

## **Use of PET and PET/CT for Radiation Therapy Planning: IAEA expert report 2006-2007.**

Michael MacManus<sup>1</sup>, Ursula Nestle<sup>2</sup>, Kenneth E Rosenzweig<sup>3</sup>, Ignasi Carrio<sup>4</sup>, Cristina. Messa<sup>5</sup>, Otakar Belohlavek<sup>6</sup>, Massimo Danna<sup>7</sup>, Tomio Inoue<sup>8</sup>, Elizabeth Deniaud-Alexandre<sup>9</sup>, Stefano Schipani<sup>7</sup>, Naoyuki Watanabe<sup>10</sup>, Maurizio Dondi<sup>10</sup>, Branislav Jeremic<sup>10</sup>

From

- 1 Peter MacCallum Cancer Centre, and University of Melbourne, Melbourne, Australia
- 2 Saarland University Medical Center, Homburg/Saar, Germany
- 3 Memorial Sloan-Kettering Cancer Center, New York, USA
- 4 Autonomous University of Barcelona, Barcelona, Spain
- 5 University of Milano Bicocca, Monza, and IBFM-National Research Council, Italy
- 6 Na Homolce Hospital, Prague, Czech Republic
- 7 Scientific Institute H San Raffaele, Milano, Italy
- 8 Yokohama City University, Yokohama, Japan
- 9 Hopital Tenon, Paris, France
- 10 International Atomic Energy Agency, Vienna, Austria

Address for correspondence and reprints:

Associate Professor Michael MacManus  
Department of Radiation Oncology  
Peter MacCallum Cancer Centre  
St. Andrews Place.  
Smorgon family Bldg.  
East Melbourne, 3002 VIC  
AUSTRALIA  
Phone: 0061 39656 1111  
Fax: 0061 3965 61424  
Email: michael.macmanus@petermac.org

**Abstract**

Positron Emission Tomography (PET) is a significant advance in cancer imaging with great potential for optimizing radiation therapy (RT) treatment planning and thereby improving outcomes for patients. The use of PET and PET/CT in RT planning was reviewed by an international panel. The International Atomic Energy Agency (IAEA) organized two synchronized and overlapping consultants' meetings with experts from different regions of the world in Vienna in July 2006. Nine experts and three IAEA staff evaluated the available data on the use of PET in RT planning and considered practical methods for integrating it into routine practice. For RT planning,  $^{18}\text{F}$  fluoro-deoxyglucose (FDG) was the most valuable pharmaceutical. Numerous studies supported the routine use of FDG-PET for RT target volume determination in non-small cell lung cancer (NSCLC). There was also evidence for utility of PET in head and neck cancers, lymphoma and esophageal cancers, with promising preliminary data in many other cancers. The best available approach employs integrated PET/CT images, acquired on a dual scanner in the radiotherapy treatment position after administration of tracer according to a standardized protocol, with careful

optimization of images within the RT planning system and carefully considered rules for contouring tumor volumes. PET scans that are not recent or were acquired without proper patient positioning should be repeated for RT planning. PET will play an increasing valuable role in RT planning for a wide range of cancers. When requesting PET scans, physicians should be aware of their potential role in RT planning.

**Key Words.** positron emission tomography, computed tomography, radiation therapy, chemotherapy, treatment planning

## Introduction

Positron Emission Tomography (PET) scanning is a significant advance in cancer imaging [1]. When combined with structural imaging, such as computed tomography (CT),  $^{18}\text{F}$ -fluorodeoxyglucose (FDG)-PET provides the best available information on tumor extent for many common cancers [2]. Significant experience with PET in radiation therapy (RT) planning is largely confined to academic centres. The Applied Radiation Biology and Radiotherapy (ARBR) and Nuclear Medicine (NM) sections of the International Atomic Energy Authority (IAEA) assembled a group of experts in radiation oncology and nuclear medicine to review the use of PET in RT planning. The experts were chosen by the IAEA following a process of international consultation with leaders in nuclear medicine and radiation oncology. Criteria for selection included specific technical expertise and/or a track record of relevant publications. This paper summarizes discussions of the group, reviews relevant literature and provides suggestions for the use of PET for RT planning. After two overlapping meetings in Vienna in 2006, discussions continued by correspondence in 2006-2007 and written contributions were made by the participants. These contributions were combined and a synthesis was circulated to all co-authors for revision until no further amendments were required. The final report represents a consensus of opinion of the group in 2007.

