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The Role of PET/CT in Radiation Treatment Planning for Cancer Patient Treatment

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FOREWORD

Positron emission tomography (PET) and, more recently, integrated positron emission tomography/X ray computed tomography (PET/CT) have appeared as significant diagnostic imaging systems in clinical medicine. Accurate recognition of cancers in patients by means of PET scanning with Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) has illustrated a need to determine a mode of therapy to achieve better prognoses. The clinical management of cancer patients has improved dramatically with the introduction of clinical PET.

For treatment of cancer patients, on the other hand, radiation therapy (RT) plays an important role as a non-invasive therapy. It is crucial that cancers are encompassed by high dose irradiation, particularly in cases of curative RT. Irradiation should precisely target the entire tumour and aim to minimise the size of microscopic extensions of the cancer, as well as minimize radiation damage to normal tissues. A new imaging technique has therefore been sought to allow precise delineation of the cancer target to be irradiated.

Clinical PET, combined with utilization of ^{18}F-FDG, may have an important role in radiation treatment planning (RTP) in lung cancer. In addition to determining if RT is appropriate and whether therapy will be given with curative or palliative intent, ^{18}F-FDG-PET is useful for determining therapy ports. It can be used both to limit ports to spare normal tissue and to include additional involved regions. Several studies have shown that PET has an impact on RTP in an important proportion of patients. It is to be hoped that treatment plans that include all the ^{18}F-FDG-avid lesions or the ^{18}F-FDG-avid portions of a complex mass will result in more effective local control with less unnecessary tissue being treated.

The IAEA has placed emphasis on the issue of application of clinical PET for radiation treatment planning in various cancer patients. Two consultants meetings were held in 2006 and their results are summarized into this IAEA-TECDOC.

This IAEA-TECDOC should be seen as a guide and useful resource for clinical researchers and practitioners alike in both the nuclear medicine and radiation oncology fields. Recent coordinated research projects have shown that this is an important subject which should be addressed through clinical trials in order to best meet the needs of developing countries.

The IAEA officers responsible for this publication were N. Watanabe and B. Jeremic of the Division of Human Health.

EDITORIAL NOTE

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1. INTRODUCTION

Accurate imaging is central to the treatment planning process for most malignancies managed with curative intent using radiation therapy. Positron emission tomography (PET) scanning has brought about a revolution in the imaging of many common cancers and, as it becomes widely available in developed countries, is increasingly being incorporated into routine radiation therapy planning. PET scanning, usually employing Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) [1] as the radiopharmaceutical, in combination with structural imaging, such as X ray computed tomography (CT) scanning, currently provides the most accurate available information on tumour extent and distribution for many common cancers, including lymphomas and epithelial malignancies of the lung, oesophagus, cervix and head and neck. As PET becomes more widely used for radiation therapy planning, it is important that it is introduced rationally and used appropriately for malignancies in which it provides significant incremental information aside from that obtained from structural imaging. Some potential technical pitfalls need to be avoided when incorporating PET into the radiotherapy planning process and, at present, significant experience with PET planning is only available in relatively few academic centres. In 2006, at a meeting sponsored by the IAEA, a group of experts in nuclear medicine and radiation oncology met and reviewed the available evidence for the use of PET in radiation therapy planning. This report is a synthesis of the information that was reviewed both at that meeting and in subsequent discussions. This report expresses the consensus reached by the expert group. This is a dynamic area of research and with the publication of more studies in this area it is likely that the field will change rapidly [2]. This report reflects our current state of knowledge.

2. RADIATION THERAPY PLANNING

Radiation therapy is one of the pillars of modern cancer treatment and plays a central role in the management of a wide range of potentially curable malignancies, either as sole treatment or in combination with other modalities, such as chemotherapy or surgery. To be cured by radiation therapy, a tumour must be entirely contained within a volume of tissue treated to a tumouricidal dose. Patients selected for curative or 'radical' radiation therapy must have disease confined to a region that can be safely treated to the chosen tumouricidal dose. An optimum radiation therapy plan will deliver a sufficiently high dose of radiation to attain durable local tumour control while delivering the least possible dose to the smallest possible volume of critical normal tissues. To plan potentially curative radiation therapy, the precise location and extent of the tumour must be known.

Structural imaging techniques such as contrast enhanced CT and magnetic resonance imaging (MRI) have become de-facto standard modalities in the definition of gross tumour volume (GTV). CT simulators are key items of equipment in all well-equipped radiation oncology departments. CT images have historically provided the basic information used to define treatment volumes and, because they contain information on electron density, also form the basis for calculating three dimensional radiation dose-distribution within treatment planning computer programmes.

In a conventional three dimensional treatment planning process, the patient is placed in the treatment position and a planning CT scan is acquired. After CT data are loaded into the radiation therapy treatment planning workstation, the next step is the contouring of tumour and normal tissues. Regions of tumour or the GTV are identified and contoured by the radiation oncologist using a pointing device on individual CT (or MRI) slices. Definition of

the GTV is the single most important step in planning treatment and all other steps depend upon it. If the tumour is not well imaged and the GTV is wrong, then the entire treatment process may be futile. For many tumour types, once the GTV is delineated, a clinical target volume (CTV) is defined, taking into account the biological behaviour of the specific tumour and allowing sufficient margins to account for subclinical extension of disease beyond the imaged tumour boundary. This CTV is used to generate the planning target volume (PTV), which takes into consideration uncertainties caused by physiological displacement of organs and tissues (forming a tumour related subvolume known as internal target volume: (ITV)), as well as the effects of patient movement, set-up errors that occur during each daily delivery of radiation (intra-fraction) as well as day-to-day variation (inter-fraction).

Rapid and continuing advances in computer assisted 3D planning have resulted in developments such as three dimensional conformal radiotherapy (3DCRT) and intensity modulated radiation therapy (IMRT) [3]. These methods can facilitate the delivery of higher radiation doses to the tumour [4, 5] and allow relative sparing of normal tissues, with potential for higher tumour control rates and/or less toxicity for the patient. Three dimensional treatment planning allows for the design of complex treatment plans that conform closely to the high-dose volume and to the shape of the tumour. Advances in computerized treatment delivery, patient immobilization and positioning, dynamic multi-leaf collimators and other refinements, facilitate highly complex multi-field conformal plan delivery. In IMRT each beam can be subdivided into multiple beamlets of different intensities. In addition, image guided radiation therapy (IGRT) employs imaging of the patient's tumour, or of fiducial markers corresponding to the patient's tumour, while the patient is on the treatment table.

To take full advantage of these dramatic advances in modern radiotherapy, the most accurate and precise delineation of the target is needed. In the pre-PET era, definition of tumour volumes and treatment volumes was based primarily on structural imaging with contrast CT or MRI, which together with clinical judgement were used to estimate the likely extension of microscopic disease in each case and thereby define the CTV. Molecular imaging, using radioisotope tracers to identify molecular tumour targets, in combination with PET and single photon emission tomography (SPECT), has allowed a more complex functional and biologic evaluation of tumours. In many tumour types, clinicopathological studies have shown that the estimate of tumour extent is most accurate when functional and structural imaging data are combined. With rapid advances in molecular imaging and the increasing availability of integrated positron emission tomography/X ray computed tomography (PET/CT) and single photon emission computed tomography/C ray computed tomography (SPECT/CT) systems, it is now possible to introduce a new dimension to radiation treatment planning beyond the structural information offered by conventional imaging techniques [6]. To help create biologically defined target volumes, functional information given by PET or SPECT can be projected onto the anatomical CT images. Clearly the usefulness of the biological signal depends upon the radiopharmaceutical used to evaluate and characterize the tumour and the biology of the tumour itself. Biological processes that can usefully be imaged include glucose metabolism, cellular proliferation and hypoxia. These biological signals can be used to specifically identify biologically different regions in given tumours and could theoretically be used to apply 'dose painting' [7] in radiation therapy, in which potentially radio-resistant regions could be treated to a higher dose.

PET, and in particular PET/CT [8], is very likely to revolutionise treatment planning and tumour response assessment following radiation therapy of many common cancers. SPECT will not be considered further in this discussion because technical factors, including its relatively poor resolution, make it so inferior to PET as to be unworthy of further

consideration for radiotherapy treatment planning at present. The exciting area of PET-assisted radiation therapy planning is developing rapidly, as techniques to deliver radiation continue to improve and new tracers to image different molecular targets are being developed. This report, which reflects the opinions of an international panel of experts assembled by the IAEA, attempts to address the most significant and controversial issues that relate to PET/CT in radiation treatment planning, with emphasis on the well established and agreed facts. The report will offer some recommendations that we hope may be useful for those intending to start their own clinical practice in this field.

