beyer T, Antoch G et al. Positron emission tomography/computed tomography--imaging protocols, artifacts, and pitfalls. Mol Imaging Biol 2004; 6: 188–199.
11. Boellaard R, Krak NC, Hoekstra OS et al. Effects of noise, image resolution, and ROI definition on the accuracy of standard uptake values: a simulation study. J Nucl Med 2004; 45: 1519–1527.
12. Boellaard R, O'Doherty MJ, Weber WA et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging 2010; 37: 181–200.
13. Boellaard R. Standards for PET image acquisition and quantitative data analysis. J Nucl Med 2009; 50 (Suppl 1): 11S-20S.
14. Brechtel K, Heners H, Mueller M et al. Fixation devices for whole-body ^{18}F-FDG PET/CT: patient perspectives and technical aspects. Nucl Med Commun 2007; 28: 141–147.
15. Busemann Sokole E, Plachcínska A, Britten A. Acceptance testing for nuclear medicine instrumentation. Eur J Nucl Med Mol Imaging 2010; 37: 672–681.
16. Busemann Sokole E, Placinska A, Britten A et al. Routine quality control recommendations for nuclear medicine instrumentation. Eur J Nucl Med Mol Imaging 2010; 37: 662–671.
17. Caldwell CB, Mah D, Ung YC et al. Observer variation in contouring gross tumour volume in patients with poorly defined non-small-cell lung tumours on CT: the impact of ^{18}FDG-hybrid PET fusion. Int J Radiat Oncol Biol Phys 2001; 51: 923–931.
18. Chiti A, Kirienko M, Grégoire V. Clinical use of PET-CT data for radiotherapy planning: what are we looking for? Radiother Oncol 2010; 96: 277–279.
19. Coffey M, Vaandering A. Patient setup for PET/CT acquisition in radiotherapy planning. Radiother Oncol 2010; 96: 298–301.
20. Covens P, Berus D, Vanhavere F et al. The introduction of automated dispensing and injection during PET procedures: a step in the optimisation of extremity doses and whole-body doses of nuclear medicine staff. Radiat Prot Dosimetry 2010; 140: 250–258.
21. Czernin J, Allen-Auerbach M, Schelbert HR. Improvements in cancer staging with PET/CT: literature-based evidence as of September 2006. J Nucl Med 2007; 48 (Suppl 1): 78S-88S.
22. Daisne JF, Sibomana M, Bol A et al. Tri-dimensional automatic segmentation of PET volumes based on measured source-to-background ratios: influence of reconstruction algorithms. Radiother Oncol 2003; 69: 247–250.
23. Evans PM. Anatomical imaging for radiotherapy. Phys Med Biol 2008; 53: R151–R191.
24. Frings V, de Langen AJ, Smit EF et al. Repeatability of metabolically active volume measurements with ^{18}F-FDG and ^{18}F-FLT PET in non-small cell lung cancer. J Nucl Med 2010; 51: 1870–1877.
25. Geets X, Lee JA, Bol A et al. A gradient-based method for segmenting FDG-PET images: methodology and validation. Eur J Nucl Med Mol Imaging 2007; 34: 1427–1438.
26. Geworski L, Knoop BO, de Witt M et al. Multicenter comparison of calibration and cross calibration of PET scanners. J Nucl Med 2001; 43: 635–639.
27. Geworski L, Reiners C. Qualitätsprüfung nuklearmedizinischer Messsysteme: Konstanzprüfung. In: Empfehlungen zur Qualitätskontrolle in der Nuklearmedizin–Klinik und Messtechnik. Geworski L, Lottes G, Reiners Chr, Schober O (eds). Stuttgart: Schattauer 2003; 217–289.
28. Gregoire V, Chiti A. PET in radiotherapy planning: Particularly exquisite test or pending and experimental tool? Radiother Oncol 2010; 96: 275–276.
