Positron emission tomography imaging approaches for external beam radiation therapies: current status and future developments

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ABSTRACT. In an era in which it is possible to deliver radiation with high precision, there is a heightened need for enhanced imaging capabilities to improve tumour localisation for diagnostic, planning and delivery purposes. This is necessary to increase the accuracy and overall efficacy of all types of external beam radiotherapy (RT), including particle therapies. Positron emission tomography (PET) has the potential to fulfil this need by imaging fundamental aspects of tumour biology. The key areas in which PET may support the RT process include improving disease diagnosis and staging; assisting tumour volume delineation; defining tumour phenotype or biological tumour volume; assessment of treatment response; and in-beam monitoring of radiation dosimetry. The role of PET and its current developmental status in these key areas are overviewed in this review, highlighting the advantages and drawbacks.

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Positron emission tomography (PET) is the most specific and sensitive means of imaging molecular pathways and molecular interactions in humans; it provides unique functional *in vivo* imaging data that are not made available by other modalities [1, 2]. PET exploits the physics of positron decay after injecting a patient with a positron emitting tracer or “probe”, *i.e.* a molecule of interest linked to a positron-emitting radioisotope such as fluorine-18 (^{18}F), carbon-11 (^{11}C) or oxygen-15 (^{15}O). Each single emitted positron combines with an electron, up to a few millimetres away from the point of emission, forming a positronium. This is immediately annihilated, producing two photons of equal energy (511 keV), which are simultaneously emitted at 180° to each other (Figure 1a). An external PET scanner, which is essentially a circular array of scintillation detectors, detects both of these photons and associates them using a coincidence filter (Figure 1b). After correction for attenuation of the annihilation photons in the surrounding tissues of the body by transmission scan, the resulting PET data directly describe the three-dimensional (3D) localisation of the radiation event, thereby revealing the position of the source probe within the patients’ body.

PET scan data may be acquired either statically or dynamically. Subsequent analysis of PET imaging data can be qualitative, by subjective visualisation, alternatively, qualitative analysis may be carried out following manual definition or automatic segmentation to define regions of interest (ROI). Using subsequent modelling techniques, the spatial and temporal variation of the

radiolabelled compound(s) may be determined in specific tissue with exquisite sensitivity (picomolar resolution). For example, one commonly used semi-quantitative method involves determining the standardised uptake value (SUV) of tumour tissue by measuring the radioactivity present at a specific time, usually normalised against injected radioactivity and body surface area [3].

Fluorodeoxyglucose positron emission tomography

Fluorodeoxyglucose (FDG) labelled with ^{18}F (^{18}F -FDG) is the most common radioisotope used in PET imaging in oncology to identify and localise tumour tissue. Its biological characteristics and methodological considerations have been previously reviewed [3, 4]. To summarise, FDG is an analogue of glucose that is taken up into cells via glucose transporter receptors (such as GLUT-1) and subsequently phosphorylated by hexokinase to FDG-6-phosphate. Unlike glucose-6-phosphate, FDG-6-phosphate is rarely metabolised further; thus the level of FDG-6-phosphate accumulation reflects the metabolic rate of glucose (MR_{glu}). When compared with normal tissue, tumours have greater FDG uptake, reflecting their generally higher MR_{glu} , as well as the degree of hypoxia, levels of glucose transporter and hexokinase molecules and cell density [3, 4]. ^{18}F -FDG-PET can therefore provide valuable functional, biological and anatomical imaging information that can be used to distinguish metabolically active disease from normal tissue. FDG uptake has relatively high tumour specificity, but it also accumulates in other tissues with physiologically or pathologically high glucose metabolism, such as macrophages, salivary gland, brown fat and muscle tissue. Furthermore, the anatomical information provided by

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Figure 1. (a) Positron decay and (b) detection of radiation events in positron emission tomography.