3. IMAGING FOR RADIATION THERAPY PLANNING: STRUCTURAL AND FUNCTIONAL

The advent of three dimensional structural imaging in the 1980s with CT scanning and the subsequent introduction of MRI revolutionised the imaging of tumours and made three dimensional radiation therapy planning a routine part of cancer management. For the first time, physicians had a seemingly good impression of the three dimensional distribution of disease and importantly could appreciate the shape and structure of many critical normal tissues. However, despite this enormous step forward, determination of the true margins of the gross tumour could be problematic and inaccurate due to poor contrast between tumour and normal tissues. Additionally, because lymph node size was the sole criterion for involvement by tumour with structural imaging, many small cancerous nodes would be excluded from the GTV and many large reactive nodes would falsely be included. Microscopic extension of the tumour around the GTV remains a conundrum and cannot be imaged by any technique, no matter how sensitive. However it can be estimated by extrapolation from clinicopathological studies of resected cases and a margin for microscopic extension applied to the GTV. Nevertheless, microscopic disease may well be missed if margins around the GTV are inadequate because imaging failed to accurately portray the true extent of the tumour. As discussed above, the volume that requires treatment to the prescribed radiation dose is the PTV. The margin of the PTV around the CTV encompasses all positions of the tumour due to organ motion expected during the time of irradiation (ITV) and also accounts for uncertainties in set-up. It is important that the CTV is based on an accurate GTV. Inadequate margins around the GTV cannot be compensated for by dose escalation [9].

Precise and accurate localization of radiotherapy targeted to the PTV is critical for optimizing the therapeutic ratio, by limiting the amount of normal tissues receiving radiation, and maximizing coverage of tumour volumes using conformal radiation techniques. At present, specific three dimensional physiological and molecular information about the tumour can be incorporated into RT planning, thus improving the accuracy of clinically relevant radiotherapy target definitions and dose delivery.

Functional imaging with PET can provide information that can influence RT planning in a number of ways. Some of the most important include the following:

(a) PET can reveal targets that are not well visualised by CT/magnetic resonance (MR) structural imaging. These targets may be remote from the primary tumour, such as unsuspected lymph node or distant metastases, or they may be additional neoplastic regions adjacent to the tumour volume defined by CT/MR imaging.

(b) PET makes it less likely that treatment will be given to ‘equivocal’ regions on CT/MR which do not actually contain tumour. These regions may also be remote, such as benign

reactive lymphadenopathy, or adjacent to the tumour volume defined by CT/MRI, such as atelectatic regions of lung.

(c) The imaging of biologic inhomogeneities within sub volumes of the tumour may offer the possibility to adapt doses to local differences in radiosensitivity (known as dose painting, not yet been shown to be of value in any tumour site).

(d) PET can be useful for the evaluation of residual masses after chemotherapy in conditions like lymphoma, helping to determine which regions, if any, require radiation therapy and helping to choose between a lower dose for presumed microscopic residual disease or a higher dose for gross residual disease.

Feasibility studies have found that the use of ^{18}F-FDG-PET/CT for planning three dimensional conformal radiation therapy improves the standardization of volume delineation compared with CT alone for a number of cancers that are well-imaged on PET. It is simply easier for physicians to visualise the tumour clearly. In addition, there is the attractive possibility that sub-regions within the tumour can be targeted selectively, either with higher radiation doses, [10] on a gross level or more feasibly with specific pharmaceutical agents at a molecular level. A good example is the use of the hypoxic cell cytotoxin tirapazemine in patients with PET-detected hypoxia. Although only preliminary data are available, it is possible to foresee a major advantage of these methods, allowing a better modulation of the radiation beam over a complex target. Other radioligands aimed at studying specific biological parameters (e.g. proliferation, angiogenesis and apoptosis) may further change the present definition of target volumes. Another potential role for PET is in the development of 'response adapted therapy', allowing changes to be made during a treatment course, [11], [12]. Van Baardijk and colleagues have recently shown that changes in standardized uptake values (SUV) that occur during radiation therapy have prognostic significance, [13].

4. RADIOPHARMACEUTICALS FOR FUNCTIONAL CHARACTERIZATION OF CANCERS

In the field of PET oncology, ^{18}F-FDG is the most widely used radiopharmaceutical and in fact is the best imaging agent currently available for many of the most common cancer types. It is the only pharmaceutical widely and routinely used in radiation therapy planning. ^{18}F-FDG is an analogue of glucose which is incorporated into the tumour cell via a glucose transporter mediated mechanism and is metabolically trapped, [14] after being phosphorylated by hexokinase. Accumulation of ^{18}F-FDG in tumour cells is affected, among other things, by tumour blood flow, the activity of glucose transporters and hexokinase, and by cellular glucose consumption. When examined pathologically, tumour mass lesions consist of neoplastic cells, stroma and a variable proportion of associated reactive inflammatory cells such as macrophages and lymphocytes. ^{18}F-FDG uptake shown on PET/CT images occurs both in tumour cells and in tumour-associated inflammatory cells. In other words, ^{18}F-FDG is not a specific tracer for detecting tumour cells. Nevertheless, because of the high uptake of ^{18}F-FDG in many malignancies [15], the excellent imaging characteristics of ^{18}F can provide superb images for staging. Nevertheless, because of the potential for uptake in inflammatory processes, we must consider these biological characteristics of ^{18}F-FDG when we interpret the uptake of ^{18}F-FDG on PET/CT images. It is important that the PET physician is expert and can use broad clinical experience to recognise both common patterns of inflammatory disease and normal physiological uptake, such as in muscle or brown fat.

There is now an enormous body of published evidence proving the clinical utility of ^{18}F-FDG-PET in a wide range of clinical settings in oncology, including differential diagnosis between benign and malignant tumours, staging prior to surgery or radiation therapy and re-staging after therapy in various malignant diseases such as lung cancer, malignant lymphoma, colorectal cancer, head and neck cancer, malignant melanoma and gynaecologic cancer. The superiority of ^{18}F-FDG-PET for monitoring therapeutic efficacy after or during chemotherapy and/or chemo-radiotherapy has also been demonstrated or suggested in several reports. There is strong evidence that ^{18}F-FDG-PET is superior to CT in assessment of response to chemoradiation in non-small cell lung cancer (NSCLC) and that early PET scans can provide a clear estimate of prognosis after only a couple of cycles of chemotherapy in patients with Hodgkin and non-Hodgkin lymphomas.

With respect to the clinical application of PET/CT in radiation treatment planning, there is strong evidence from numerous surgical and clinical follow-up studies that prove that PET-assisted staging is much more accurate than conventional staging. Radiation therapy planning should be based on the most accurate available assessment of the three dimensional distribution of disease and for many cancers that means PET/CT [16] should be used. For any cancer in which there is clearly a large increase in accuracy of systemic and locoregional staging with the use of PET, there is a case for its routine use for radiation therapy planning. Strong evidence for superior outcomes as a consequence of better radiation therapy planning due to PET is not yet available but there is already evidence of superior outcomes when PET is incorporated into the overall selection and planning process. PET-selected patients treated with radical chemoradiation for NSCLC have superior outcomes to those who undergo conventional staging only.

After ^{18}F-FDG, carbon-11-methionine (^{11}C-MET) [17] is probably the second most widely used PET radiopharmaceutical for imaging tumour cells [18]. It is an amino acid analogue which is actively transported into cells. Its uptake reflects amino acid metabolism in tumour cells and other tissues. For central nervous system neoplasms, tumour uptake of ^{11}C-MET is considered to be more specific than that of ^{18}F-FDG and, due to the normal high physiological uptake of ^{18}F-FDG in healthy brain tissue, may also be the most suitable available PET tracer for delineating brain tumour contours. It may also be a useful tracer for monitoring therapeutic efficacy after treatment with radiation therapy or chemotherapy. The use of ^{18}F-labeled amino acids, [19] such as fluorine-18-fluoromethyl tyrosine (^{18}F-FMT) [20] and fluorine-18-fluoroethyl tyrosine (^{18}F-FET) [21] is being explored to overcome the inconveniently short half life of ^{11}C. These PET radiopharmaceuticals have been shown to be useful in radiation treatment planning in patients with brain tumours [22].

Another potentially useful PET radiopharmaceutical is carbon-11-choline (^{11}C-CH), which is also incorporated into the tumour cell. Its uptake is related to the metabolic activity of phospholipids in the cell membrane and is elevated in proliferating tumour cells. Limited urinary excretion, and therefore low accumulation of this radiopharmaceutical in the bladder, provides an advantage in detecting intra-pelvic tumours such as prostate cancer. Some preliminary use of fluorine-18-fluorocholine (^{18}F-FCH) has been reported in patients with prostate cancer [23–26]. However, recent data show that there may be a significant overlap in uptake between malignant and benign diseases of the prostate, [27]. Nevertheless local recurrences after prostatectomy and distant metastatic disease seem to be depicted more accurately than with conventional imaging, especially using PET/CT rather than stand-alone PET. The most effective use of this radiopharmaceutical in radiation therapy planning is yet to be established.

