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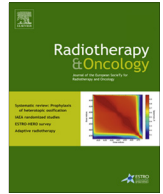
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IAEA consensus report

PET/CT imaging for target volume delineation in curative intent radiotherapy of non-small cell lung cancer: IAEA consensus report 2014



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ABSTRACT

This document describes best practice and evidence based recommendations for the use of FDG-PET/CT for the purposes of radiotherapy target volume delineation (TVD) for curative intent treatment of non-small cell lung cancer (NSCLC). These recommendations have been written by an expert advisory group, convened by the International Atomic Energy Agency (IAEA) to facilitate a Coordinated Research Project (CRP) aiming to improve the applications of PET based radiation treatment planning (RTP) in low and middle income countries. These guidelines can be applied in routine clinical practice of radiotherapy TVD, for NSCLC patients treated with concurrent chemoradiation or radiotherapy alone, where FDG is used, and where a calibrated PET camera system equipped for RTP patient positioning is available. Recommendations are provided for PET and CT image visualization and interpretation, and for tumor delineation using planning CT with and without breathing motion compensation.

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¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is recommended as a useful tool in helping staging accuracy and treatment planning [1]. FDG-PET is superior to computed tomography (CT) alone in the staging of lung cancer [2,3]. It is now considered a routine investigation in the baseline staging evaluation of patients with non-small cell lung carcinoma (NSCLC) who are being considered for radical intent treatment [4]. When PET is acquired in conjunction with a CT (PET/CT), the combined PET/CT information has been shown to have greater

staging accuracy than PET imaging alone [5–10]. A combined PET/CT acquisition is now the standard method of acquiring FDG-PET images for the purposes of baseline staging and for radiotherapy treatment planning (RTP) [1].

The introduction of FDG-PET has been shown to have a significant impact in selecting patients for curative intent or “radical” radiotherapy [11–14]. PET imaging also has been noted to reduce inter-observer variation when used to guide target volume delineation in RTP in NSCLC patients [15–18]. Furthermore the acquisition of a dedicated PET/CT scan for the purposes of RTP in patients who have had a previous staging PET/CT has been shown to have further impact in reducing inter-observer variation [19].

A number of techniques have been used to generate RTP target volumes using the information gleaned from PET and CT. Most clinical studies have used a visual interpretation technique, while others have reported the use of automated segmentation techniques to either guide or generate the relevant target volume [1,20–23]. A previous International Atomic Energy Agency (IAEA) publication provided guidance on the use and role of PET/CT imaging for RTP in a range of tumor sites [24].

Abbreviations: Ave-IP, average intensity projection; CT, computed tomography; CTV, clinical target volume; EBUS, endobronchial ultrasound sampling; EUS, endoscopic ultrasound sampling; FDG, ¹⁸fluorodeoxyglucose; GTV, gross tumor volume; IAEA, International Atomic Energy Agency; ITV, internal target volume; MDE, microscopic disease extension; NMP, nuclear medicine physician; NSCLC, non-small cell lung cancer; PET/CT, positron emission tomography/computed tomography; PTV, planning target volume; reGTV, respiration expanded gross tumor volume; RO, radiation oncologist; RTP, radiation treatment planning; TVD, target volume delineation; W/L, window/level.

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Methods

Following an IAEA Expert Meeting on the use of PET/CT imaging for RTP in Vienna in July 2013 it was decided to update the previous IAEA report to provide clear guidance on target volume delineation (TVD) using PET/CT imaging, specifically for the applications in lung cancer and taking advantage of the considerable research activity that has occurred since the last reports. This publication focuses entirely on the use of FDG-PET/CT in defining the target for RTP in NSCLC and seeks to update the previous guidance in light of emerging evidence and consensus opinion.

To ensure the inclusion of relevant publications the following search was undertaken. The terms “positron emission tomography”, “Non-Small Cell Lung Cancer”, “target volume delineation” and “Radiotherapy”, along with their derivatives were used to search PubMed. All studies relating to PET/CT for target volume delineation in the treatment of NSCLC with radiotherapy and of relevance to this overview were included in the preparation of the review. No limitations were placed on language or year of publication.