PET is limited by the relatively low inherent spatial resolution of positron decay: positronium annihilation occurs up to 2 or 3 mm from the actual tracer molecule. The capture of data by cameras also introduces another level of finite resolution, giving a resolution of approximately 7–9 mm for reconstructed images from many PET systems and leading to relatively “fuzzy” images. Increased spatial resolution (<5 mm) has been achieved with current research on emitted photon time-of-flight analysis, with the advent of high-definition PET scanners and with the development of advanced algorithms that decrease the signal-to-noise ratio of the image formation process. To refine the spatial accuracy of PET images for tumour localisation substantially, however, PET imaging data must be combined with detailed anatomical information from other imaging modalities, such as CT or MRI. This is best performed by co-registering (fusing) imaging data, ideally from images taken within a short period of time and with the patient remaining in the same position. Subsequent interpretation of the scans should be carried out with scan acquisition times, interscan time and patient-motion issues in mind. The development of integrated PET/CT scanners has circumvented many of the logistical problems associated with individual scan acquisition and the ensuing consequences for image interpretation, enabling faster scanning times (as CT data can be used for attenuation correction rather than an additional PET scan) and providing automatically fused images [5]. These benefits have led to the increasingly widespread installation and use of combined PET/CT. However, the PET and CT scans are still acquired sequentially and with very different acquisition times, thus time and motion issues remain important considerations in the accurate interpretation of the resulting images.

A further consideration is the radiation dose imparted to patients. The average dose burden for whole-body PET/CT using ^{18}F -FDG for adults is reported as 10–32 mSv, although this is dependent on many variables including the radioactivity of the injected radioisotope, the CT protocol used, and hardware/software optimisations [6–8]. Four-dimensional (4D) scans (*i.e.* PET and CT) require a higher dose. PET/CT patient dose becomes more relevant if serial scans will be taken prior to, during

and/or after treatment (*e.g.* to monitor treatment response or if PET is to be used for treatment monitoring during particle therapy). There are currently no caveats relating to patient dose burden, other than the report of the International Commission for Radiation Protection, which associates doses >100 mSv with stochastic effects. In the context of risk/benefit and ensuing treatment radiation dose, however, serial PET/CT dose burden is likely to be considered acceptable for most patients if dose is minimised through optimisation, but this is an area that requires further investigation.

FDG-PET for tumour diagnosis and staging

The use of ^{18}F -FDG-PET for the diagnosis and staging of many cancer types is now well established. With the advent of whole-body scanners, FDG uptake has increasingly been used to determine the presence and location of tumour within soft tissue, similar to a bone scintigram. This application has proven particularly useful in the identification of distant metastases, involved nodes and primary tumours that were previously unidentifiable with CT alone. It is also valuable where the limitations of other imaging techniques can cause uncertainty in diagnosis, such as difficulties in distinguishing tumour from other pathological states (*e.g.* atelectasis in the lung) or inability to determine tumour in normal-sized lymph nodes. Using PET for tumour diagnosis and staging should lead to more effective patient treatment but, in practice, this is actually very difficult to assess. Hence, most studies have focused on whether or not PET information results in a change in patient management, with the assumption that this leads to improved patient outcome.

A seminal overview and pooled data analysis of ^{18}F -FDG-PET literature by Gambhir et al [9] estimated that the sensitivity of PET was in the range of 84–87%, its specificity 88–93% and its accuracy 87–90%. The average management change across all applications was estimated to be 30%. This information was used successfully to request expanded Medicare reimbursement for ^{18}F -FDG-PET in the USA. Diagnostic accuracy may be increased by combining PET and CT data. For example,

early studies in lung cancer showed superior diagnostic capability using PET/CT compared with PET or CT alone [10–12]. As such, the integrated PET/CT scanner has become a valuable tool for diagnostic purposes.