RT plays a central role in the management of many potentially-curable malignancies, often in combination with other modalities. In curative RT, the target volume of tissue irradiated to high dose must encompass the entire tumor and any microscopic extensions of disease but should be kept as small as possible to minimize damage to normal tissues. Advances in computer assisted 3D planning such as three-dimensional

conformal radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT) [3] and image guided radiation therapy (IGRT) facilitate delivery of higher radiation doses to the tumor [4, 5] and increase normal tissue sparing. To exploit these advances, accurate target delineation is essential. PET-based staging has proven to be more accurate than non-PET staging for many cancers and it is therefore rational to use PET for RT planning in situations where it is known to be more accurate than conventional imaging. However, high quality evidence, specifically supporting the use of PET in RT planning, is lacking. The potential benefits of PET in RT planning are generally inferred from studies of staging or patient selection that show the superior accuracy of PET in specific clinical situations. For many patients, a single PET scan is used for all three purposes ( staging, selection and treatment planning). The participants in this review were therefore free to consider all data that they considered relevant to the use of PET in RT planning. Levels of evidence were not formally assessed because no high level evidence (for example randomized controlled trials) has been published on the use of PET in RT planning. In addition to explicit studies of RT planning, relevant investigations of patient selection, tumour staging, tumor movement and tumor biology were reviewed. Of all the common cancers, lung cancer has been most intensively studied with PET and a significant proportion of the published RT planning literature concerns this group of malignancies. For this reason, the use of PET in RT patients with lung cancer is considered in most detail. There is a growing body of evidence concerning the use of PET for RT planning in head and neck (H&N) tumors, esophageal tumors and lymphoma and these are each discussed briefly as they represent different challenges. There are many other cancers for which PET may play a role in RT planning but a detailed discussion of each of these is beyond the scope of this review.

## **The central role of imaging in Radiation Therapy Planning**

### *Structural Imaging*

RT planning is critically dependent on imaging. Soon after its introduction in the 1980's, CT-based conformal RT (CRT) planning became a routine part of cancer management. While modalities such as magnetic resonance (MR) imaging can sometimes provide superior tumor imaging (e.g. in brain tumors [6]), CT remains essential for dosimetry and for imaging dose-limiting normal organs. Nevertheless, structural imaging has significant limitations for imaging some tumors and lymph node metastases. These shortcomings can lead to significant interobserver variability when contouring tumors for RT [7]. Failure to encompass the tumor resulting from inadequate imaging cannot be compensated for by dose escalation [8].

### *The advent of PET*

With PET and PET/CT, sensitive, quantifiable and accurate molecular information on the biology and extent of many common cancers became available. PET often provides superior sensitivity, specificity and accuracy, compared to conventional staging. With the increasing availability of integrated PET/CT [9] exciting new possibilities now exist for RT planning [10]. Some of the most important include:

- a) Imaging of lesions not apparent on CT or MR, such as unsuspected lymph node or distant metastases

- b) Prevention of futile irradiation of abnormalities that do not contain tumour, such as atelectasis.
- c) Imaging of biologically diverse tumor sub-volumes could potentially allow dose painting (administration of different radiation doses to different tumor regions based on suspected tumor burden or radiosensitivity of the region of interest)
- d) Superior evaluation of tumor masses during or after chemotherapy (CHT)
- e) Development of “response adapted therapy”, in which changes to target volumes could potentially be made during a treatment course [11, 12]

### **PET Radiopharmaceuticals**

The scope for developing new PET tracers is vast, but currently only a few radiopharmaceuticals have the combination of high tumor uptake and favorable pharmacokinetics required to provide the high sensitivity and specificity at low cost needed for tumor imaging in busy clinical settings in radiation oncology.

#### *Fluorodeoxyglucose*

Many malignancies have higher uptake of FDG than nearby normal tissues [13] This allows FDG-PET to image them, although FDG uptake is not cancer-specific. Uptake of FDG in tumors is affected by a range of factors, including tumour

blood flow [14], activity of glucose transporters [15] and hexokinase, and by glucose consumption [16].

FDG-PET is invaluable in many cancers for differential-diagnosis, staging, evaluation of therapeutic response and for restaging. FDG-PET is superior to CT for assessment of response to RT-CHT in non-small cell lung cancer (NSCLC) and CHT response assessment in the Hodgkin and non-Hodgkin lymphomas. PET-assisted staging is more accurate than conventional staging in a wide range of cancers commonly treated with RT. For these cancers it is rational to use FDG-PET/CT [17] for RT planning.

#### *Other Radiopharmaceuticals*

The amino acid  $^{11}\text{C}$ -methionine [18] is one of the most widely used PET radiopharmaceuticals in oncology [19]. In brain tumors  $^{11}\text{C}$ -methionine is more sensitive than FDG, because of high glucose utilisation by normal brain and is currently the best available PET tracer for delineating brain tumor contours. Initial studies indicate, that  $^{18}\text{F}$ -labeled amino acids [20] such as  $^{18}\text{F}$ -alphamethyl-tyrosine [21] and  $^{18}\text{F}$ -ethyl-tyrosine [22] may have potential for RT planning in patients with brain tumors [23].

For imaging pelvic tumors,  $^{11}\text{C}$ -choline is promising because it has limited urinary uptake. Tumor uptake is related to the metabolic activity of phospholipids in the cell membrane and is increased in proliferating tumour cells. Some promise for



$^{18}\text{F}$ -labeled choline has been reported in prostate cancer [24-27] . Recent data show significant overlap in uptake between malignant and benign diseases of the prostate [28].