Background of PET based radiotherapy target volume delineation in NSCLC

The first human PET scanner was constructed in 1974, but it is only in the last 16 years that clinical studies have examined the impact of using FDG-PET for TVD in NSCLC [25,26]. Early studies simply described the impact on the treatment volume, often without any quantification [26]. Several staging studies clearly demonstrated the superiority of PET/CT over CT for identification of involved mediastinal lymph nodes [27,28]. PET based TVD was also shown to improve the inclusion of truly involved mediastinal lymph nodes [29]. In patients with atelectasis, it was apparent from the earliest studies that PET could help discriminate collapsed lung from tumor [30]. This approach is now widely accepted and clinically applied, although few studies have undertaken a direct validation of imaging against pathological specimens due to the difficulties with correlation and processing artefacts [31–33]. A number of studies have sought to measure the impact of FDG-PET/CT based TVD on inter-observer variation or against a ‘gold standard’. Besides the impact on staging, FDG-PET/CT imaging greatly reduces the undesirable impact of inter-observer variation [19]. In addition, PET/CT based target volume delineations are on average smaller than their non-PET counterparts, thereby reducing the dose to normal structures. This may open the possibility of dose escalation [34,35].

Acquiring a PET/CT scan for the purposes of target volume delineation

FDG-PET/CT imaging for the purposes of baseline staging is now considered as ‘standard of care’ in patients with NSCLC being considered for treatment with radical intent [4]. Hence any patient considered for radical radiotherapy should have had a staging PET/CT. When used in its most basic form, without specific adaptations for RTP, images from a staging PET/CT scan can be visually correlated with the RTP CT to identify areas of disease for inclusion within the treatment volume. The accuracy of correlating a staging PET/CT scan and a planning CT will be improved by fusing both image sets. However, most staging scans are acquired on a curved top couch, possibly with the patient’s arms positioned down by their side, while an RTP CT is usually acquired on a flat top CT couch with arms immobilized above the patient’s head. The resulting differences in position between the two scans may make anatomical registration of these image sets difficult, leading to

interpretation issues and potential inaccuracies in TVD. Therefore, these images should not be coregistered in a treatment planning system for the purpose of tumor delineation. Deformable registration has been used in an effort to account for differences in patient positioning between imaging studies acquired in different positions. However, elastic registration is difficult due to the differences in acquisition technique between PET and CT, and deformation of PET images would compromise their inherently good representation of average tumor positions in case of breathing motion. The use of deformable registration to combine a diagnostic PET/CT scan with an RTP CT scan has not been consistently validated and at present is not recommended for this purpose [36]. In conclusion, there are no validated strategies available that would allow the use of a diagnostic PET/CT for reliable image fusion with an RTP CT.

Technically the best available option is to acquire a PET/CT scan exclusively for the purpose of RTP. This scan may be performed when a staging PET has already been acquired and the patient is deemed suitable for radical radiotherapy [37]. This approach requires two separate PET scans, which has as advantage that it removes any staging or patient selection issues. However, this approach is expensive and therefore may not be possible in all health care systems because of financial or logistical limitations. Another valid approach is to acquire a single PET/CT scan in radiotherapy treatment position to serve the dual purposes of staging and TVD. This approach avoids the costs, radiation dose and delay due to repeated imaging. It requires a complete RTP procedure on the PET/CT scanner for all potential candidates for radical irradiation despite the fact that a significant number of patients will be classified with stage IV disease after interpreting the PET images. It is imperative that the time interval between any imaging used for the purposes of radiotherapy target volume delineation and the radiotherapy treatment delivery should be as short as possible. Several studies examined the effect of radiotherapy field changes size and the effect of staging accuracy with different time scales from PET/CT scan acquisition [38–41]. All of them demonstrate that PET/CT scan accuracy reduces with increasing time from the scan acquisition and that some patients may develop more advanced stage disease in the time to treatment, which will affect their chances of long-term survival. Long delays in time to treatment could result in a geographic miss if RT fields based on prior PET/CT scans no longer encompass the entire tumor or all involved lymph node stations. To avoid this issue, it is suggested that radiotherapy treatment should commence no later than 4 weeks after acquisition of the PET/CT scan.

Regardless of the selected approach, the PET/CT scanner has to be equipped with a flat RT table top, RT patient positioning devices and the CT component has to be calibrated to be safely used for RTP and RT dose calculation [42].

It is essential that where PET/CT imaging is used for TVD, that each part of the process has undergone appropriate quality assurance testing and that the entirety of this process has been validated [43]. This includes patient preparation, scan acquisition, review of the images acquired, the alignment of the CT and PET components of the PET/CT scan, transfer of the images to the radiotherapy planning system and the final display of the PET/CT images on the planning computer.