29. Grgic A, Ballek E, Fleckenstein J et al. Impact of rigid and nonrigid registration on the determination of ^{18}F-FDG PET-based tumour volume and standardized uptake value in patients with lung cancer. Eur J Nucl Med Mol Imaging 2011; 38: 856–864.
30. Grgic A, Nestle U, Schaefer-Schuler A et al. 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: 103–111.
31. Hamacher K, Coenen HH, Stöcklin G. Efficient stereospecific synthesis of no-carrier-added 2-[^{18}F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. J Nucl Med 1986; 27: 235–238.
32. Hatt M, Cheze le Rest C, Turzo A et al. A fuzzy locally adaptive Bayesian segmentation approach for volume determination in PET. IEEE Trans Med Imaging 2009; 28: 881–893.
33. Hill DL, Batchelor PG, Holden M et al. Medical image registration. Phys Med Biol 2001; 46: R1-R45.
34. Hoetjes NJ, van Velden FH, Hoekstra OS et al. Partial volume correction strategies for quantitative FDG PET in oncology. Eur J Nucl Med Mol Imaging 2010; 37: 1679–1687.
35. Hofheinz F, Pötzsch C, Oehme L et al. Automatic volume delineation in oncological PET. Evaluation of a dedicated software tool and comparison with manual delineation in clinical data sets. Nuklearmedizin 2012: 51: 9–16.
36. Hurkmans CW, van Lieshout M, Schuring D et al. Quality assurance of 4D-CT scan techniques in multicenter phase III trial of surgery versus stereotactic radiotherapy (Radiosurgery Or Surgery for operable Early stage (Stage 1A) non-small-cell Lung cancer [ROSEL] Study). Int J Radiat Oncol Biol Phys 2010; 80: 918–927.
37. IEC 61223–2–6: Evaluation and routine testing in medical imaging departments, Part 2–6: Constancy tests – Imaging performance of computed tomography X-ray equipment, 2006.
38. IEC 61223–3–5: Evaluation and routine testing in medical imaging departments, Part 3–5: Acceptance tests – Imaging performance of computed tomography X-ray equipment, 2004.
39. Kearns WT, Urbanic JJ, Hampton CJ et al. Radiation safety issues with positron-emission/computed tomography simulation for stereotactic body radiation therapy. J Appl Clin Med Phys 2008; 9: 2763.
40. Kessler RM, Ellis Jr JR, Eden M. Analysis of emission tomographic scan data: limitations imposed by resolution and background. J Comput Assist Tomogr 1984; 8: 514–522.
41. Kinahan PE, Hasegawa BH, Beyer T. X-ray-based attenuation correction for positron emission tomography/computed tomography scanners. Semin Nucl Med 2003; 33: 166–179.
42. King MA, Long DT, Brill AB. SPECT volume quantitation: influence of spatial resolution, source size and shape, and voxel size. Med Phys 1991; 18: 1016–1024.
43. Kotzerke J, Oehme L, Lindner O et al. Positron emission tomography 2008 in Germany – results of the query and current status. Nuklearmedizin 2010; 49: 58–64.
44. Krause BJ, Beyer T, Bockisch A et al. FDG-PET/CT in oncology. German Guideline. Nuklearmedizin 2007; 46: 291–301.
45. Lee JA. Segmentation of positron emission tomography images: some recommendations for target delineation in radiation oncology. Radiother Oncol 2010; 96: 302–307.
46. Ling CC, Humm J, Larson Amols H et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. Int J Radiol Oncol Biol Phys 2000; 47: 551–560.
47. Lockhart CM, MacDonald LR, Alessio AM et al. Quantifying and reducing the effect of calibration error on variability of PET/CT standardized uptake value measurements. J Nucl Med 2011; 52: 218–224.
48. Lonsdale MN, Beyer T. Dual-Modality PET/CT instrumentation – Today and tomorrow. Eur J Radiol 2010; 73: 452–460.
49. MacManus M, Nestle U, Rosenzweig KE et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006–2007. Radiother Oncol 2009; 91: 85–94.