For lung cancer in particular, a large body of literature documents the value of ^{18}F -FDG-PET for diagnosis and staging. This is because of its capability in identifying distant metastases or regional nodal involvement that was not previously appreciated [13, 14] and the impact of this information on treatment management decisions relating to suitability for surgery. Meta-analysis studies of ^{18}F -FDG-PET have determined the sensitivity and specificity of PET in diagnosing single pulmonary nodules or masses to be 96% and 78%, respectively; the sensitivity and specificity of PET in mediastinal staging is estimated to be 83% and 92%, respectively ([13] and references therein). As a result, ^{18}F -FDG-PET is now widely used in the routine diagnosis of lung cancer and has been approved by official bodies in the USA, Germany and the UK. Guidelines on the diagnosis and treatment of lung cancer in the UK were published by the National Institute for Health and Clinical Excellence (NICE; a UK governing body that provides guidance on healthcare practice efficacy and cost effectiveness) in 2005 [14], following systematic review of published research. NICE stated that rapid access to ^{18}F -FDG-PET is a key priority in the diagnostic work-up in lung cancer. They recommended its use following CT when a subsequent biopsy is not possible or has failed, and made it a requisite for staging all patients who are candidates for surgery or radical radiotherapy (RT) following CT staging [14]. For subsequent RT, these recommendations imply both improved patient selection and the availability of potentially useful PET or PET/CT data for RT planning.

Target volume definition for RT planning

Despite our current capabilities for high-precision RT delivery, considerable uncertainty still exists in tumour volume definition (TVD) for RT purposes. This is due to ambiguity and inter- and intra-observer variability when defining tumour boundaries using anatomical imaging data produced from CT or MRI. Consequently, there is great interest in the use of PET for RT planning purposes. The first critical step in TVD for RT involves outlining a gross tumour volume (GTV). This depends on the resolution capabilities of the imaging modality used; thus it is usually based on variations in tissue density, signal intensity, volume effects and contrast enhancement. However, delineation may be inhibited by dependence on these criteria. Pathological conditions, such as necrosis and inflammation, may be indistinguishable from tumour, as may normal tissue in complex tumour sites. Once defined, the GTV is expanded to incorporate surrounding regions that are suspected to be involved, or considered to require treatment, to create a clinical target volume (CTV). ^{18}F -FDG-PET, when used in conjunction with conventional imaging to improve anatomical resolution, may enable more confident and reproducible delineation by assisting the distinction between metabolically active disease and normal tissue in areas of uncertainty. To date, ^{18}F -FDG-PET has been used to define the GTV, and it is increasingly being used to define the CTV, particularly

when suspicious nodal areas are to be included. PET data may also be used to inform the final planning target volume, a further expansion of the CTV that allows for set-up error and target motion, as PET acquisition over a matter of minutes arguably incorporates the extent of target motion [15]. The manner in which PET is used in clinical practice, however, is often determined by the equipment and imaging capabilities of the treatment centre. Independent staging information from an ^{18}F -FDG-PET scan, acquired in a stand-alone PET unit, may be used to complement CT or MRI data. Alternatively, PET images may be coregistered with anatomical images, although for images to be fused optimally, the patient must be set up and aligned for PET scanning by a radiation therapist as per RT planning. The development and increasing availability of combined PET/CT scanners has facilitated this process [5] and, in turn, most recent research has focused on the use of combined PET/CT for RT planning (reviewed in [16–22]).

Because of the interest generated in ^{18}F -FDG for TVD, a group of international experts at The International Atomic Energy Agency (IAEA) reviewed the available data on the use of PET in RT planning in 2006, and published a final report in 2009 [19]. The report concluded that ^{18}F -FDG was the most useful PET tracer used to date for RT planning, and supported the routine use of ^{18}F -FDG-PET for TVD in non-small cell lung cancer (NSCLC). Evidence supporting the use of PET in head and neck cancers, lymphoma and oesophageal cancers was also cited. The experts agreed that the best available approach was to use integrated PET/CT images, acquired on a dual scanner in the RT treatment position. They also advised careful consideration of contouring because of the limitations of PET methodologies. It was noted that there were, as yet, no data to show any improved outcome when PET TVD is incorporated into RT. The experts did recommend, however, that patients should have their treatment volumes defined with the most accurate imaging available, which in their opinion, for lung cancer, included PET scanning.