Guidance for PET/CT based visual target volume delineation

The combined procedure consisting of image interpretation, patient staging, treatment selection, and target volume definition requires many different aspects of multidisciplinary clinical expertise. It is recommended that a radiation oncologist (RO) and a nuclear medicine physician (NMP) / PET radiologist are both

involved where PET is used for TVD [44,45]. In any discussion regarding tumor volume delineation based on PET, emphasis should be given to the opinion of the NMP / PET physician in interpretation of the images and to the opinion of the RO in interpretation of all relevant clinical aspects. This also implies that the use of unmodified automated delineation of PET images for TVD is not recommended and that the final contour assessment should be made based on human visual interpretation of the images [24]. To ensure adequate and reproducible visual interpretation and application of PET images for RTP, this procedure should be standardized. The following principles are followed for visual TVD in using PET/CT imaging in NSCLC patients.

General approach of target volume delineation with PET and CT

Target volume definition involves the identification of all recognizable tumor locations, both the primary tumor and involved lymph nodes, to delineate a gross target volume (GTV) as a primary step and secondly the lymph nodes [46]. Depending on the applied strategy, this GTV may also include the full motion path of all tumor locations to create a respiration expanded GTV (reGTV). This volume, analogous to a respiration correlated GTV, contains the tumor at all times of its excursion and with suitable expansions is capable to form the basis for the clinical target volume (CTV) and the planning target volume (PTV) [47,48]. How the combined information in the PET and CT scans contributes to the generation of a GTV or reGTV depends on the characteristics of both of the available image sets, as described here.

Where a PET/CT scan is not acquired in the RTP position

Where the PET/CT used for interpretation has not been acquired in the treatment planning position and is only visually compared with a 3D radiotherapy planning CT, PET should only be used to identify those tissues which contain tumor. The RTP CT should be used when delineating the edge of the GTV and lymph nodes [37].

The radiation oncologist should work together with the nuclear medicine physician to identify tissues that contain tumor and need to be included in the GTV.

Where a PET/CT scan is acquired in the RTP position, without respiration compensation

Standard CT for RTP is acquired during free breathing without specific measures for compensation of breathing motion, resulting in deformation and misplacement of tumor locations. In some cases a general impression of the breathing motion is identified using fluoroscopy or slow CT, but these approaches are considered insufficient for RTP procedures. Since PET is acquired during free breathing, the images are blurred according to the breathing motion and provide a good impression of the shape and average location of tumor sites [49,50]. Therefore, in the most common scenario for RTP, where 3DCT and 3D PET scans are acquired, a reGTV approach is suggested. In this approach, the tumor should be delineated using the PET to guide both the location and the boundary of the reGTV. Where suspected disease is located outside the PET based target volume, for example on CT or based on clinical information such as positive biopsy locations, those areas should also be included in the reGTV [51]. When a margin for the CTV is added to this reGTV, an internal target volume (ITV) can be generated. Since PET has a poor resolution of 4–8 mm, it should be noted that 3D PET/CT may not fully define the ITV of highly mobile lung tumors and tumors with low FDG uptake. Hence, in the absence of 4DCT, the approach of defining a reGTV using PET should be used with caution in these circumstances [52]. To compensate for underestimation of motion in these circumstances, larger expansion

margins from CTV to PTV in the superior and inferior direction should be considered.

In summary, tumor delineation is a multidisciplinary procedure. The NMP should provide the RO with information about the shape and location of tumor sites from PET imaging during delineation of the GTV or reGTV. The RO should use his/her expertise to detect suspicious tissue outside the PET based target volume and include this in the GTV or reGTV.

Where a PET/CT scan is acquired in RTP position, with breathing compensation

Where adequate respiration compensation is used in the treatment planning CT, such as with 4DCT, the CT images may provide reliable information on the shape and location of tumor sites, except in cases where there is insufficient contrast between tumor and non-tumor tissues, for example where there is atelectasis or postobstructive pneumonia (Fig. 1). With 4DCT acquisition the GTV should be based on the 4DCT, with the PET being used to discriminate tumor and non-tumor sites to adapt the GTV where appropriate. It is important that where a RTP 3D PET/CT scan is registered to a RTP 4DCT scan, the limitations of this registration are appreciated. It is suggested that PET/CT images should be registered to the average intensity projection (Ave-IP) scan set using a rigid registration focusing on bony anatomy which is not affected by respiratory motion (e.g., spinal column). It is advised that this approach should not be used routinely for gated treatments.