Imaging of proliferation and tumour hypoxia [29] using PET/CT is promising [30], but not yet useful in treatment planning. For some tracers [31], dynamic data, that take account of different tracer kinetics in different physiological compartments, could help define target volumes [32]. Agents such as,  $^{62}\text{Cu}$ -ATSM and  $^{68}\text{Ga}$ -ATSM,  $^{60}\text{Cu}$ -ATSM,  $^{18}\text{F}$ -FAZA and  $^{18}\text{F}$ -misonidazole can image hypoxic tumour cells [33].  $^{18}\text{F}$ -misonidazole uptake predicts for responsiveness to the hypoxic cell cytotoxin tirapazemine in head and neck (H&N) cancers [34]. Thymidine kinase activity, a surrogate for proliferation, can be imaged using  $^{18}\text{F}$ -fluorothymidine [35].

### **How should PET be incorporated into Radiotherapy Planning?**

#### *Some Key Concepts in Radiation Therapy Planning*

Gross tumor volume (GTV) definition is the critical step in conformal RT planning [36]. All subsequent steps depend the accurate delineation of the primary tumor and involved lymph nodes. The clinical target volume (CTV), derived from the GTV by adding margins around it, accounts for subclinical disease extension. The planning target volume (PTV) is usually an expansion of the CTV and includes factors such as movement of organs and tissues and set-up errors.

*Need for meticulous Imaging Protocols for PET in RT Planning*

PET or PET/CT imaging protocols used in RT planning must be rigorous and consistently applied [37]. The PET suite effectively becomes a link in the chain of RT quality control [38]. Patient positioning tools and procedures used on simulators and linear accelerators should be used equally conscientiously in the PET suite. These tools include a firm flat couch top, immobilization devices, laser beams for patient alignment and a wide-bore scanner (70 cm or more). Quality control processes [39], especially geometrical alignment, must include the PET scanner. Software for contouring and image quantification must be linked with the RT planning system. If the software is part of the PET/CT console, it must be able to provide Radiation Therapy Structure Set (RTSS) data (DICOM). If incorporated directly into the RT planning system workstation, PET images should be checked for correct normalization and quantification (e.g. Standardised Uptake Value, or SUV) [40].

Unfortunately, many diagnostic PET scans are carried out with the patient in an unsuitable position for RT delivery and without immobilisation or other measures needed for RT planning. Most health-care providers disallow reimbursements for separate RT planning PET scans despite the fact that technically unsatisfactory studies must be repeated for RT planning. To avoid this problem, PET scans that potentially could serve the dual purposes of staging and RT planning should be coordinated with the radiation therapy team in advance. A recent study from Germany suggests that a separate PET scan in the RT planning position is required if only a diagnostic PET is available [41]. Methods for combining poorly-matched, separately-acquired PET and CT studies include deforming or “warping” one image so that it lines up better with

the other [42]. However, for PET/CT planning, warping is an unproven approach. Images used for RT planning must be contemporaneous or very recent, especially in rapidly-progressive malignancies such as NSCLC or epithelial H&N cancers.

### *Target volume definition with PET/CT: General Principles*

Most published RT planning studies involve FDG and NSCLC is the most commonly studied cancer [43]. PET dramatically reduces the extreme variability that is observed when tumors are contoured in the same patient by different radiation oncologists [44-46]. Target volume delineation is influenced by the lower resolution of PET compared to CT (approximately 4.5 mm in the last generation PET/CT scanners). PET positive lesions are almost always detected if they are larger than 1 cm and tracer uptake is  $>4$  times that of the surrounding background. Aggressive cancers often have high FDG uptake and lesions of  $\leq 5$ mm can be detected. The margins of PET-detected lesions can appear fuzzy and visual definition of the volume depends on the experience of the operator. Lesion margins are influenced by the display (e.g. windowing, colour scale), contrast between the lesion and the background and by artefacts including spill-over. Some deficiencies of PET are well-compensated for by anatomical data provided by CT in fused PET/CT images. The semi-quantitative nature of PET invites attempts to use mathematical modelling to define the edges of tumors. An alternative approach to this problem is the application of the human eye and intelligence to estimate the most likely border of the tumor, based on a synthesis of experience and available clinical information.

### ***Target Volume definition using a Visual assessment***

Visual tumor contouring is commonly used in clinical practice, despite the fact that visual methods are not well reported in the literature. Without careful consideration, *ad hoc* and poorly designed planning procedures may become established in RT centers. A detailed protocol should be followed, keeping as consistent as possible the numerous parameters that can influence the apparent contours of the tumour on PET. Before commencing the visual planning process, the correctness of the co-registration must be checked and a diagnostically-adequate window must be adjusted for the image display, ideally in consultation with the nuclear medicine physician.

A rigorous visual contouring protocol using predefined window and colour settings and with input from the nuclear medicine physician can give highly reproducible results in NSCLC. This method was used in a prospective study of RT planning in esophageal cancer [46]. Visual planning methodology relies on human intelligence and experience to recognise various processes that lead to physiological uptake of FDG in the human body. Nevertheless, without a carefully-designed contouring protocol, it is likely that significant variations in GTV will occur. In lung cancer, PET defined GTV's are often larger than CT-defined GTV's because PET captures the location of the tumor at all phases of the respiratory cycle [47]. Even when using a standardised software-based contouring protocol there may still be significant inter-observer variation [48].