Practical considerations

There are a number of practical considerations when using PET/CT for simulation work. First, the patient must be scanned in the RT treatment position; therefore, a flat bed may need to be inserted in the scanner couch and the patient must be set up and immobilised in the treatment position. This can pose a problem if certain immobilisation devices are to be used, as the bore size of a PET scanner is typically smaller than that of the RT simulators or large-bore CT scanners used for RT planning. Second, using the PET/CT scanner for simulation increases the radiation dose to therapy personnel: set-up and marking of a patient who has been injected with ^{18}F -FDG will result in exposure to those in the room. Even when personnel exposure is minimised, the mean total radiation dose received by each of two RT radiographers during PET/CT simulation of NSCLC patients has been reported as $5.1 \pm 2.6 \mu\text{Sv}$ per patient [23]. Third, there may be software, data transfer and registration problems, although these have largely been solved in new generation

compatible scanning equipment, RT planning systems and software versions capable of directly using PET and CT data sets for RT planning.

PET/CT image interpretation

Radiation oncologists are not trained in the interpretation of PET imaging, and need to have an awareness of the methodological considerations and limitations of ^{18}F -FDG-PET in oncology (reviewed in [24]). Of particular concern is the undue reliance on automated thresholding software for target delineation. Such software works by applying limits to automatic segmentation algorithms that segment a volume from a background level, according to the relative ratio of tracer SUV in tumour. Generally, 30–50% of maximal SUV is used, based on previous phantom validation work. Although this automation is useful, the more defined images that result can impart false reassurance to the outliner. It must be remembered that what is actually being imaged is a measure of glucose metabolism and not a cancer-specific tracer. Further, the imaging data have been reconstructed algorithmically, modelled using a semi-quantitative technique, and then arbitrarily thresholded. There is no guarantee therefore that positive regions are tumours and negative regions are normal. The spatial limitations of PET, plus reports that it often fails to detect disease ≤ 5 mm [25], also need to be borne in mind. The application of a thresholding limit means that, by definition, areas that have a lower SUV value are excluded, but these may still contain tumour cells. This point is well illustrated in Figures 2 [26] and 3 [27].

As previously mentioned, time and motion issues need to be considered when interpreting combined PET/CT images. Even in a combined PET/CT scanner, images are acquired sequentially, which can contribute to misalignment upon image registration. Organ motion, particularly respiratory and cardiac motion, must also be taken into account. The increasing use of high-speed, multislice CT scanners enables fast image acquisition, effectively producing “snap-shot” images in time. PET, however, is typically acquired over a number of minutes, so although the extent of motion is incorporated, the images represent a time-averaged activity distribution (*i.e.* objects that are static have a high activity concentration, whereas those that move exhibit a “smeared” activity distribution with poorer contrast and larger volume). This can result in artefacts in the image appearance and quantification, such as compromised quantification of ROI kinetic parameters including SUV, thereby impacting treatment volume delineation. These issues are being addressed by the introduction of respiratory-correlated (4D) CT and PET acquisition, which uses gating or similar methodologies to take into account physiological respiratory motion [17, 28]. For instance, 4D PET/CT using gated acquisition in lung malignancies has been shown to reduce smearing, improve the accuracy in PET/CT coregistration and increase the measured SUV, all of which are expected to result in improved tumour assessment [29].

Lung tumours

PET/CT has proven very useful for the diagnosis and staging of lung tumours. The IAEA has recommended

Figure 2. Positron emission tomography (PET) images from a patient with right hilar cancer. (a) The PET threshold is set at 40% of the maximum standard uptake value (SUV_{max}) of the tumour; (b) PET threshold set at 30% of the SUV_{max} . Reprinted from Bradley et al [26] with permission from the Society of Nuclear Medicine.

Figure 3. Fluorine-18(^{18}F)-fluorodeoxyglucose (FDG)-positron emission tomography (PET) target volume definition in head and neck cancer. (a) CT scan, (b) corresponding ^{18}F -FDG-PET scan and (c) fused image from a patient with a T4N2M0 tongue carcinoma. Gross tumour volume (GTV) delineated on CT is shown in red. Upon PET, the GTV obtained by visual interpretation is light green; using a fixed threshold of 40% of the maximum standard uptake value (SUV_{max}) is yellow; and using a fixed threshold of 50% SUV_{max} is blue. The latter GTV (blue) is indistinguishable on this transversal slice from the GTV obtained using an adaptive threshold based on the signal-to-background ratio. Reprinted from Schinagel et al [27] with permission from Elsevier.