Specific guidance for PET/CT based TVD

The FDG uptake of the primary tumor and any involved lymph node(s) may require evaluation with separate FDG-PET “window/level (W/L) settings.” It is important to standardize these settings, as variations in W/L settings will result in significant differences in the apparent tumor size on PET images and thus in the resulting target volumes. In addition, patients may have significant variations in biological factors, such as renal clearance of FDG, resulting in unpredictable background activity with impact on visual and quantitative strategies to discriminate tumor from physiological FDG uptake. There are no validated quantitative approaches for PET contouring that will result in ideal tumor delineation for all patients and tumor locations. However, the procedure can be standardized to some extent using visual calibration of the W/L settings, for example:

- Standardize signal intensity visually according to the biology of the patient (e.g., always start with a signal brightness of the liver (Fig. 2), vessels or other normal tissue which is familiar to the NMP/PET radiologist as normal background physiological uptake).
- Use a simple linear grayscale (e.g., black to white) for reviewing the PET images alone. For image fusion of PET with CT use a linear scale to one or at most two colors (e.g., black to red to yellow). Avoid polychromatic scales to avoid misleading color scaling contours.

Similarly, the W/L settings of CT images will influence the tumor delineation procedure. Depending on tumor localization, the appropriate CT window should be chosen. For example:

- Where the tumor is surrounded by lung tissue, lung window level settings should be used.
- For delineation of lymph nodes and where tumor invades the chest wall or mediastinum, soft tissue window settings should be used.

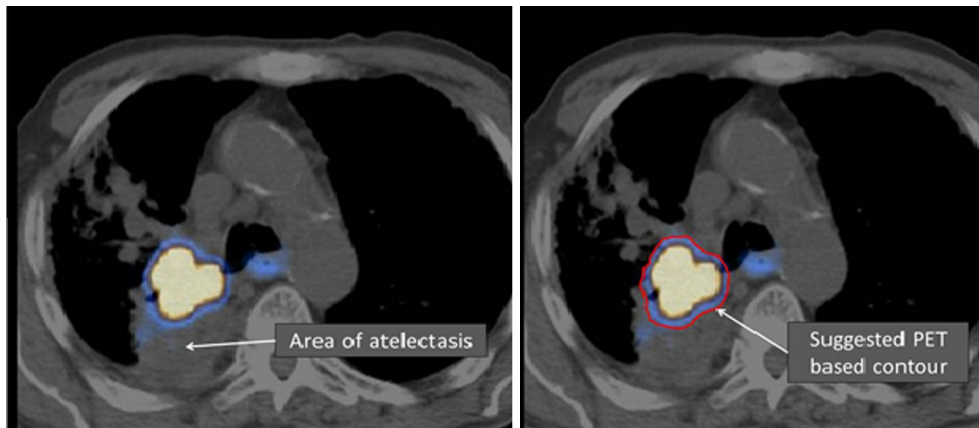


Fig. 1. Area of atelectasis in the right upper lobe. CT images show insufficient contrast between tumor and non-tumor tissue where atelectasis is present, therefore delineation should be defined by PET FDG avid areas.