### ***Target Volume definition using automated or semi-automated methods***

To reduce inter-observer variability in FDG-based GTV definition, various automatic or semi-automatic methods have been proposed. These must be used with caution, because none can distinguish between FDG uptake caused by neoplastic processes and common physiological or inflammatory process. FDG uptake occurs within macrophages and granulation tissue, thymic hyperplasia, brown fat, fat necrosis, smooth muscle, skeletal muscle and cardiac muscle [49]. A true gold standard for studies of 3D or 4D tumor contouring is unavailable so careful observation of local failure patterns is essential.

### ***SUV-based contouring***

Estimation of the maximum standardized uptake value (SUV<sub>max</sub>) in a lesion can help distinguish between malignant and benign tissue [50]. SUV contours have commonly been used in attempts to define the edges of tumors for RT planning [51]. To define the PET-GTV, many investigators have chosen a threshold, or cut-off value [51]. Some authors employ a percentage of the maximum or peak SUV concentration, whereas others recommend an absolute SUV value (e.g. an SUV contour of 2.5 [52] to represent the edge of the lesion). However, SUV measurement can be unreliable and can suffer from problems with accuracy and reproducibility [53]. By itself, an SUV cut-off may be inadequate for RT planning.

### *Thresholding*

The most widely used thresholding [54] approach involves outlining the lesion as the region encompassed by a given fixed percent intensity level relative to the maximum activity in the tumour lesion. However, a fixed threshold value in the commonly-reported range of 40-50%, can lead to significant errors in the volume estimation [55]. This approach may render significantly too small GTVs in large inhomogenous primary lung cancers [47]. Therefore, contrast dependent adaptive thresholding methods have been proposed.

### *Background Cut-off*

Another automated approach involves defining a cut-off with respect to the background and contouring the region with intensity above the cut-off (e.g. intensity greater than three standard deviations above the background level or a SUV above 2.5). This approach is independent of heterogeneity of lesional tracer uptake, which could hamper the application of threshold methods. The assessment of activity in the lesion and in the background is strongly affected by statistical fluctuations. Furthermore, the robustness of the contour definition may also be affected by statistical noise. Three-dimensional (3D) PET acquisition has the potential to reduce image noise [56] compared to 2D acquisition.

### *Source / background algorithms*

Phantom studies with varying “lesion” and background activities were conducted to derive the relationship between the true volume of homogeneously-filled, (usually spherical) “lesions” and various thresholds applied to the PET images [57] [58].

Optimum thresholds varied according to the signal-to-background (S/B) ratios. This relationship is described by relatively simple equations, which render the threshold value depending on the mean background accumulation and the signal of the lesion. Thresholds vary depending on the background definition in patient datasets. Gradient-based methods rely on a model that determines the appropriate threshold of activity on the basis of the signal-to-background ratio [59]. This method was shown to be accurate for segmenting PET images in a study of pharyngeal–laryngeal tumors [60]. In that study, a quantitative comparison of CT, MRI, and FDG-PET showed that automatic segmentation of PET images led to tumor volumes that were significantly smaller than those obtained by either CT or MRI. Moreover, these FDG-PET determined volumes were by far the closest to the reference volume assessed from the surgical laryngectomy specimens. A comparison of methods [47] in primary NSCLC showed, that the application of S/B ratios led to reasonable volumes, compared with breath-expanded CT volumes. S/B algorithms may be applied to very low contrast lesions [61]. In another study auto-contouring, using source to background ratios, reduced interobserver variability compared to visual contouring and the estimated maximum tumor width was closely correlated with tumour diameter determined by pathology [62].

The availability of multiple automated methods for contouring tumors and the absence of any reliable intercomparisons makes it difficult to recommend any single technique. However, automated methods that employ a single crude parameter, such as a particular SUV contour, are too simplistic and rigid to be useful across a wide variety of clinical scenarios and are therefore not recommended.

### ***Tumor Movement***

Tumors usually undergo physiological movement. In NSCLC movement with respiration can be dramatic [63]. Motion can be compensated for by gating, which uses a physical trigger, such as motion of the chest wall or changes in airflow from respiration to instruct the scanner when to acquire images or how to sort them after acquisition. If a single CT planning image is acquired without breath-holding [64] or gating, it portrays a random instant in the respiratory cycle. PET is performed over many respiratory cycles and provides an image of the lesion representing the integral over the whole volume within which the lesion moves. The resulting image may show an apparent increase in lesion size and a decrease in the maximum activity concentration. Target volume definition in non-gated PET should take tumour motion into account and the thresholding level should be carefully chosen when automated methods are used. When planning using a visual method, the intensity of FDG uptake will seem less intense at the extremes of movement of a mobile tumour. Phantom studies show that, in the case of a moving object, a lower threshold should be used for an accurate assessment of its volume than for a static one [44, 54]. Unlike a single random CT scan, PET helps define the volume within which the lesion moves, defining the Internal Target Volume (ITV). CRT must account for organ motion [65], because tumor movement can carry parts of the target into areas of low dose. Normal tissue doses may be decreased by implementation of 4D gated PET/CT acquisition protocols, synchronized to the patient's respiratory cycle [66]. An ideal treatment



would continuously adapt beam delivery to changes in the tumour position (real time tracking [67]) or deliver radiation at only one specific phase of the movement cycle.