50. Mantlik F, Hofmann M, Werner MK et al. The effect of patient positioning aids on PET quantification in PET/MR imaging. Eur J Nucl Med Mol Imaging 2011; 38: 920–929.
51. Mutic S, Palta JR, Butker EK et al. Quality assurance for computed-tomography simulators and the computed tomography-simulation process: Report

© Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.

of the AAPM Radiation Therapy Committee Task Group No. 66. Med Phys 2003; 30: 2762–2792.
52. Nehmeh SA, El-Zeftawy H, Greco C et al. An iterative technique to segment PET lesions using a Monte Carlo based mathematical model. Med Phys 2009; 36: 4803–4809.
53. Nehmeh SA, Erdi YE, Meirelles GS et al. Deep-inspiration breath-hold PET/CT of the thorax. J Nucl Med 2007; 48: 22–26.
54. NEMA. DICOM Supplement 12, Addendum to part 3, positron emission tomography image objects, Final Text, 9 June 1996, http://dicom.nema.org/
55. NEMA. DICOM, Part 10, Media Storage and File Format for Media Interchange, 2008, http://dicom.nema.org
56. NEMA. DICOM, Part 3, Information Object Definitions, 2008, http://dicom.nema.org
57. NEMA. DICOM, Supplement 11, Addendum to part 3, Radiotherapy Objects, Final Text, 29 April 1997, http://dicom.nema.org/
58. Nestle U, Kremp S, Grosu AL. Practical integration of [^{18}F]-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: 209–225.
59. Nestle U, Kremp S, Schaefer-Schuler A et al. Comparison of different methods for delineation of ^{18}F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-Small cell lung cancer. J Nucl Med 2005; 46: 1342–1348.
60. Nestle U, Schaefer-Schuler A, Kremp S 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: 453–462.
61. Nestle U, Weber W, Hentschel M et al. Biological imaging in radiation therapy: role of positron emission tomography. Phys Med Biol 2009; 54: R1-R25.
62. Nevinny-Stickel M, Sweeney RA, Bale RJ et al. Reproducibility of patient positioning for fractionated extracranial stereotactic radiotherapy using a double-vacuum technique. Strahlenther Onkol 2004; 180: 117–122.
63. Otani Y, Fukuda I, Tsukamoto N et al. A comparison of the respiratory signals acquired by different respiratory monitoring systems used in respiratory gated radiotherapy. Med Phys 2010; 37: 6178–6186.
64. Pakbiers MTW, Kemerink GJ. Radiation exposure as a result of PET/CT. In: Radiation Dosimetry in Medicine: State of the Art in 2007. Vynckier S, Bos JJ, Lammertsma AA, Heijmen BJM, Zweers D (eds). Proceedings Fifth NCS Lustrum. Delft, The Netherlands: NCS 2007; 51–60.
65. Pan T, Sun X, Luo D. Improvement of the cine-CT based 4D-CT imaging. Med Phys 2007; 34: 4499–4503.
66. Paulino AC, Johnstone PA. FDG-PET in radiotherapy treatment planning: Pandora's box? Int J Radiat Oncol Biol Phys 2004; 59: 4–5.
67. Pham DL, Xu C, Prince JL. Current methods in medical image segmentation. Ann Rev Biomed Eng 2000; 2: 315–337.
68. Pietrzyk U. Does PET/CT render software registration obsolete? Nuklearmedizin 2005; 44 (Suppl 1): S13-S17.
69. Rapisarda E, Bettinardi V, Thielemans K et al. Image-based point spread function implementation in a fully 3D OSEM reconstruction algorithm for PET. Phys Med Biol 2010; 55: 4131–4151.
70. Sattler B, Lee JA, Lonsdale M et al. PET/CT (and CT) instrumentation, image reconstruction and data transfer for radiotherapy planning. Radiother Oncol 2010; 96: 288–297.