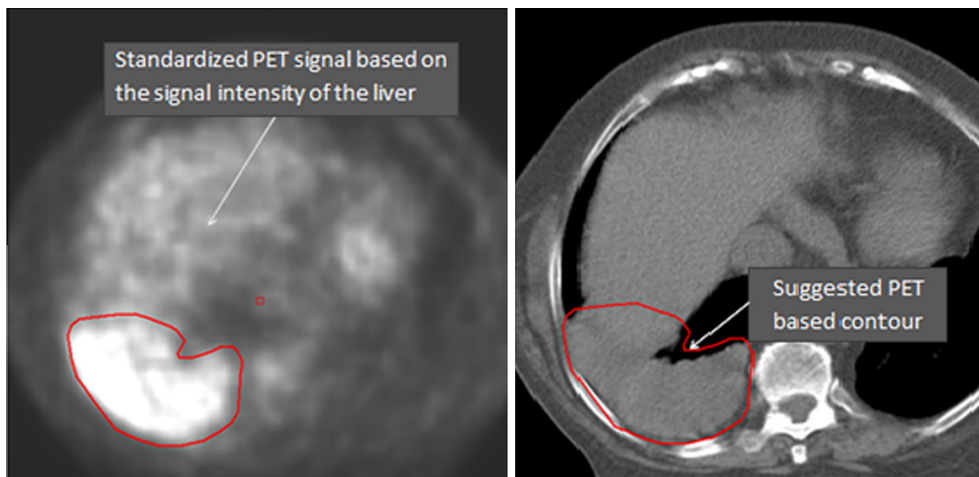


Fig. 2. Example of a standardized signal intensity based on the signal brightness of the liver. The PET signal is very intense in the right lower lobe. When the tumor is contiguous with a non-tumor structure that has a similar density and where no tumor boundary can be distinguished on CT (e.g., when the tumor is adjacent to the liver), the reGTV should be defined by the PET FDG avid areas.

The nuclear medicine physician should assist the radiation oncologist in selecting standardized PET W/L settings in case of delineating the reGTV. Variations in W/L settings on PET images will result in significant differences in the apparent tumor size and thus in the resulting target volumes.

Standard delineation procedure for combined PET/CT imaging

When contouring is based on two image sets, discrepancies between the two scans may lead to uncertainty as where to draw the final contour. It is important to acknowledge these issues and to standardize solutions, in order to avoid observer variations and potential geographic miss.

An important question is whether the GTV (or reGTV) may contain areas where PET is positive for tumor but CT shows normal lung tissue. When delineating a reGTV based on PET (e.g., when using 3DCT), all tumor locations should be defined primarily by the FDG avid signal including their full motion paths, and this may include areas at the surface where there is no tumor apparent on the non-respiration correlated CT (Fig. 3). However, when delineating a GTV based on CT (e.g., when using 4DCT), the primary tumor should be defined primarily by the structures as seen on CT and therefore not include air. However, as the PET scan may reveal a so-called

“baseline shift” i.e., the change of the basic position of the tumor, in the case of perfect coregistration of bony structures, a clear deviation of the PET signal from the 4DCT created ITV should not be disregarded and might be used to further expand the ITV.

Another common issue is the distinction between tumor and adjacent soft tissues. In areas where the tumor is contiguous with a structure that has a similar density and where no tumor boundary can be distinguished on CT (e.g., in the presence of extrathoracic extensions, see Fig. 4), the reGTV should be defined by the FDG avid areas [30]. Where the PET scan is compromised by FDG uptake that is apparently not explained by tumor (e.g., physiological uptake in the heart, or active infection), the reGTV should be defined by the CT images.

For lymph nodes the same approaches for GTV and reGTV can be applied as for a primary tumor. An additional issue is the identification of the lymph nodes that need to be included in the delineation. A pathological lymph node is defined as a lymph node which is involved on FDG-PET in the opinion of a trained NMP/PET radiologist. Non FDG avid (negative) nodes that appear enlarged on CT and that have a low likelihood of containing macroscopic tumor, do not need to be included in the GTV under certain circumstances [34]. PET negative nodes may be included in the final GTV volume based on information obtained through bronchoscopy, mediastinoscopy, endoscopic ultrasound sampling

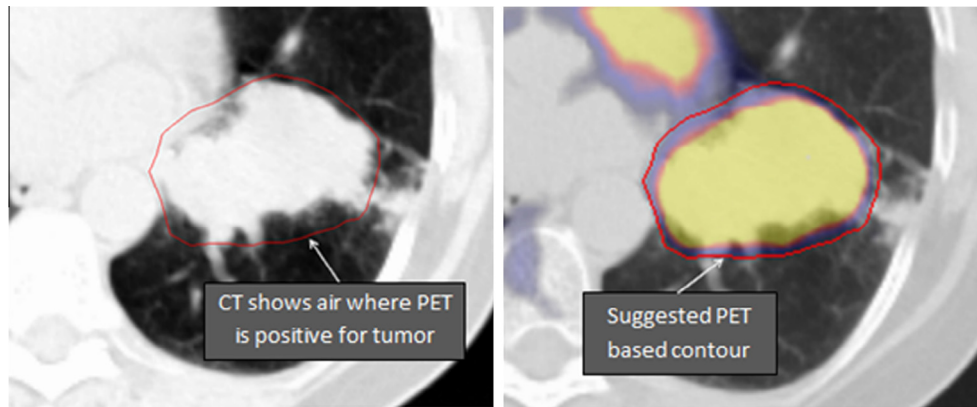


Fig. 3. Example of a delineation of the reGTV based on PET in combination with a 3DCT. A primary tumor can be seen in the left upper lobe with high FDG uptake. The PET signal shows FDG uptake in air when the modalities are combined which is due to the movement of the tumor.