Tumour characterization with respect to processes such as angiogenesis, apoptosis, and tumour hypoxia, [28] using PET/CT are of great scientific interest but so far have not been proven to be clinically useful in treatment planning. Several PET radiopharmaceuticals have been developed to explore these properties and processes, [29] but clinical studies for radiation treatment planning are limited or as yet unavailable. As discussed above hypoxic tumour cells are relatively radioresistant and would be more likely to be controlled if a higher radiation dose could be accurately targeted at regions of imaged hypoxia [30]. Agents such as copper-60-diacetyl methyl thiosemicarbazone) (^{60}Cu-ATSM), copper-62-diacetyl methyl thiosemicarbazone) (^{62}Cu-ATSM), gallium-68-diacetyl methyl thiosemicarbazone) (^{68}Ga-ATSM), fluorine-18-fluoroazomycin-arabinoside (^{18}F-FAZA) and fluorine-18-fluoromisonidazole (^{18}F-FMISO) may be useful for detecting hypoxic tumour cells [31]. Among these PET radiopharmaceuticals, ^{62}Cu-ATSM and ^{68}Ga-ATSM are unique agents because they are produced with generators and instant kits, similar to conventional radiopharmaceuticals for SPECT, which largely enhances their availability. There is evidence that ^{18}F-FMISO uptake predicts for responsiveness to the hypoxic cell cytotoxin tirapazemine in head and neck cancers [32]. PET radiopharmaceuticals designed to detect thymidine kinase (TK1) activity such as fluorine-18-fluorothymidine (^{18}F-FLT) have also been developed [33] but are in limited human use and so far have no useful role in routine radiation therapy planning.

5. IMAGING PROTOCOLS FOR PET IN RADIATION THERAPY PLANNING

The imaging protocols used when PET or PET/CT is employed for radiotherapy planning should be rigorous and consistently applied to make them reproducible between patients [34]. The PET suite effectively becomes part of the radiation therapy department and the chain of radiation therapy quality control extends to the acquisition of the PET images [35]. Regardless of the tracer used, it is important that some basic elements are present. All set-up and patient positioning tools currently used in the radiation oncology department on simulators and linear accelerators should be equally conscientiously used in the PET suite when images are acquired for treatment planning. These tools include the use of a firm flat couch top, use of immobilization devices such as customised plastic casts, installation of laser beams for patient alignment and use of a scanner with a wide gantry aperture to permit a range of limb placements (70 cm or more). All quality controls required in the radiation therapy process [36], particularly those for geometrical alignment between all parts of the radiotherapy chain, must also include the PET scanner. Software for imaging analysis, including PET volume contouring and image quantification must be available, and be connected with the planning system (directly or via remote transfer). This software can be part of the PET/CT console, in which case it must be able to provide RTSS data (DICOM), or it can be incorporated directly in the radiation therapy treatment planning system workstation, in which case PET imaging should be checked for correct normalization and quantification (e.g. SUV). For stand-alone PET or PET/CT studies used for radiotherapy treatment planning, suggested imaging protocols for ungated and gated ^{18}F-FDG-PET/CT can be found in Appendix I.

6. ROLE OF PET IN RADIATION THERAPY PLANNING FOR SPECIFIC TUMOUR TYPES

6.1. ^{18}F-FDG-PET IN NON-SMALL CELL LUNG CANCER

Most of the published PET and PET/CT studies in radiation treatment planning have addressed the evaluation of patients with NSCLC [37]. Indeed, this malignancy has been a testing ground for the utility of PET in radiation therapy planning in general and lessons learned in NSCLC can usefully be applied to many other tumours. For this reason, and because the literature is most extensive on this topic, NSCLC will be discussed in some depth below. There has been growing interest in the application of PET/CT planning to other tumours where radiation treatment plays an important role. These tumours include head and neck cancer, lymphomas and gynaecological cancer and will be discussed later in this report in brief separate sections. A summary of published PET and PET/CT studies aimed at the evaluation of treatment volume changes caused by including PET information into the standard planning is reported in Table 1. Almost all of these studies concern NSCLC.

The rationale for using PET in target volume delineation in NSCLC is the higher sensitivity and specificity of ^{18}F-FDG for tumour tissue in comparison to CT, the standard structural imaging modality [38]. The average ^{18}F-FDG-PET sensitivity and specificity were reported to be 83% and 91%, respectively, whereas for CT they were 64% and 74%, respectively [39]. In studies of solitary pulmonary nodules, where a negative predictive value of about 90% is reported, some factors, which influence the incidence of false negative findings have been reported [38]. Some histological subgroups like carcinoid tumours or low-grade adeno-carcinomas may not accumulate ^{18}F-FDG, but this does not usually affect radiotherapy planning as these cases are relatively uncommon. However, it is important to appreciate that very small lesions (<1cm) may not be detectable on ^{18}F-FDG-PET imaging, that in patients with diabetes false negative ^{18}F-FDG-PET findings may occur if the blood sugar is elevated at the time of scanning and that during the first weeks after chemotherapy residual tumour cells may have reduced glucose metabolism and be undetectable, giving rise to a false negative scan [40]. A reduction in standardized uptake value (SUV) in the post-chemotherapy setting may be of prognostic significance in certain clinical conditions [41], but may make some lesions undetectable on PET. Therefore, because effective neo-adjuvant chemotherapy can obscure active tumour and because NSCLC is never controlled permanently with chemotherapy alone, radiation therapy planning after neo-adjuvant chemotherapy should be based on the extent of disease apparent on the pre-chemotherapy PET scan, unless disease progression has occurred. No site of initial disease should be un-irradiated no matter how good the response to chemotherapy. For definitive assessment of treatment response after chemoradiation, PET is superior to CT [42].

There is a large body of surgical literature on the accuracy of ^{18}F-FDG-PET in the lymph node staging of NSCLC [6], [43], [44], [45]. Although PET and PET/CT staging are clearly much better than CT staging, the diagnostic accuracy of ^{18}F-FDG-PET is, of course, not 100%, as no macroscopic external imaging test can currently detect microscopic disease. Therefore, one should not mistakenly assume that a negative PET scan excludes microscopic disease. As estimated from literature and the data of Graeter and colleagues [46], the rate of false-negative lymph node stations (post-test probability) in NSCLC radiotherapy candidates is in the range of 5–10%. When planning radiation therapy, the risk of microscopic disease in normal nodes must always be considered. In NSCLC, elective nodal irradiation (ENI) is not of proven benefit but in head and neck cancer it is routine for many clinical scenarios. The need for ENI after PET is therefore disease and site specific.

TABLE 1. A BRIEF SUMMARY OF PET AND PET/CT STUDIES AIMED AT THE EVALUATION OF TREATMENT VOLUME CHANGES CAUSED BY INCLUDING PET INFORMATION INTO THE STANDARD PLANNING.

Authors	PTs	Site	PET/CT fusion	Segmen-tation method	Para-meter	% PTs with variation	↑%	↓ %
Kiffer 1998	15	Lung-	Graphical	None	Rad Field	27	27	-
Munley 1999	35	Lung	Visual	Visual	Rad field	> 34	34	nq
Nestle 1999	34	Lung	Visual	None	Rad field	35	9	26
Vanuystel 2000	73	Lung	Visual	None	GTV	62	22	40
Giraud 2001	12	Lung	Sw	Th 40%	Rad field	33	33	-
Caldwell 2001	30	Lung	Sw	Th 50%	GTV>5mm	100	53	47
Mac Manus 2001	102	Lung	None	None	GTV	38	22	16
Mah 2002	23	Lung	Sw	Th 50%	PTV	100	30–76	24–70
Erdi 2002	11	Lung	Sw	Th 42%	PTV	100	64	36
Bradley 2004	24	Lung	Sw	Th 40%	GTVCLEAR	58	46	12
Ciernik 2003	39	Varied	Hw	Th 50% (max-bkg)	GTV>25 % PTV>20%	10–50 10–20		
Vrieze 2004	14	Oes.	None	Visual	GTV PTV	100 42	43 21	57 21
Nishioka 2002	21	Oro-Naso-ph.	Sw	Visual	GTV	89	5	5
Scarfone 2004	6	Head/Neck.	Sw	Th 50%	GTV	60	6	-
Brianzoni 2005	25	Lung cancer NHL	Sw	Th 40% plus visual	GTV or CTV	44	6	5
Messa 2005	18	Lung	Sw	Th 40–50%	GTV>25 %	55	39	16

Van Der Wel 2005	21	Lung	Sw	None	GTV Rad Field	100 100	19 14	57 52
Ashamalla 2005	19	Lung	Hw	Visual	GTV PTV	52 42	5	
Moureau-Zabatto 2005	34	Oes.	Sw	Visual	GTV	56	21	35
Deniaud-Alexandre 2005	92	Lung	Sw	Visual	GTV GTV>25 %	48	21 14	24 7
Leong 2006	21	Oes.	Sw	Visual	GTV	86	69	-
Wang 2006	28	Head and Neck	Sw	Visual	GTV	88	-	-
Hutchings 2007	30	Hodg-kin's	Sw	Visual	GTV	33	23	7

^{18}F-FDG-PET has a major role in the selection of patients with NSCLC for treatment with definitive RT. Its ability to frequently detect unsuspected distant metastases and to identify very advanced locoregional disease [45], means that inclusion of PET in the staging workup is enough to improve apparent survival of patients treated with RT or chemo RT with curative intent [47]. In a large prospective trial, 30% of 153 patients who were candidates for high dose RT on the basis of conventional staging received only palliative therapies after PET, because PET showed unexpected distant metastases (20%) or very extensive intrathoracic disease (10%) [48]. PET staging predicted survival much more accurately than conventional staging and whereas radically treated patients had good survival, those denied radical therapy had a very short survival.