### **Role of PET in RT Planning for Specific Tumor Types**

A summary of published studies, which contain evaluations of treatment volume changes caused by incorporating PET information into the RT planning process, is shown in Table I. Studies were included if they contained an estimation of the actual or potential effect of PET on treatment or target volumes in patients planned for treatment with RT.

#### *NSCLC*

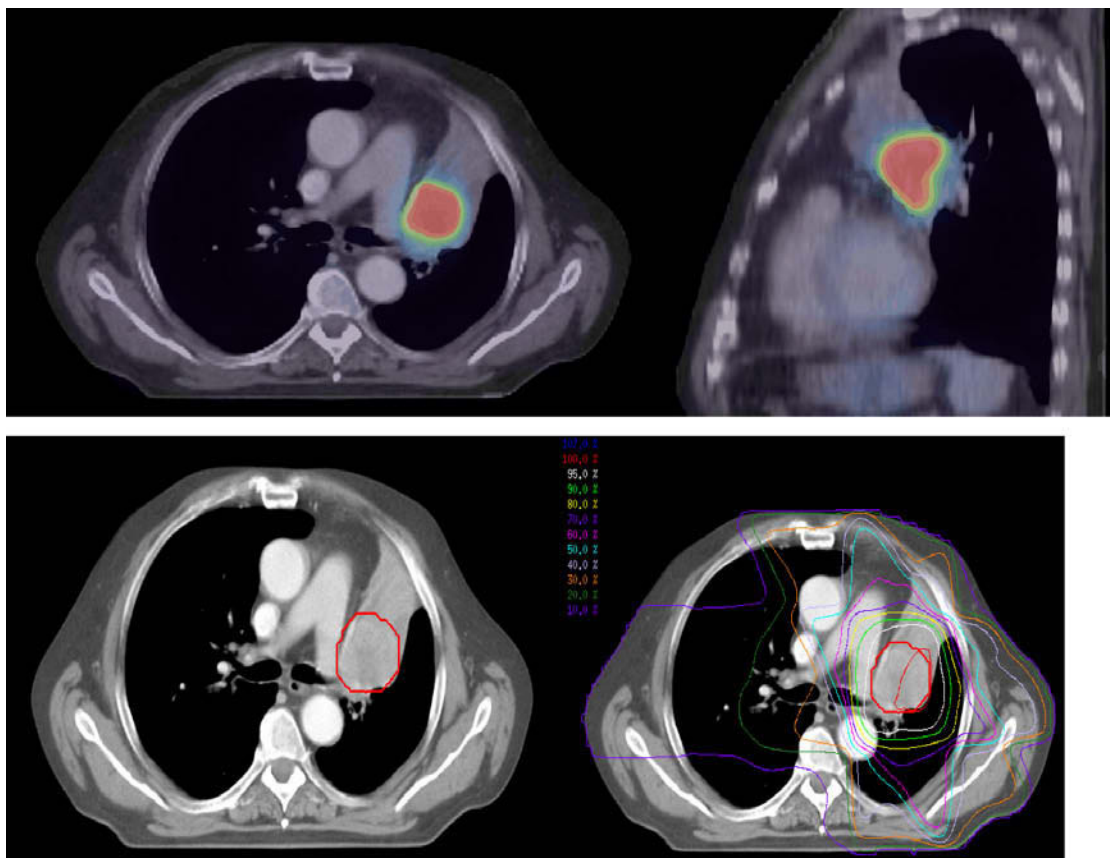
When available, FDG-PET should be used to select patients with NSCLC for treatment with definitive RT. It frequently detects unsuspected distant metastasis (>20% of pre-PET stage III) and identifies patients with very advanced locoregional disease [68] unsuitable for radical therapy. Inclusion of PET in the staging workup improves the apparent survival of patients treated with RT or RT-CHT [69], by excluding incurable patients. In a large prospective trial, 30% patients who were candidates for high dose RT on the basis of conventional staging received only palliative therapies after PET, because of unexpected distant metastasis (20%) or very extensive intrathoracic disease (10%) [70]. PET stage accurately predicted survival and patients denied radical therapy had a very short survival. Ideally, FDG-PET staging scans for potential RT candidates should be performed in the RT treatment position, to enable dual use of PET images for staging and RT planning. Integrated

PET/CT [71] is best but PET/CT image coregistration, ideally using fiducial markers, can be used [72].