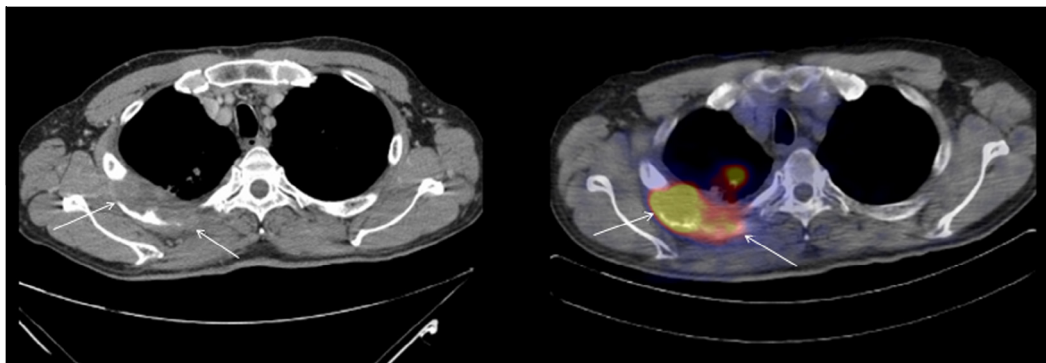


Fig. 4. Example of a histopathologically proven primary tumor with high FDG uptake in the apical segment of the right upper lobe with a diameter of more than 6 cm, and the adjacent pleural mass with extrathoracic growth and destruction of the dorsal third to sixth rib on the right. Difficulties arise when distinguishing between normal tissue and tumor in the thoracic wall using CT alone. In this case PET should be used to define the boundary of the tumor.

(EUS), and endobronchial ultrasound sampling (EBUS). Any biopsy proven lymph node should be included in the GTV. Recently, an update of guidelines for preoperative mediastinal lymph node staging is published, recommending EBUS/EUS with fine needle aspiration as the first choice [53]. If EBUS/EUS findings are negative and if uncertainty regarding the involvement of mediastinal lymph nodes remains, video-assisted mediastinoscopy is preferred over mediastinoscopy as the next most appropriate staging procedure. It should be noted that patients with lymph nodes measuring >16 mm on CT and a negative FDG-PET result should undergo mediastinoscopy before possible thoracotomy [54]. Combination of endoscopic staging and surgical staging results in the highest accuracy [55]. In addition, clinical considerations may contribute to identification of suspect lymph nodes, e.g., small FDG-negative lymph nodes that are directly adjacent to the tumor or are located between other evidently pathological nodes or those which show progression (tumor growth) as determined from multiple (low dose) CT scans over a certain period of time.

Automated delineation methods for PET/CT imaging

As discussed earlier the one source of error and potential miss in TVD is the accuracy of delineation of contours by the oncologist [56]. Given the nature of PET images a number of investigations have examined the use of automated methods to define the edge of the tumor [57,58]. Auto contours may provide consistent contours, but have difficulty dealing with normal tissue adjacent to the tumor with high SUV uptake such as the heart. There is also

no clear consensus on which method most closely approximates to the tumor position and tumor edge and pathological correlation has proven difficult [59]. Another difficulty with PET based auto-contouring is the variability of SUV values due to factors other than tumor activity such as patient biological factors and technical factors [60]. When delineating a reGTV to include the full motion path of all tumor locations, the value of auto contours is without any supporting evidence. Furthermore the information obtained from the PET component of the scan is complementary to that contained within the CT scan and the use of information from both may lead to more successful auto-contouring [49]. Automated PET based contours can be useful as a starting point for PET based TVD and are worthy of further investigation, particularly in the era of 4D PET/CT imaging. At present the IAEA panel recommendation remains that, outside of a clinical trial context, target volumes generated with the use of PET should be delineated using visual interpretation alone or should be visually edited following any automated target volume delineation [24].