For those patients who remain candidates for radical RT after PET staging, the PET images can serve a further purpose; they can and should be used to help the RT planning process [49]. Ideally, ^{18}F-FDG-PET staging scans for RT candidates should be carried out in the RT treatment position, with suitable immobilisation devices fitted to enable direct use of PET images in RT planning. If integrated PET/CT [50] is not available, PET and CT image coregistration, typically using fiducial markers, will be required [51]. If the staging PET scan is not carried out in the correct position (i.e. with arms raised to prevent oblique radiation fields passing through the upper limbs), it would be best practice to repeat the PET scan in the treatment position, especially, if some time has elapsed since the initial staging scan. In

preliminary results of a prospective study, 4 of 9 patients who had both staging and treatment planning scans separated by a median of 24 days showed progression of disease between the scans.

The role of ^{18}F-FDG-PET in RT planning has been addressed in a number of studies of NSCLC patients, [49, 52–59]. The proportion of lung cancer cases in which there are significant changes in target volume after the integration of ^{18}F-FDG-PET/CT into the radiation treatment planning process ranges in the literature from 20%–70%.

The two most important reasons for significant changes in target volumes in lung cancer with PET are:

(a) ^{18}F-FDG-PET significantly changes lymph node staging in the thorax, most often by showing more positive nodes than are apparent on CT;

(b) In cases with atelectasis, PET helps to demarcate the border between tumour and collapsed lung [56].

The wide range in percentages of significant changes in treatment volumes reported in these studies reflects the absence of a commonly agreed definition of what a significant change is. In virtually every case, PET could be considered to cause at least a minor change in tumour contour. In many cases, changes to the target volume simply influence the margin around gross disease to an insignificant degree. Nevertheless, in a very high proportion of cases the changes associated with PET are profound and at their most extreme can lead to avoidance of geographic miss or sparing of large volumes of normal tissue by incorporating the PET information.

Incorporation of PET into routine treatment planning will therefore lead to the following consequences:

(1) Inclusion of previously undetected regional nodal involvement, will significantly alter the GTV in between 10% and 25% of patients;

(2) Exclusion of enlarged but PET negative lymph nodes, and exclusion of uninvolved collapsed/consolidated lung tissue leads to a significant reduction in GTV.

The remarkably consistent surgical literature proves beyond reasonable doubt that, on average, when PET is added to the standard staging workup for NSCLC, a more accurate estimate of the distribution gross tumour is made compared to standard imaging. It is indisputable that radiotherapy planning should be made using the best available information concerning the true tumour distribution. A strong case, therefore, can already be made for the routine use of PET planning, especially as the rate of incremental findings is greatest in those patients already known to have locoregionally advanced disease before PET. Such patients are the very population most likely to receive radical RT. However, whilst PET and PET/CT clearly have a role in treatment planning, the impact of such planning can be very difficult to study in a meaningful way. The very factors that make lung cancers inoperable preclude routine biopsy of all PET-imaged lesions. However the true impact of PET should be studied intensively, where possible, using direct experimental means (e.g. correlation with pathology when this is available), by studying the clinical outcomes in PET staged patients, such as survival and patterns of relapse, and by performing cost–benefit analyses. One problem that confronts researchers is the absence of a true gold-standard for the absolute location in three (or four) dimensional space of a moving tumour inside an unperturbed living breathing body.

Resected lesions used for clinicopathological correlations may lose their precise three dimensional structures as soon as they are removed from the body. Lobectomy or pneumonectomy specimens will also lose their anatomical structure and relations as the lung is deflated. Nevertheless, simply by excluding one third of patients from aggressive radical therapy PET could prove cost–saving in some funding models even if no further use was made of the scans.

Known patterns of spread and microscopic involvement may help in deciding how best to use PET information for treatment planning, but can complicate decision making. The potential risk of missing undetected lymph node metastases when using ^{18}F-FDG-PET-based planning must be weighed against the very high probability of central local tumour progression in locally advanced disease. The former consideration would encourage elective treatment of large volumes of normal sized lymph-node bearing tissue and the latter would encourage dose escalation to tight volumes. This might actually be less of an issue with more accurate PET/CT than has historically been the case with less accurate CT. Nevertheless there is still controversy over the best way to cope with this problem, with some centres routinely recommending elective irradiation of uninvolved lymph node stations, while others prefer to concentrate dose conformally to the gross disease, permitting such elective nodal irradiation as occurs by chance due to spill-over from the adjacent high dose volume [60]. With accurate imaging, the trend away from elective irradiation and towards conformal dose escalation is likely to become stronger.

6.1.1. Target volume definition with PET

After image acquisition and co-registration (hardware co-registration for PET/CT systems and software co-registration with separate PET and CT acquisitions), the next steps are the sequential definitions of tumour volume and target volume. These represent the most important and possibly most contentious steps in the process [61]. Because every nuclear medicine tracer has a different bio-distribution, dynamics and imaging characteristics, the rules for image display and tumour contouring must be individualised for each one. For some tracers [62], it is possible that dynamic data could be useful for defining target volumes. For these reasons no ‘standard-PET-based’ target volume definition is universally applicable across all radiopharmaceuticals.

Because it is the most successful PET imaging agent to date and because it is the most widely available, the great majority of the published treatment planning studies relate to ^{18}F-FDG-based target volume delineation in NSCLC [63]. Not only does the functional information provided by ^{18}F-FDG-PET, combined with detailed anatomical information from CT, provide the clinician with a more accurate definition of the true GTV but it also leads to a dramatic reduction in the extreme variability which characterizes the definition of GTV when it is contoured in the same patient by a number of different radiation oncologists [64]–[66]. More recently, it has also been demonstrated that the accurate co-registration of PET and CT can further decrease the variability in GTV definition, compared to the visual analysis of individual PET and CT images shown side-by-side.

Consistent and accurate delineation of the target volume on PET images can be affected by several factors. Firstly, an accurate delineation of PET-based GTV is complicated by the physically limited spatial resolution of PET itself (approximately 4.5 mm in the last generation PET/CT scanners). As a result of this relatively poor resolution, PET can suffer from limited lesion detectability. PET positive lesions can almost always be detected if their size is larger than approximately 1 cm and the tracer uptake in the lesion is at least 4 times the

uptake in the surrounding background. Smaller lesions may only be detected if there is a substantially more intense uptake. Fortunately, many aggressive tumours, including most lung cancers, have very high ^{18}F-FDG uptake and lesions of 5mm can often be detected. As a result of its relatively poor spatial resolution, the margins of a PET-detected lesion can appear fuzzy and indistinct and for this reason the visual definition of the volume can be very subjective, dependent on the experience of the operator. It can also be influenced by the way the PET images are visualized (e.g. windowing, colour scale), the contrast between the lesion and the background and by artefacts such as spill-over of signal from intensely avid lesions into adjacent normal structures. However, some of the spatial resolution deficiencies of PET are well-compensated for by the exquisite anatomical data provided by CT scan in fused PET/CT images. Such images are often truly more than the sum of their parts and can identify and characterise more lesions than either modality alone.

The semi-quantitative nature of PET invites attempts to use mathematical modelling to define the edges of tumours for treatment planning. An alternative approach to this problem is the application of the human eye and intelligence to estimate the most likely border of the tumour based on a synthesis of experience and all known clinical information. Both approaches to contouring have their advocates and will be discussed below

6.1.2. Target volume definition using a visual assessment

Visual contouring is commonly used in clinical practice around the world despite the fact that virtually all published studies on radiotherapy planning methodology report the use of SUV contours or similar parameters. Visual methods have not been well described or studied in the literature and there is a danger that ad hoc and poorly thought out planning procedures can take root in radiotherapy centres if the issues are not considered carefully. To ensure consistency and accuracy when using a visual contouring method, a detailed protocol should be used and followed, keeping as constant and 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 (also in PET/CT datasets) must be checked using anatomical landmarks, and a diagnostically adequate window must be adjusted for the image display, which should be done in collaboration of the radiotherapist with the nuclear medicine physician.

Unpublished data from the Peter MacCallum Cancer centre suggest that a rigorous visual contouring protocol [MacManus and colleagues, personal communication], using predefined window and colour settings and with input from the nuclear medicine physician can give highly reproducible results in NSCLC. This method was also used successfully in a prospective study of radiotherapy planning in oesophageal cancer. Visual planning methodology relies on human intelligence and experience to distinguish between the various processes that lead to uptake of ^{18}F-FDG in the human body, not just cancer. Visual methods employing fused PET/CT images combine the strengths of the two imaging modalities and allow each to compensate for the weaknesses of the other. Nevertheless, without a carefully designed contouring protocol, there is a risk that the different training and experience of clinicians may lead to wide variations in GTV.