the routine use of PET/CT for improving TVD in NSCLC [19], citing evidence that it reduces interobserver variability (reviewed in [19, 20, 30]). In turn, this has accelerated the development and availability of multi-modality planning in lung cancer. Studies that have investigated PET in RT planning for lung cancer have reported both increases and decreases in target volumes. The major causes of GTV increases were tumour volume enlargement and the incorporation of regional nodes with ^{18}F -FDG avidity that were previously judged to be

uninvolved according to CT criteria. The major causes of GTV decreases were the exclusion of lung tissue affected by atelectasis and the omission of suspicious nodes without ^{18}F -FDG avidity. The addition or subtraction of involved nodes is strictly a staging criterion, but nevertheless can significantly impact RT at the point of planning, as patients can move from a radical situation to a palliative one. The ability of PET to distinguish regions of tumour that are associated atelectasis is one of its most useful advantages for GTV delineation in lung

cancer, with considerable impact on RT field size for affected patients [31]. However, whether or not PET truly improves the accuracy of target definition in lung tumours, and hence improves the efficacy and outcome of RT, remains untested. The increasing availability of combined PET/CT imaging data used for patient diagnosis and TVD in the UK (following the NICE recommendations [14] and IAEA report [19]) may enable further study of these fundamental questions.

Brain tumours

There have been more than 30 publications since 1998 reporting the use of PET for TVD in brain tumours (reviewed in [16, 20–22, 32]). This work has been largely driven by the central role that imaging plays in the diagnosis of brain tumours and by the limitations of CT and MRI for imaging this site. Yet interpretation of ^{18}F -FDG-PET data in the brain is complex: background uptake of ^{18}F -FDG by normal brain cells (which almost exclusively consume glucose) is high, differentiation in grey matter is generally insufficient and image resolution is often inadequate. Research with ^{18}F -FDG in the brain has shown that tumour volumes defined with ^{18}F -PET are generally smaller than those defined with T_1 weighted MRI images. When combined with other imaging modalities, however, the ^{18}F -PET-defined volumes are often increased. Thus, although ^{18}F -FDG PET may be used to aid in the identification of active disease, it is unlikely that we will see the widespread use of TVD in this disease site. More recently, other PET tracers have been investigated, such as ^{11}C -methionine (^{11}C -MET), ^{18}F -fluoroethyltyrosine and ^{18}F -fluorothymidine. These amino-acid tracers have greater specificity for brain tumour tissue than normal brain, and are independent of disturbance from the blood–brain barrier; thus they show more promise as tools to aid TVD for RT planning in brain tissue.

Head and neck tumours

Owing to the limitations of CT and MRI, and the close proximity of crucial organs at risk in complex head and neck (H+N) tumours, PET imaging has the potential to significantly augment TVD for highly conformal RT at this site (reviewed in [33]). However, GTV boundaries can differ significantly from one another when determined using CT, MRI or PET in the same patient. Further, PET/CT does not appear to reduce inter-observer GTV variation when delineation is subjective [34], although there is evidence that tumour volume determined by ^{18}F -FDG-PET most closely approximates the true tumour volume of histopathological specimens [35, 36]. The greatest impact of PET for patients with H+N cancer usually results when ^{18}F -FDG-PET information changes the nodal stage status [36, 37]. But this is not straightforward, as the PET results for both GTV definition and nodal involvement can depend on the applied segmentation methodology. Recent studies using the largest series of patients to date ($n=78$) have investigated the use of ^{18}F -FDG-PET for GTV delineation and nodal status determination [27, 38]. Results showed

that when comparing coregistered PET and CT, the successful contouring, shape and volume of the resulting GTV was substantially influenced by the segmentation methodology ([27]; Figure 3). When eight methods of ^{18}F -FDG-PET delineation of involved nodes were subsequently assessed in the same patients, PET-defined nodal involvement did not correspond well to CT-defined nodal involvement, with specific differences again depending on the PET segmentation methodology [38]. The authors concluded that ^{18}F -FDG-PET may provide valuable biological information that could potentially improve GTV definition and nodal staging accuracy in H+N cancer, but additional histological validation studies are needed, particularly to determine the optimal segmentation methodology.