71. Schaefer A, Kremp S, Hellwig D et al. 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: 1989–1999.
72. Seierstad T, Stranden E, Bjering K et al. Doses to nuclear technicians in a dedicated PET/CT centre utilising 18F fluorodeoxyglucose (FDG). Radiat Prot Dosimetry 2007; 123: 246–249.
73. Skerl D, Likar B, Fitzpatrick JM et al. Comparative evaluation of similarity measures for the rigid registration of multi-modal head images. Phys Med Biol 2007; 52: 5587–5601.
74. Slomka PJ. Software approach to merging molecular with anatomic information. J Nucl Med 2004; 45 (Suppl 1): 36S-45S.
75. Söhn M, Weinmann M, Alber M. Intensity-modulated radiotherapy optimization in a quasi-periodically deforming patient model. Int J Radiat Oncol Biol Phys 2009; 75: 906–914.
76. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumour imaging. J Nucl Med 2007; 48: 932–945.
77. Souvatzoglou M, Bengel F, Busch R et al. Attenuation correction in cardiac PET/CT with three different CT protocols: a comparison with conventional PET. Eur J Nucl Med Mol Imaging 2007; 34: 1991–2000.
78. Stergar H, Krause BJ, Eschmann SM et al. Lesion concordance, image quality and artefacts in PET/CT: results of a multicenter study. Nuklearmedizin 2010; 49: 129–137.
79. Thorwarth D, Geets X, Paiusco M. Physical radiotherapy treatment planning based on functional PET/CT data. Radiother Oncol 2010; 96: 317–324.
80. Thorwarth D, Schaefer A. Functional target volume delineation for radiation therapy on the basis of positron emission tomography and the correlation with histopathology. Q J Nucl Med Mol Imaging 2010; 54: 490–499.
81. Townsend DW, Carney JPJ, Yap JT et al. PET/CT today and tomorrow. J Nucl Med 2004; 45 (1 Suppl): 4S-14S.
82. Townsend DW. Multimodality imaging of structure and function. Phys Med Biol 2008; 53: R1-R39.
83. Van Baardwijk A, Bosmans G, Boersma L 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: 771–778.
84. Van Dalen JA, Hoffmann AL, Dicken V et al. A novel iterative method for lesion delineation and volumetric quantification with FDG PET. Nucl Med Commun 2007; 28: 485–493.
85. Vanderhoek M, Perlman SB, Jeraj R. Impact of the definition of peak standardized uptake value on quantification of treatment response. J Nucl Med 2012; 53: 4–11.
86. Van Lin EN, van der Vight L, Huizenga H et al. Set-up improvement in head and neck radiotherapy using a 3D off-line EPID-based correction protocol and a customised head and neck support. Radiother Oncol 2003; 68: 137–148.
87. Vogel WV, Oyen WJ, Barentsz JO et al. PET/CT: panacea, redundancy, or something in between? J Nucl Med 2004; 45 (Suppl 1): 15S-24S.
88. Vogel WV, Schinagl DA, Van Dalen JA et al. Validated image fusion of dedicated PET and CT for external beam radiation and therapy in the head and neck area. Q J Nucl Med Mol Imaging 2008; 52: 74–83.
89. Wanet M, Lee JA, Weynand B et al. Gradient-based delineation of the primary GTV on FDG-PET in non-small cell lung cancer: A comparison with threshold-based approaches, CT and surgical specimens. Radiother Oncol 2011; 98: 117–125.
90. Weigert M, Pietrzyk U, Muller S et al. Whole-body PET/CT imaging: combining software- and hardware-based co-registration. Z Med Phys 2008; 18: 59–66.

 © Schattauer 2012

Downloaded from www.nuklearmedizin-online.de on 2012-04-11 | ID: 76861 | IP: 62.242.200.62
Note: Uncorrected proof, prepublished online
For personal or educational use only. No other uses without permission. All rights reserved.