Comparing different methods for ^{18}F-FDG-PET-based GTV contouring in 25 patients with primary NSCLC, it has been shown that the resulting volumes may differ substantially, but that visual contouring may lead to volume sizes, which are comparable to CT volumes expanded for breathing movements as routinely done in CT based radiotherapy planning [67].

However, the Dresden group showed, that there may still be significant inter-observer variation when using a standardized software based contouring protocol [68].

6.1.3. Target volume definition using automated or semi-automated methods

To reduce the inter-observer variability in ^{18}F-FDG-based GTV definition, several image processing methods have been proposed to contour the PET volume in an automatic or semi-automatic and therefore more objective way. However, all automated methods have a common inherent weakness; an inability to distinguish between ^{18}F-FDG uptake caused by neoplastic processes and various common physiological and inflammatory states. All of these methods work well in phantoms but require careful editing and correction if they are used in human subjects. It must be remembered that an ^{18}F-FDG-PET scan is a three dimensional map of glucose uptake, not a cancer cell map. ^{18}F-FDG uptake occurs within macrophages and granulation tissue as well as tumour cells [69]. Automated methods can never be the entire answer to tumour contouring but may potentially assist the human operator to produce more consistent results. Some of the more intensively studied approaches are discussed below.

6.1.4. SUV

Much research has been conducted on the use of SUV to help distinguish benign from malignant tissue in the setting of diagnostic nuclear medicine. For example, the determination of maximum standardized uptake values (SUVmax) of lesions has been performed to help distinguish between malignant and benign tissue. Because SUVmax represents the point of highest uptake in a suspicious lesion, neither the lesion size nor the localization of the tumour contour plays an important role in these investigations, except where lesions are too small for SUVmax to be reliably calculated. These diagnostic studies have repeatedly confirmed that PET is invaluable in helping to determine if lesions are benign or malignant but the investigators did not seek to determine the location of the 'edge' of the lesion in three dimensional space. Determining the edges of lesions, the appearance of which is influenced strongly by factors that are directly linked to the size and shape of target volumes, is however crucial for radiotherapy planning.

In the available literature, the methodology for GTV definition with ^{18}F-FDG-PET has varied, but has most often been based on standardized uptake value in some way [70]. To define the PET GTV, many investigators have chosen a threshold, or cut-off value [70], i.e. they performed a segmentation of the lesion of interest on the basis of a given level of lesion activity. In these studies, a percentage of the maximum or peak SUV concentration has been used by some authors, whereas others have utilized an absolute SUV value (for example, an SUV contour of 2.5 [71] or some other number could be chosen to represent the edge of the lesion). The fact that absolute SUV measurement can be unreliable under some circumstances and can suffer from problems with accuracy and reproducibility needs to be remembered [72].

6.1.5. Thresholding

The most widely used thresholding [73] 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 range of 40–50% as in most applications reported in the literature might lead to significant errors in the volume estimation, depending on the lesion size homogeneity and the lesion to background contrast [74]. The comparison of various contouring methods has shown that this approach may render

significantly too small GTVs in large inhomogenous primary NSCLC [67]. Therefore, contrast dependent adaptive thresholding methods have been proposed, which are worthy of further investigation.

6.1.6. Background cut-off

Another automated approach to contouring is based on defining a cut-off with respect to the background and on contouring the region with intensity above the cut-off (e.g. intensity greater than three standard deviations above the background level as in [15] or a SUV above 2.5). An advantage of this approach is that it is quite independent of the heterogeneity of the tracer uptake in the lesion, which might conversely hamper the application of the threshold methods above. The accuracy of this background cut-off approach is however dependent on the accuracy of the statistical model employed for the assessment of the background.

In fact, a crucial aspect for all these contouring methods is represented by the statistical noise in the PET images. The assessment of the activity in the lesion and in the background is strongly affected by statistical fluctuations, implying erroneous definition of the threshold and cut-off levels. Furthermore, the robustness of the contour definition may also be affected by statistical noise. Recent improvements of both PET scanner electronics and reconstruction/correction algorithms make the three dimensional (3D) acquisition modality feasible for clinical PET whole body scanning [75], resulting in a significant increase in the detection efficiency and in the consequent improvement of image quality and reduction of noise, without increasing the acquisition time. The introduction of the 3D PET technique in clinical practice, not just in brain studies but also in whole body acquisitions, could potentially overcome the problem of statistical noise.

6.1.7. Source/background algorithms

Phantom studies with varying 'lesion' and background activities were conducted to derive the relationship between the true volume of the homogenously filled, usually spherical 'lesions' and the threshold to be applied on the PET images [76, 77]. The thresholds found varied according to the signal-to-background (S/B) ratios. This coherence can be expressed by relatively simple equations, which calculate the threshold value depending on mean background accumulation and the signal of the lesion. As with background cut-off methods, thresholds vary depending on the background definition in patient datasets. In head and neck tumours, contouring by an S/B algorithm led to the most exact volumes compared to CT and MRI-based volumes, as verified by review of pathological specimens [78]. The comparison of methods cited above [67] in primary NSCLC showed, that the application of S/B ratios led to reasonable volumes, compared with breath-expanded CT volumes. It has further been shown, that S/B algorithms may be relatively robust with varying acquisition times, and can be well applied even in very low contrast lesions [79].

6.1.8. Automated methods

Fully automatic thresholding methods have been developed and validated for ^{18}F-FDG-PET in patients with lung tumours. For automated thresholding complex S/B algorithms are most commonly used. However, automation suffers from serious shortcomings, at least when functional imaging is to be used for radiotherapy treatment planning purpose. First, such automatic segmentation often requires a previous estimate of the volume of the lesion of interest from CT slices or other anatomical images. Secondly, pathological and physiological

uptake of the tracer can not be distinguished by automated thresholding methods. Therefore, input and editing by the operator is usually required.

With all of the limitations inherent in automated methods, it is essential that the physician responsible for signing the radiotherapy prescription knows exactly how the PET-based GTV contours were produced and what are the potential sources of error in each method. Unfortunately there can never be a true gold standard for such studies because one is trying to estimate the absolute location of a three dimensional structure in time and space without any independent method of verification of the edge of structure. If we get it wrong, that fact may be reflected in higher locoregional relapse rates due to geographic miss, or in a higher risk of normal tissue toxicity due to excessively large target volumes. Therefore, clinical studies with standardized PET-based target volume definition are needed, ideally with pathological confirmation. A recent study by Baardwijk and colleagues from Maastricht [80] has not surprisingly shown, that use of auto-contouring reduces interobserver variability compared to a non-automated visual method, but more significantly that the maximum width of the tumour determined on auto-contour of the PET scan gave a good correlation with the maximum diameter of the tumour determined by pathology in 23 cases. The auto-contoured delineations could be edited at the discretion of the observer [80] and were derived using source to background ratios.

6.1.9. Tumour movement

An important issue in the definition of the target volume for thoracic malignancies is represented by the movement of the lesion as a result of the internal organ motion, primarily due to respiration [81] and to a lesser degree associated with the cardiac cycle or other factors. Due to its short acquisition time, CT provides a frozen 'snapshot' image of the tumour representing its position at a single instant in time but not all of its potential locations during the whole breathing cycle. If a single image is acquired without breatholding [82] or some other attempt to confine the image to one part of the respiratory cycle, the image will represent a random instant in the cycle. On the contrary, PET is performed during free respiration 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 shows an apparent increase in lesion size and an apparent decrease in the maximum activity concentration. The definition of the target volume in ungated PET should take tumour motion into account and the thresholding level has to be carefully chosen when automated methods are used. When planning using a visual method, the radiation oncologist will remember that intensity of ^{18}F-FDG uptake will seem less intense at the extremes of movement of a mobile tumour. As one would expect, phantom experiments have proved that, in the case of a moving object, a lower threshold should be used for an accurate assessment of its volume than is the case if the object is static [64, 73]. No tumours are entirely static and movement should always be considered in the planning process in lung cancer. With respect to the target volume definition, ungated PET can be used to help define the volume within which the lesion moves and thus describe the Internal Target Volume (ITV). This is a major advantage over ungated CT acquisitions which give no clue as to the location of the tumour in space over time. PET has the potential to allow an individualized target volume to be defined, accounting for the actual movement of the lesion with a resulting reduction of the expansion margins added in the PTV and better sparing of normal tissues. Highly conformal radiotherapy needs to account for organ motion [83], for example by target localization and tracking so that treatments can be even more accurate and precise. When margins are tight, tumour movement can easily carry parts of the target into areas of low dose. Several (non-randomised) studies suggest that there may be an advantage for higher dose levels in the

treatment of lung cancer [84], but side effects have been shown to correlate with mean lung dose. Thus, there is clinical evidence that PTV volume reduction achievable with four dimensional (4D) radiotherapy will allow an increased dose to the tumour while sparing healthy tissue, improving the balance between side effects and efficacy, theoretically increasing the probability of cure.