PET/CT should be used for RT planning in NSCLC because it more accurately images tumor extent than CT alone [73], This is proven by a large surgical literature on the accuracy of FDG-PET in the lymph node staging of NSCLC [10, 68, 74, 75]. Average sensitivities and specificities for FDG-PET in series with pathological confirmation have been reported as 83% and 91%, respectively, whereas for CT they were 64% and 74%, respectively [76]. Despite its higher accuracy, the limitations of PET should be remembered. The rate of false-negative lymph node station assessment (post-test probability) in NSCLC RT candidates is 5-10%[77] . In studies of solitary pulmonary nodules, a negative predictive value of about 90% is reported for FDG-PET. Some factors [78] are associated with false negative findings, including carcinoid tumors or low-grade adeno-carcinomas including broncho-alveolar carcinomas. Very small lesions (<1cm) may not be seen and, in elevated blood glucose may cause false negative FDG-PET findings. False negative scans can occur soon after CHT [79], although a reduction in SUV is a positive prognostic factor [80]. PET is superior to CT for response-assessment after RT. In a prospective study, PET and CT assessments performed at a median of 70 days after RT, were concordant in only 40% of cases [81]. PET response was the best predictor of survival, was strongly-correlated with patterns of failure [82] and was not confounded by normal tissue reactions [83] .

The two most important and consistent reasons for significant changes in target volumes in NSCLC with PET, cited in the literature [84] were:

1. FDG-PET significantly changed lymph node staging in the thorax, usually by showing more positive nodes than CT.
2. In cases with atelectasis, PET helped to demarcate the border between tumor and collapsed lung, allowing a smaller volume of lung to be treated [85] (Figure 1).



**Figure 1**

Treatment of clinically uninvolved regional nodes remains controversial. Some centers routinely recommend elective nodal irradiation (ENI), while others prefer 3D CRT confined to gross disease [86], although ENI may occur by chance due to spillover from the adjacent high dose volume [87]. Significant portions of the

lymph node stations near the PTV would, in many 3-DCRT plans, incidentally receive useful doses of irradiation [88]. Some centers include high risk nodal tissue in the CTV in addition to the FDG-positive structures in the GTV. This may mean including lymph nodes which are enlarged on CT but FDG-negative [89]. Some authors advocate ENI for whole nodal stations because the diagnostic literature deals with N-stage as whole, describing nodal stations rather than individual nodes [10, 68, 90]. The prospective RTOG 9311 study of conformal RT in NSCLC showed a failure rate of only 8% in elective nodes [91]. The elective nodal failure rate was 7% in the conformal arm of a randomized trial reported by Yuan et al [92], in which patients randomized to conformal therapy received higher doses and had better outcomes than those randomized to ENI. The role of ENI may be clarified in future clinical trials [93].

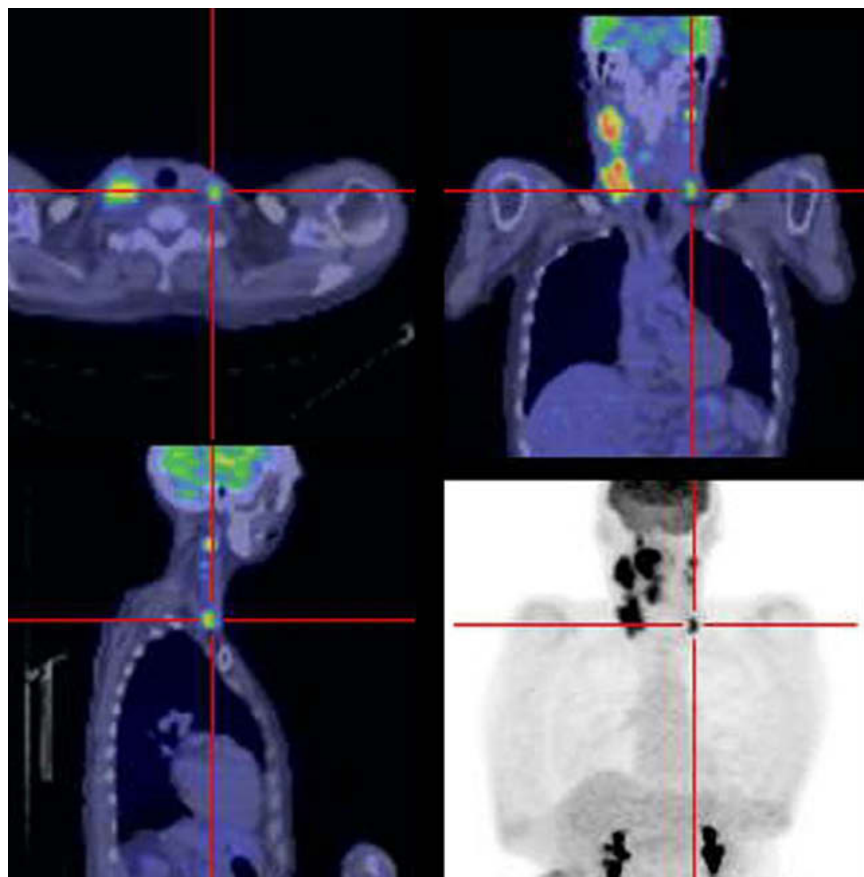
### *Small Cell Lung Cancer (SCLC)*

SCLC is well imaged by FDG-PET [94] but few studies have directly addressed the role of PET in RT planning. Potential roles for PET include selection for radical RT-CHT, RT planning and selection of patients for prophylactic cranial irradiation (PCI). In one prospective study [95], FDG-PET demonstrated findings consistent with extensive disease (ED) in three of 24 patients thought to have limited disease on the basis of conventional staging. FDG-PET correctly upstaged 8.3% patients to ED. PET had a lesion-based sensitivity relative to CT of 100%. PET identified unsuspected regional nodal metastasis in 25% patients, and the RT plan was significantly altered to include the PET-positive/CT-negative nodes within the high-