Other tumour sites: lymphoma, oesophageal and prostate cancer

A review of published studies on the use of PET showed its higher sensitivity and specificity for detecting lymphoma over CT [39], leading to a significant impact on the design of involved RT fields. Again, the key advantages of PET are its abilities to demonstrate disease in sites where CT contrast is limited and to distinguish involved nodes that are negative according to structural imaging criteria. PET is also capable of non-invasively identifying bone marrow disease in patients with negative bone biopsies [40] and has been reported to decrease subjectivity in the RT planning of thoracic lymphoma [41].

The main role that ^{18}F -FDG-PET has taken in RT planning of oesophageal cancer has been in distinguishing involved lymph nodes and metastasis, thereby contributing to staging improvement [42–44]. However, its value for pre-operative staging assessment may be limited, especially in combination with other modern techniques [42, 45]. When compared with CT, ^{18}F -FDG-PET shows a higher specificity for the detection of histologically verified lymph nodes and distant metastasis [45], but false-positive and -negative results are a problem [39, 42]. Discordances between CT- and PET-defined lymph node involvement have been reported, which could increase or decrease the target volume in some patients. But decreasing treatment volumes on the basis of a negative PET finding has been considered too risky because of the relatively low sensitivity of this technique [39]. One recent report comparing ^{18}F -FDG-PET-defined oesophageal tumour length with surgically resected tumours showed that the optimal method to estimate the length of the gross tumour varied with tumour length and maximum SUV [46]. Taken together, these results indicate a less than simple relationship between FDG avidity and tumour pathology, confirm that different automated PET methods can generate variable results and suggest reservation in its clinical implementation.

There are limitations to the use of ^{18}F -FDG-PET in prostate cancer. Delineation is inhibited by the close proximity of ^{18}F -FDG in the excretory system in combination with the relatively low metabolic activity of prostate cancers. As a result, other PET tracers with greater specificity for prostate tissue, such as labelled

acetate, choline or prostate-specific membrane antigen (PSMA), may have more value for TVD.

Summary

The fundamental limitations of using PET for TVD in RT are related to its methodologies. In RT planning, the anatomical extent of the tumour with a defined edge is sought, in order to deliver RT with high geometric precision. But there are, as yet, no tumour-specific PET tracers in clinical use. The inherent relatively low spatial resolution of PET also prevents highly accurate anatomical definition. As such, we are far from having perfect anatomical definition of tumours with PET. The interpretation of PET images using segmentation methodologies can further confound the issue of where the tumour is, and how its "edge" is defined. The emerging literature highlights these underlying incompatibilities, but also shows that PET has the potential to provide biological information that may aid TVD in many disease sites (Table 1).

Further studies investigating segmentation methodologies for TVD, and more research on time, motion and coregistration issues that confound image interpretation, are required to improve the use of PET for TVD. There is also a great need to develop and research more tumour-specific probes to enable the improved localisation of tumour tissue. For example, the development of radio-labelled antibodies that are specific for tumour antigens, such as PSMA, is showing promise for future PET/CT-guided tumour imaging [47].

It remains to be shown whether or not PET/CT-defined RT targets are "better" than CT-defined targets. Certainly, PET information can be a very useful aid for diagnostic and staging purposes, such that the resulting "stage drift" is expected to translate into overall improved RT outcome. However, there is currently insufficient evidence to allow us to conclude whether PET-based RT planning translates into improved tumour response or RT outcome measures. For example, planning studies have shown that the addition of PET can reduce the risk of geographical miss, yet allows meaningful dose escalation with acceptable normal tissue complication probabilities [48–50]. One prospective trial has indicated improved survival time when ^{11}C -MET-PET was used to define GTV for recurrent glioma [51]. When attempting to assess whether PET is "better", there are confounding difficulties in validation methodology. To verify true tumour extension, pathological inspection of samples is the "gold-standard". However, comparing volumes between *ex vivo* (often fixed) tissue and prior images of tumours *in situ* can introduce inaccuracies due to the

complex relationship between pathological specimens, ^{18}F -FDG uptake and subsequent PET quantitative modelling [35, 46, 52]. Ultimately, randomised clinical trials examining outcomes following the use of CT-, PET- or PET/CT-defined tumour volumes for RT planning will be required to determine whether or not the incorporation of biological PET data improves quality of life or survival.