Much effort is currently dedicated to the implementation of 4D gated PET/CT acquisition protocols, acquiring both PET and CT images that are synchronized to the patient's respiratory cycle. A 4D PET/CT study provides a set of images representative of specific phases of the respiratory cycle, thus describing the movement of the tumour and of the body during patient respiration [85]. A 4D gated acquisition can allow a more accurate tumour definition resulting in increased lesion conspicuousness, improved target volume definition and better sparing of normal tissues, which are crucial for optimising radiation therapy.

Target motion is a major challenge for the radiation oncologist, particularly where highly conformal radiotherapy is used, for reasons discussed above. In an ideal radiation therapy treatment episode, the treatment delivery system would continuously adapt beam delivery to changes in the tumour position (real time tracking [86]) or deliver radiation at only one specific phase of the breathing cycle. The incorporation of the time dimension into the 3D-conformal radiotherapy process is termed 4D radiotherapy. Because the technology is not yet widely available and because there are often unsolved technical and compliance problems, gating procedures cannot be applied to all patients with lung cancer. Therefore, PET based radiotherapy planning must be optimized for both the gated and the ungated setting.

6.1.10. Clinical concepts for target volume

Besides the technical and geometrical problems in defining the boundaries of ^{18}F-FDG-positive areas, new clinical concepts need to be developed for each tumour type, defining how we should integrate these new PET-defined volumes into the planning process. These concepts mainly affect the definition of the CTV. Again, most data are available on lung cancer.

As discussed above, because of the high diagnostic accuracy of ^{18}F-FDG-PET in NSCLC, there may be a chance for a significant reduction of the CTV in patients with atelectatic lung tissue and in patients with enlarged nodes that are clearly ^{18}F-FDG-negative. Because of the inoperability or unresectability of most patients with atelectasis, no histological evidence of this assumption is available, nor is this likely to be shown conclusively in the near future because large pathological resection specimens do not retain their *in vivo* anatomical shape. Therefore, currently only pathophysiological considerations support the hypothesis that a tumour, which is otherwise ^{18}F-FDG-positive, does not have gross ^{18}F-FDG-negative extensions into neighbouring atelectasis. The probability of tumour-infiltration of atelectatic lung undetected by ^{18}F-FDG-PET is as low as that of an infiltration of any other neighbouring tissue. CT imaging does a poor job of distinguishing atelectasis from tumour. Detailed clinical studies with thorough follow up and careful investigations of patterns of local relapse may shed some light on this question but such studies are notoriously difficult and complicated by competing patterns of failure.

For nodal spread, there are various philosophies to cope with the problem of residual diagnostic uncertainty. One concept, commonly adopted in other fields of oncology, is only to treat regions at a perceived risk of microscopic/subclinical disease of more than a particular level, for example over 10%. If the risk is considered less than 10%, ^{18}F-FDG-negative nodes would be left out of the target volume. Another idea is to consciously leave the treatment of

potential microscopic spread to the effect of accompanying chemotherapy. In NSCLC however, chemotherapy has a borderline effect on microscopic disease and cannot be assumed to reliably eliminate it. Interestingly, it has been shown that significant portions of the lymph node stations in the neighbourhood of the PTV would, in most 3-DCRT plans, incidentally receive relevant doses of irradiation [87]. Another method for coping with ^{18}F-FDG-negative nodes is to include additional tissue into the CTV in addition to the ^{18}F-FDG-positive structures in the GTV. This may mean lymph nodes which are enlarged in CT but ^{18}F-FDG-negative, as done in some current multicentre protocols, or the whole UICC/AJCC lymph node station, as done by the Maastricht group [88]. The latter approach has the additional advantage that lymph nodes, which are not detectable by CT, do not pose a problem in contouring and that co-registration is not mandatory. A further point advocating the inclusion of whole nodal stations is that data from diagnostic literature, which is the basis for estimating the residual risk of missing tumour tissue when targeting ^{18}F-FDG-positive lesions only, deals with N-stage as whole or nodal stations rather than individual nodes [6, 45, 89]. This fact derives from histopathological comparisons between imaging and mediastinoscopy, where samples are categorized by nodal stations. However, the best concept of dealing with diagnostic uncertainties must be evaluated in prospective clinical studies.

It must be emphasized, that the rationale and methodology for the integration of PET data into the radiation treatment planning may vary widely depending on the tumour location and histology (e.g. risk of false ^{18}F-FDG-positives in head and neck cancers, absence of need for nodal CTV in brain tumours and most sarcomas) and the tracer used (e.g. the different image contrast attained in hypoxia imaging), and possibly even on the part of the world in which the treatment is performed (e.g. regions with higher prevalence of tuberculosis with consecutive false positive findings in ^{18}F-FDG-PET). Therefore, our detailed discussions of treatment planning in this section are strictly confined to ^{18}F-FDG based RT planning in NSCLC patients in regions with little incidence of infective lung diseases. As always, an intelligent consideration of all of the relevant clinical factors must be made when defining the target volume in any particular patient in any specific location in the world.

6.2. ROLE OF PET IN RADIATION THERAPY PLANNING FOR OTHER CANCERS

6.2.1. Small cell lung cancer

Small cell lung cancer (SCLC) is well imaged by ^{18}F-FDG-PET [90] but relatively few studies have directly addressed the role of PET in radiation therapy planning for this disease. The potential role for PET includes selection for radical chemoradiation, radiation therapy planning and selection of patients with complete remission for prophylactic cranial irradiation (PCI). In a prospective study by Bradley and colleagues [54], ^{18}F-FDG-PET demonstrated findings consistent with extensive-stage SCLC in three of 24 patients thought to have limited stage disease on the basis of conventional staging. ^{18}F-FDG-PET correctly upstaged two (8.3%) of 24 patients to extensive-stage disease (95% CI, 1.03% to 27.0%). PET correctly identified tumour in each SCLC mass (primary or nodal) that was suspected on CT imaging, thus giving a lesion-based sensitivity relative to CT of 100%. PET identified unsuspected regional nodal metastases in six (25%) of 24 patients, and the radiation therapy 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) [91]. Of 15 patients who had PET for staging, 5 (33%) were upstaged from limited to extensive disease and treated without thoracic radiotherapy. Twenty-five patients underwent 32

restaging PET scans, of which 20 (63%) were discordant with conventional imaging. In 13 patients, 14 untreated discordant lesions were able to be evaluated; PET was confirmed accurate in 11 (79%) sites by last follow-up. These results are similar to those reported by other groups [92], [93], [94], suggesting that PET may have a role to play in selecting patients for RT and in designing the RT fields. PET-response may define complete remission more accurately so that patients may be appropriately selected for PCI. Good quality prospective studies are required to clarify the role of PET in SCLC.

6.2.2. Head and neck tumours

Although the diagnostic accuracy of ^{18}F-FDG-PET in head and neck tumours is sometimes hampered by false positive uptake in muscles and inflammatory tissue, some authors have reported a change in volume delineation when adding ^{18}F-FDG-PET information to CT [95], mainly due to a different detection of lymph node involvement [96]. However, although the use of PET/CT for staging and detecting both primary and recurrent head and neck cancer is valuable, ^{18}F-FDG-PET-based tumour volume contouring is not ready for routine clinical practice. In particular, the accuracy of anatomical co-alignment, and variability in defining the threshold of imaging signals on PET images can affect the contour of the biological tumour volume. Recently, significant differences in GTV delineation were found between multiple observers contouring on PET/CT fusion, mainly due to the lack of a delineation protocol [97]. PET may be more helpful for delineating nodes than for delineating primary tumours [98].

When PET is used to determine a radiotherapy target volume in head and neck cancer, the situation is complex [99]. The boundaries of primary tumours 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 radiotherapy planning. In head and neck cancers this is an especially important issue because very high does of radiation (70 Gy) are commonly delivered to lesions close to radiosensitive vital structures such as the brainstem or optic chiasm and consequently radiotherapy margins are often tight around tumour. Immobilization techniques allow treatment at these sites to be delivered with millimetre accuracy and it is essential that tumour margins are well appreciated [96].

Careful comparison of ^{18}F-FDG-PET, MRI and CT scans with the histopathology of resected tumour specimens shows that none of these three imaging modalities is 100% accurate, but ^{18}F-FDG-PET appears to be the most accurate of the three [100]. Tumour volume determined by ^{18}F-FDG-PET tends to be smaller on average than the volume determined by the other modalities but most closely approximates the true tumour volume [78]. 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.

Although ^{18}F-FDG-PET may not yet be ready for routinely determining target volumes in RT for head and neck cancer, this should remain an area for active research. Dietl and colleagues reported that changes in radiotherapy technique due to PET occurred in 40.8% of 49 patients in a prospective study [101]. Because of the complex movements of the neck, including rotation, angulation and flexion of the neck and independent movement of the mandible, the potential for mis-registration between anatomical and functional images is significant and therefore, combined PET/CT acquired in the radiotherapy treatment position is likely to provide the most accurate methodology for ensuring that all macroscopic tumour deposits are included in the high-dose treatment volume. Nevertheless, despite the great promise of PET in RT planning in head and neck cancer, as suggested by Gregoire [102], one must proceed cautiously. The consequences of geographic miss can be disastrous in this group of

malignancies. Ideally one should pursue the use of PET planning in clinical trials before it can be recommended as routine in head and neck cancer.