dose region in each of these patients. In another study 36 consecutive SCLC patients underwent 47 PET studies for either staging (n = 11), restaging after therapy (n = 21), or both (n = 4) [96]. Of 15 patients who had PET for staging, 5 (33%) were upstaged from LD to ED and treated without thoracic RT. In 13 patients, 14 untreated discordant lesions were evaluable; PET was confirmed accurate in 11 (79%) sites by last follow-up. These results are similar to those reported by other groups [97-99], suggesting that PET may have a role to play in selecting patients for RT and in designing the RT fields. PET. Prospective studies are required to clarify the role of PET in SCLC.

#### *H&N cancers*

Use of FDG-PET planning in H&N cancers is complex [100]. The boundaries of primary tumors can differ significantly from one another in the same patient when determined using PET, CT or MRI, making it difficult to decide where exactly to draw the GTV for RT planning. This is an especially important issue when very high doses (70Gy) are delivered to lesions close to radiosensitive vital structures (e.g. brainstem or optic chiasm) and margins are often tight around tumour [101].



**Figure 2**

The greatest impact of PET on patients with H&N cancer usually results from changes in nodal status [102] and/or the detection of distant metastasis. Changes in target volume delineation occur often when FDG-PET information is added to CT [103], mainly due to different nodal staging [101] (Figure 2). However FDG-PET-based RT planning is not yet ready for routine clinical practice. Recently, significant differences in GTV delineation were found between multiple observers contouring on PET/CT fused images, mainly due to the lack of a delineation protocol [104]. PET may impact delineation of nodes more than delineation of primary tumours [105].

Careful comparison of FDG-PET, MRI and CT scans with the histopathology of resected tumour specimens shows that none of these three imaging modalities is

100% accurate [60]. However FDG-PET may be the most accurate of the three for the detection of head and neck cancer [106]. Tumour volume determined by FDG-PET tends to be smaller on average than the volume determined by the other modalities but most closely approximates the true tumour volume [60]. Nevertheless some tumour regions that are apparent on CT or MRI may not be imaged on PET and in these cases an exclusive reliance on PET would potentially lead to geographic miss.

Changes in RT volumes due to PET occurred in 41% of patients in one prospective study [107]. Nevertheless, despite the great promise of PET in RT planning in H&N cancer [108], one must proceed cautiously. Uncontrolled local recurrence in the head and neck region can lead to prolonged misery and disfigurement. The results of PET studies of hypoxia imaging in H&N tumours [109-112] are provocative. A significant correlation between PET hypoxia-tracer uptake and treatment response has been reported.

### *Lymphoma*

The lymphomas are a large and heterogeneous group of diseases [113]. Early stage disease is commonly treated with “involved field” RT. PET is increasingly being used to select lymphoma patients for RT and to delineate RT fields [114]. FDG-PET is significantly more accurate in both staging [115] and treatment response assessment [116] in both Hodgkin and non-Hodgkin [117] lymphomas than conventional structural imaging. PET data are increasingly being incorporated into the RT planning process [118]. PET commonly influences RT fields in lymphoma by

upstaging small nodes that are negative by structural imaging criteria or by demonstrating disease in sites where low lesion/background contrast limits the efficacy of CT. PET can have a significant impact on design of involved RT fields in Hodgkin lymphoma [119]. Failure to include FDG avid lesions in RT fields may lead to relapse.

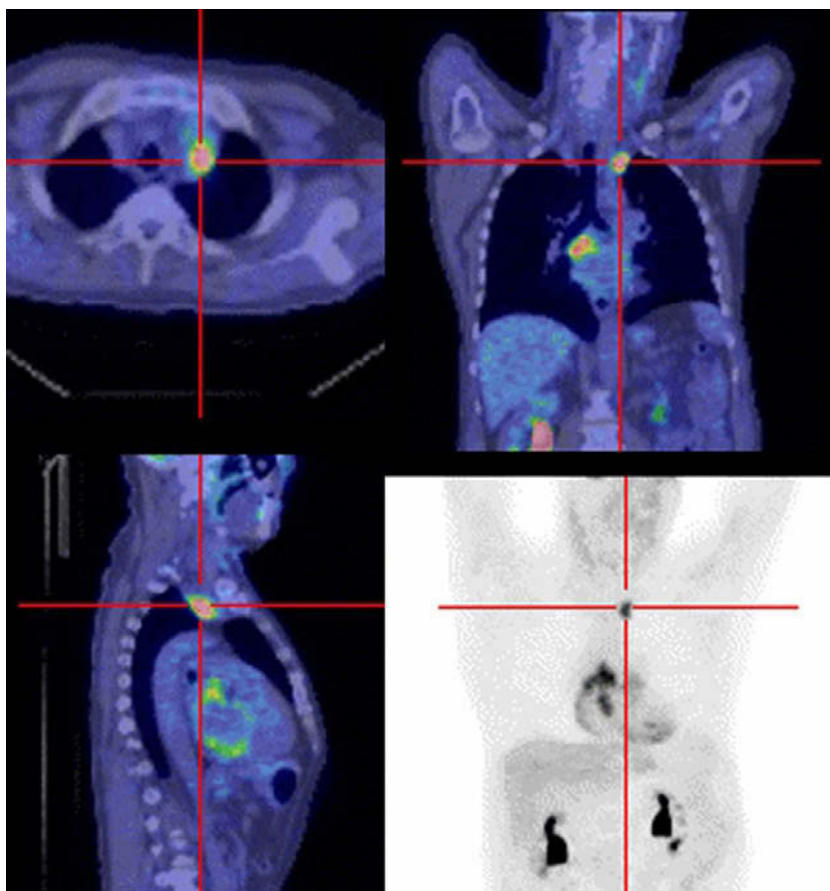
PET is also used to assess the response of lymphomas to CHT [120], either at the end of therapy, or as an interim measure, after e.g. 1-3 cycles [121-124]. Persistent interim tumor FDG uptake is a powerful negative prognostic factor in patients with Hodgkin lymphoma [125] and aggressive non-Hodgkin lymphoma [122] but early complete response cannot yet identify patients who do not require RT as part of combined modality therapy. Baseline PET scans may help determine what sites will require consolidation RT.