The use of PET to define a respiration expanded GTV for mobile lung tumors

As PET images are acquired over a number of minutes at each table position, it has been suggested that PET could define the entire motion trajectory of a lung tumor. Tumors identified as low risk of macroscopic disease extension (MDE) show lower rates of disease around the GTV than do high-risk tumors. Both PET and CT accurately visualize the CTV(path) in low-risk tumors, but

underestimate MDE in high-risk tumors [59]. When a suitable margin is added for microscopic extensions of a moving lung tumor, this volume is also known as the internal target volume (ITV). According to ICRU 62, the ITV is defined as the “internal margin” plus a CTV expansion [47]. Phantom studies have demonstrated that the PET target volume may contain all of the respiratory motion (respiration expanded GTV) of a moving lung tumor [50,61]. Hence, in the absence of other respiration motion compensation techniques (e.g., respiratory gating or real-time tracking), PET based target volumes may be used to approach a PET based ITV approach, namely the respiration expanded GTV. Unfortunately clinical investigations using 3D PET/CT imaging have not shown consistently that a PET based ITV is identical to a 4DCT based ITV for small tumors [52]. A recent study using 4D PET/CT imaging has demonstrated that a 4D PET based ITV closely approximates to a 4DCT [62]. Using 4D PET/CT imaging may lead to better quantification of tumor motion during prolonged radiotherapy treatment times but further investigation and clinical validation are required.

Four dimensional PET/CT imaging

With a 4D PET/CT the 4DCT and 4D PET scan are retrospectively binned into a number of respiratory phases correlated with the breathing cycle using a respiratory tracking system. Each phase of the 4D PET is corrected for attenuation with the respective phase of the 4DCT. 4D PET/CT imaging may overcome some of the inaccuracies associated with a free breathing PET/CT scan. One such factor is tumor motion. In 3D PET/CT imaging, the CT component is acquired as fast CT which may catch a mobile lung tumor at an extreme of the ITV or cause artefacts, while PET scans are acquired over a number of minutes. Hence the SUV for a given pixel is an average of the SUV over that time period. Furthermore, in integrated PET/CT acquisition the attenuation correction is based on the CT data and as mentioned above this may misrepresent the average density for a given pixel position. Hence, in essence, for mobile lung tumors the PET component is more akin to 4D imaging while the CT component is more akin to a 3D imaging technique. A number of studies have shown sizeable differences in SUV calculation between 3D PET/CT and 4D PET/CT imaging [63,64]. Using 4D PET/CT imaging may provide more accurate SUV quantification for moving lung cancer and has implications for auto-contouring which may lead to new methods of PET based TVD.

CTV and PTV expansions to a PET derived GTV

These guidelines have focused on the delineation of standardized GTV or reGTV contours. Subsequently, these volumes need to be expanded to a CTV and to a PTV. The CTV expansion is based on pathological tumor characteristics, and therefore not dependent on the imaging technique or GTV delineation strategy. Clinically applied expansions from the GTV to CTV are generally in the range of 5–8 mm [65]. The PTV expansion can be calculated in a probabilistic approach by considering all systematic uncertainties, all random uncertainties and also the width of treatment beam penumbra [66]. This may also include patient characteristics such as breathing motion, if this has not already been incorporated in the GTV definition. A more basic approach can be used when a PET based respiration expanded GTV has been created, and the PTV expansion is applied to compensate for setup variations alone (e.g., 1 cm in all directions). When a GTV based on 4DCT has been created, PTV expansions are primarily based on the characteristics derived from CT and other systematic errors (e.g., errors from

image fusion and target volume delineation) of which all can be taken into account with the van Herk formula [66].

PET combined with MR imaging

When envisioning the future, it is interesting to follow the recent advances in hybrid imaging systems which made it possible to combine PET and (functional) MR information. With the combination of functional MR and PET information new possibilities in functional cancer imaging are emerging [67]. However, one of the first few studies reported no significant difference in diagnostic performance when PET/MR was compared to PET/CT [68,69]. Interestingly, a recent study showed that PET/MR imaging could have an advantage in lymph node detection [70]. No study yet exists about the use of PET/MR in tumor volume delineation but further research is awaited.

Conclusions

It remains the recommendation of an IAEA expert panel that an appropriately timed and technically adequate PET/CT imaging is an essential component in the radiotherapy treatment planning process for lung cancer. Specific guidance regarding the interpretation of PET/CT imaging for TVD is provided. It is also recognized that further research is needed in the fields of 4D PET/CT imaging and automated TVD techniques.

Conflict of Interest

None to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2015.03.014>.

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