In the opinion of the authors, to date, the diagnostic literature does not allow us to recommend that there should be an ^{18}F-FDG-PET-based reduction of prophylactic target volumes in head and neck tumours. Further studies are needed to determine the post-test probability of microscopic lymph node involvement in this area correlating the findings of molecular imaging with pathology specimens. It should be emphasised again that PET dose not detect microscopic disease. Nevertheless, better estimates of the true risk of microscopic disease in a particular node can be made if the true distribution of macroscopic disease in nearby nodes is known. The results of studies conducted on hypoxia imaging in head and neck tumours [103, 104, 105, 106] could also open new perspectives in radiation treatment planning. These studies have helped demonstrate the feasibility of in vivo hypoxia imaging. Furthermore, they showed a significant correlation between hypoxia-tracer uptake and treatment response. However, the results of clinical trials analyzing the impact of dose escalation, boosting the doses to hypoxic subvolumes, are unavailable.

6.2.3. Lymphoma

PET is increasingly being used to select lymphoma patients for RT and to help delineate radiation fields [107], although the latter has not yet been widely systematically studied using integrated PET/CT scans incorporated directly into the planning process. A recent study by Hutchings and colleagues showed a high potential of PET to change the design of involved treatment fields in Hodgkin lymphoma [108]. The lymphomas are a large and heterogeneous group of diseases, often with widely varying treatments. In patients with localised disease, RT may be an important component, or indeed the only component of potentially curative therapy for this especially radiosensitive group of malignancies. Accurate staging is important in the management of three of the most common disease groups included in the WHO lymphoma classification, namely Hodgkin Lymphoma, the group of ‘aggressive lymphomas’, the most common of which is diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma [109]. In each of these malignancies, early stage disease is commonly treated with ‘involved field’ radiotherapy, where the treatment volume covers involved extranodal sites and lymph node regions only. More advanced disease is usually treated with more intensive chemotherapy, with RT reserved only for bulky masses or poorly responsive disease sites. RT may be given alone, as in stage I-II follicular lymphoma, or after a number of cycles of chemotherapy, as in stage I-II DLBCL or Hodgkin lymphoma.

^{18}F-FDG-PET is significantly more accurate in both staging [110] and treatment response assessment [111] in both Hodgkin and non-Hodgkin [112] lymphomas than conventional structural imaging. PET data may now be routinely visually incorporated into the RT treatment planning process [113]. Because large regions of the body are often irradiated to a relatively low dose, there has been less pressure to minutely shape RT fields by incorporating PET directly into the RT planning systems than for example lung or head and neck cancers. It is often sufficient to know that a lymph node region contains tumour when RT is being planned because the target volume is often determined by the anatomic boundaries of the involved region rather than the precise distribution of disease within the region.

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 there is inadequate contrast between lymphoma and normal tissues on CT, such as spleen, liver, salivary glands and bowel. A case with early relapse of Hodgkin´s lymphoma in an unirradiated CT-negative but ^{18}F-FDG-positive lymph node region published by the German Hodgkin’s lymphoma

study group [114] clearly showed the potential benefit of the consideration of ^{18}F-FDG-PET findings for RT planning. PET may also be used to assess the response of lymphomas to chemotherapy [115], either definitively at the end of therapy, or as an interim measure, after only 1–3 cycles of chemotherapy [116, 117, 118]. Persistent tumour ^{18}F-FDG uptake after several cycles of chemotherapy or at the end of chemotherapy is very highly correlated with prognosis and may assist with the decision to deliver RT. However there is as yet no good evidence to suggest that an excellent interim PET response to chemotherapy can be used to identify patients who do not require RT as part of what would normally be given as combined modality therapy in early stage Hodgkin lymphoma or aggressive lymphomas. Baseline PET scans may help determine where consolidative radiation should be delivered after attainment of a response to chemotherapy but target volumes often need to be reduced as lymphoma masses reduce or disappear with systemic therapy. Clinical studies on this topic are ongoing.

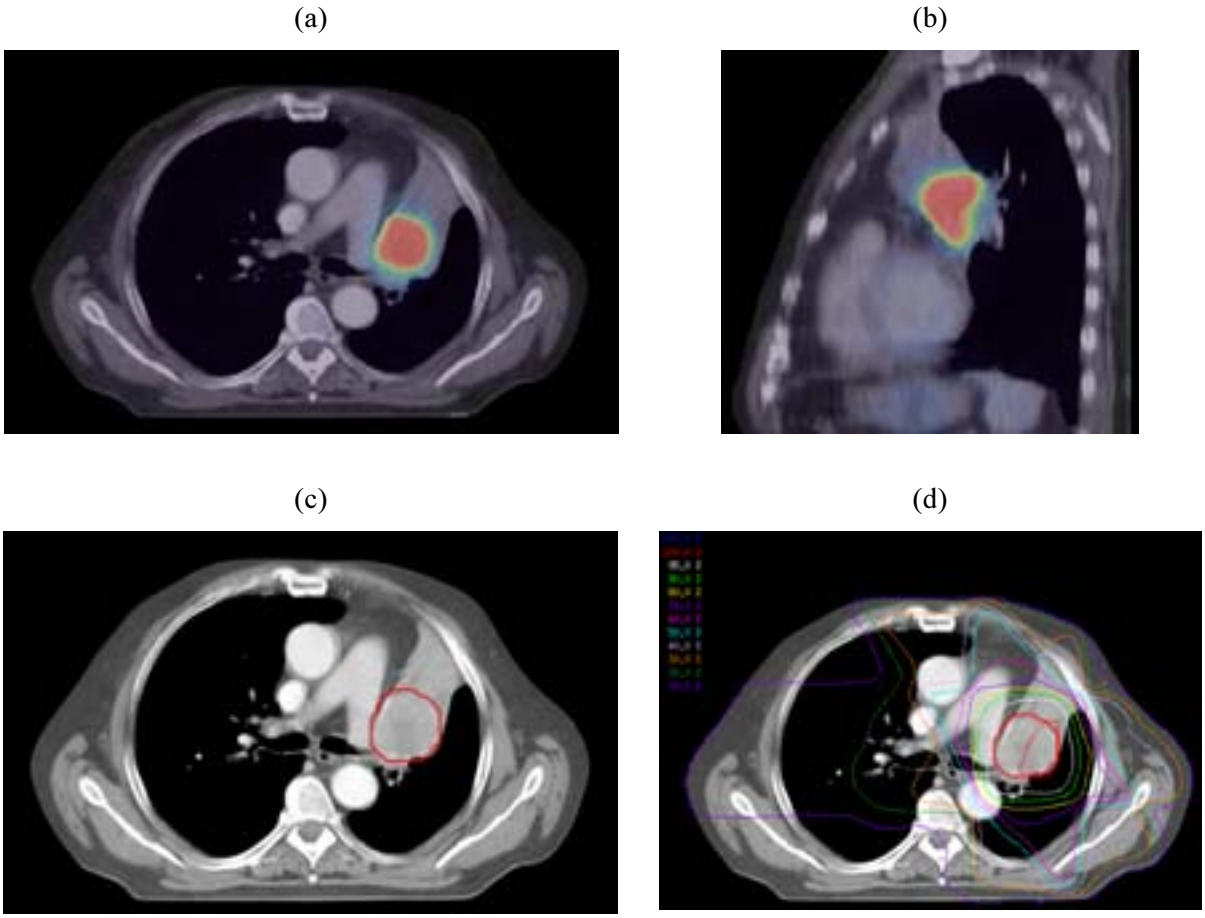

Fig. 1. NSCLC arising in the left upper lobe. The associated atelectasis did not show ^{18}F-FDG-uptake, and was therefore excluded from the GTV. Axial (a) and sagittal (b) CT reconstruction fused with ^{18}F-FDG-PET reconstruction. The GTV (red; (c) was designed using a source/ background algorithm. Recruited for the German PET-Plan study (pilot – phase), the patient received radio-chemotherapy with radiation confined to the ^{18}F-FDG-positive area (treatment plan; (d)) escalated up to 74 Gy (1,8 Gy daily).