### *Esophageal cancer*

Combined RT-CHT, with or without surgery, is commonly used to treat esophageal carcinoma. PET can improve the accuracy of RT planning [126]. Clinicopathological studies in patients undergoing resection show that CT portrays the radial tumor extent well. PET, however, is significantly more accurate for nodal assessment [127], except those that lie adjacent to the esophagus, and shows the longitudinal extent of the tumor better than CT. The systematic review of PET staging for esophageal carcinoma by van Westreenen and colleagues confirmed that PET was quite accurate in its assessment of more distant lymph nodes and for the detection of



distant metastases [128]. When endoscopy is compromised by stenosis, PET may be the only way to visualize the lower border of the tumor. A prospective trial of PET in RT planning for esophageal carcinoma [46] showed that PET had a significant impact on GTV and PTV. PET often prevented geographic miss by identifying unsuspected lymph node involvement (Figure 3). Vrieze and colleagues found that incorporation of FDG-PET findings into RT planning would have led to a decrease of the irradiated volume in 3 of 30 patients. However in 6 of 30 patients, 8 lymph node regions were found to be positive on PET but negative on CT and/ or endoscopic ultrasound examination. In three of these patients (10%) the influence of the FDG-PET would have led to enlargement of the irradiated volume [129]. In another study, employing a coincidence scanner, use of fused FDG/CT scans altered the GTV in 19 of 34 patients (56%) [130].



**Figure 3**

## Conclusions

Because of its remarkable accuracy in staging and the demonstration of a powerful effect on treatment volumes in all of the published RT planning studies, there is a strong case for the routine use of FDG-PET in RT planning for NSCLC. In malignancies such as the lymphomas, SCLC and cancers of the H&N and esophagus, the routine use of PET information in RT planning should be cautiously considered, although there are still limited supporting data. There have been promising studies in other tumor sites, such as prostate [27], cervix [131], colorectal [132], soft tissue [133] and locoregionally advanced malignant melanoma [134], for which PET is likely to prove valuable for RT planning. Incorporation of PET into three dimensional RT planning is technically challenging and requires careful attention to detail. No single methodology is recommended, but each technique must be carefully considered and implemented consistently, with attention to detail.

At present there are no compelling data to prove that patient outcomes are superior as a result of the use of PET in RT planning. Absolute proof that PET-planning is superior would require randomized trials in which some patients were randomized to a less accurate (non-PET) staging workup, thereby presenting significant ethical challenges. Nevertheless, in the opinion of the IAEA expert group, radiotherapy planning should always be based on the most accurate available assessment of tumor extent. For many cancers PET/CT provides the best available assessment.

## Legends for Figures

### **Figure 1**

NSCLC arising in the left upper lobe. The associated atelectasis did not show FDG-uptake, and was therefore excluded from the GTV. Axial (a) and sagittal (b) CT reconstruction fused with FDG-PET reconstruction. The GTV (red; c) was designed using a source/background algorithm. Recruited for the German PET-Plan study (pilot phase), the patient received radio-chemotherapy with radiation confined to the FDG-positive area (treatment plan; d)) escalated up to 74 Gy (1,8 Gy daily).

### **Figure 2**

RT-planning FDG-PET/CT scan of a patient with locoregionally-advanced squamous carcinoma of the base of tongue. PET identified unsuspected nodal disease in the left side of the neck, including a left supraclavicular node (indicated by cross-hairs) in addition to the known disease in the base of tongue and right neck. This had a significant effect on RT planning.

### **Figure 3**

RT-planning FDG-PET/CT scan of a patient with esophageal carcinoma. In addition to showing the primary tumor and known lower mediastinal lymph node involvement, the scan showed previously unsuspected left sided superior mediastinal lymph node involvement (indicated by cross-hairs) that needed to be included in the RT target volume. Without PET, there would have been a geographic miss.

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