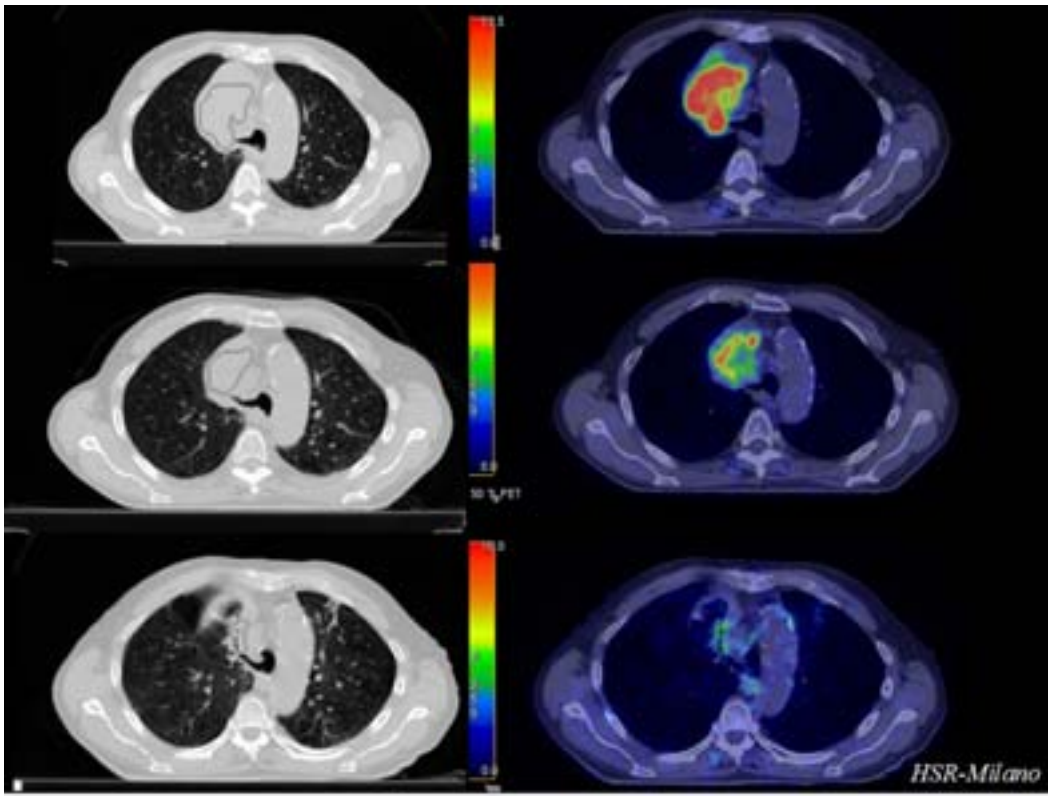

Fig. 2. A 61 year-old man with NSCLC. A ^{18}F-FDG-PET/CT study was performed before the beginning of RT treatment (upper), after a delivered dose of 50 Gy (middle), and 3 months after the end of RT treatment (lower). The region of interest corresponding to PET hypermetabolic areas are shown on the CT images. A decrease in hypermetabolic activity during and at the end of treatment is evident and quantified by SUV changes.

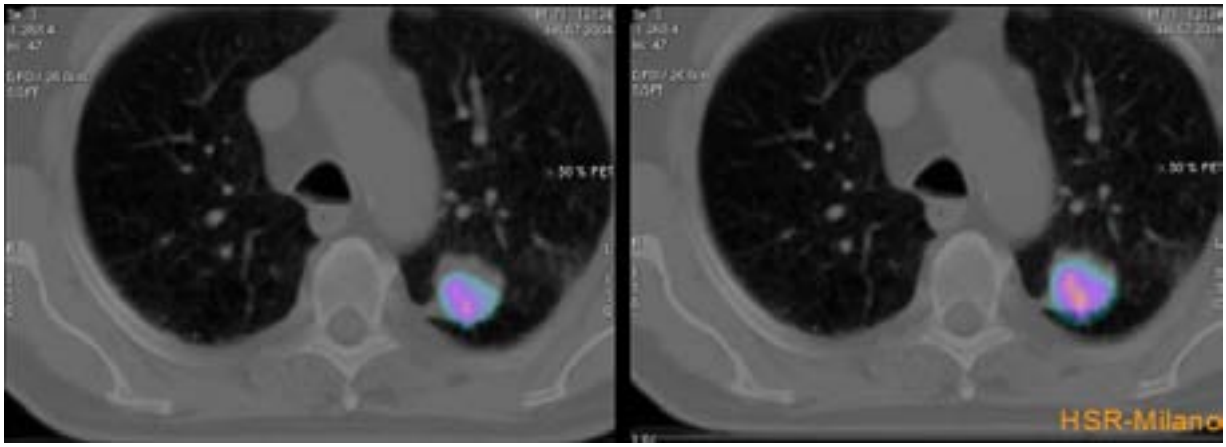

Fig. 3. An example of a lung tumour contouring using a threshold for image segmentation as percentage of the maximum pixel value of 40% on the left and on the right as a function of measured contrast between lesion and background.

6.2.4. Oesophageal cancer

Combined chemoradiation with or without surgery is commonly used to treat oesophageal carcinoma and the use of concurrent chemoradiation has been found to significantly increase overall survival and cure rates compared to radiotherapy alone. PET has the potential to improve the accuracy of the planning process [119]. Clinicopathological studies in patients undergoing resection show that CT scanning is very poor at assessing the longitudinal extent of tumour and is often inaccurate when used to estimate the extent of nodal involvement, but is reasonably good at showing radial extent. PET is significantly more accurate than CT for the assessment of nodes [120] except those adjacent to the oesophagus and better shows the longitudinal extent of the tumour than CT. In cases where an endoscope is unable to pass through a stenosed oesophagus to visualize the lower boundary of the tumour, PET may be the only way to estimate the lower border of the tumour. A prospective trial of PET in RT planning for oesophageal carcinoma [121], has shown that PET has a significant impact on GTV and PTV in oesophageal cancer, often helping to avoid geographic miss by identifying unsuspected lymph node involvement. In another study, Moureau-Zabotto and colleagues showed that the addition of PET information to CT-based RT planning altered the GTV in 19 of 34 patients (56%) [122]. GTV was reduced in 12 patients and increased in 7 (21%).

7. CONCLUSIONS

Because of its remarkable accuracy in staging and a demonstrated powerful effect on treatment volumes in all published RT planning studies, there is a strong case for the regular use of ^{18}F-FDG-PET in RT planning for NSCLS. In malignancies such as lymphomas, SCLC and cancers of the head and neck and oesophagus, the routine use of PET information in RT planning should be cautiously considered, although limited supporting data still exists. There have been promising studies in other tumour sites, such as prostate, cervix, colorectal, soft tissue and locoregionally advanced malignant melanoma [123, 124, 125, 126], for which PET is likely to prove valuable for RT planning. Introduction 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 is no compelling data to prove that patient outcomes are superior as a result of the use of PET in RT planning. Proving that PET-planning is superior would require a randomized trial in which some patients were randomized to a less accurate staging workup, thereby presenting significant ethical challenges. Nevertheless, in the opinion of the IAEA expert group, radiotherapy planning should be based on the most accurate available assessment of tumour extent. PET/CT may provide the best assessment for cancer patients at this time.

Appendix

^{18}F-FDG-PET/CT PROTOCOL

A.1. Hardware requirements

Any PET or PET/CT scanner, performing in 2D or 3D mode, any CT (multi-slice are preferred), possibility for both PET and CT of performing 4D PET/CT.

(a) *Patient preparation*: fasting > 6 hours, good hydration, avoid physical stress for the previous 2 days, check glucose levels.

(b) *FDG injection*: depending on the clinical question: if for both staging and volume delineation, use standard diagnostic dose, if only for volume delineation consider use of reduced ^{18}F-FDG dose and performing 1–2 bed position using a longer acquisition time.

(c) *Uptake time*: not less than 45 minutes. Recommended 60 minutes or more.

(d) *Patient positioning*: Position patient with their immobilisation device which can be standard (e.g. wing board) or personalised (previously built in the RT department, e.g. masks). Make sure the patient is well-immobilised in the device but can sustain the position for the whole acquisition time. PET/CT should be aligned to previously placed skin tattoos using a laser beam.

(e) Image acquisition.

A.2. Ungated PET/CT

CT acquisition parameters: use of contrast media as well as CT scanner setting depends on the clinical situation.

PET acquisition parameters:

(a) As a part of staging study: The same parameters as for standard diagnostic PET/CT study;

(b) For volume delineation: Depends on injected dose; if it is reduced, a longer acquisition time is required.

Standard reconstruction, scatter- and attenuation correction, phanto quality control (QC) regularly up to TP-System

A.3. Gated (4D) PET/CT:

Gated PET/CT imaging is used for more precise definition of PTV taking into account tumour motion. In addition, this approach is of interest in the context of gated radiation delivery.

Patients are set up with arms behind the head using a customized patient mould to assist immobilization. Injected dose should be slightly higher than for ungated acquisition to ensure appropriate statistics. A ‘standard’ whole body (WB) ^{18}F-FDG-PET/CT scan is performed for staging, followed by a single field of view (FOV) 4D-PET/CT study on the region of interest. All patients are prior trained to breath regularly and 4D-PET/CT data are then acquired during free breathing. Patient respiration is monitored by the real-time tracking system which also

allows the synchronization of 4D-PET and 4D-CT scans to the respiratory cycle: 4D-CT is gated according to physiologic signal and 4D-PET; 3D-acquisition in list mode is recommended. The typical acquisition time is at least 12 minutes per bed position. 4D-CT data are processed and usually sorted into 6–10 respiratory phases. 4D-PET data are then corrected for attenuation using the corresponding CT data at the same breathing phase. To describe the tumour motion induced by patient respiration, inspiration and expiration phase plus two intermediate phases are used. The sets of 4D-PET and 4D-CT image phases are then combined to generate a series of PET and CT images representing the full tumour motion.

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