PET for imaging the tumour phenotype: biological target volume definition for RT

Using PET to define biological target volumes (BTVs) for RT is a concept related to using this technique to aid GTV definition, but plays to PETs strength in providing non-invasive functional biological information on individual tumours. This information can then be incorporated into RT dose prescription and delivery strategies, with the aim of tailoring optimal treatments for individual patients (reviewed in [22, 53, 54]). PET has mostly been used to reveal tumour biological characteristics for targeted RT, but the reverse concept of using PET to define the biology of normal tissue to promote the avoidance of normal critical structures during RT has also been investigated. In principle, using PET to provide biological tumour information may also aid decisions on which type of RT would be most advantageous. For example, given the known reduced oxygen dependency of ^{12}C ions over protons, PET findings regarding tumour hypoxia could, in principle, be used to indicate the choice of particle type.

To date, research in this area has focused on using PET to image tumour heterogeneity using markers of radio-resistance or altered metabolism, thereby identifying high-risk gross tumour, or biological sub-volume regions, that can be targeted for escalated RT dose using "biologically guided dose escalation" or "dose painting" strategies. The aim is to overcome major biological tumour characteristics, such as tumour hypoxia or high metabolic activity, that are known to affect RT outcome adversely. This use of PET imaging in combination with dose escalation is of great interest in tumour sites such as H+N and the prostate. These sites commonly harbour sub-regions that have altered biological properties (*e.g.* hypoxia), the local failure of RT is of high concern, anatomical imaging is often contrast limited and highly conformal therapy is often required. An example of the use of ^{18}F -FDG-PET/CT for theoretical intensity-modulated RT (IMRT) planning to target high-risk gross tumour in H+N cancer is shown in Figure 4 (from [55]). An example of using ^{11}C -acetate PET/CT to demonstrate the theoretic feasibility of delineating the malignant

Table 1. Fluorine-18(^{18}F)-fluorodeoxyglucose (FDG)-positron emission tomography (PET) for tumour volume definition

Advantages	Drawbacks
Can aid in areas of uncertainty, <i>e.g.</i> where CT/MRI is contrast limited	Low spatial resolution: visual delineation is weak, cannot detect microscopic disease
High sensitivity and specificity when combined with CT	^{18}F -FDG is not tumour specific, false positives and negatives possible
Can reduce interobserver variability	Tumour volume delineated is dependent on PET methodology used
Identification of involved nodal regions and metastasis	Motion and alignment problems with PET/CT coregistered images
Identification of atelectasis	Over reliance on automated thresholding software may mislead tumour visualisation

intraprostatic lesions in prostate cancer for IMRT boost is shown in Figure 5 (from [56]).

Using PET for BTV definition, in combination with the superior biophysical and radiobiological properties of particle beams—with their associated increased relative biological effectiveness (RBE), advantageous linear energy transfer tumour effect and unique dose localisation profiles—has even greater potential as the ultimate method to treat anatomically complex and radio-resistant tumours (reviewed in [57–59]). This would allow individualised optimisation of the radiobiological effects of RT, while minimising normal tissue side effects. However, further essential research is first required to understand and quantify the RBE effects of particle therapy and therefore allow its safer practical application.

The main approaches for PET BTV definition have been to use ^{18}F -FDG-PET as a marker of high cell metabolism or to use PET markers of hypoxia, such as ^{18}F -fluoromisonidazole (^{18}F -FMISO), ^{18}F -fluoroazomycin-araboside (^{18}F -FAZA) and ^{60}Cu (II)-diacetyl-bis(N4-methylthiosemicarbazone) (ATSM), to define biological volumes. Dose escalation has then been applied using different biologically guided or dose painting strategies. The radio-resistant region can be defined by voxel values above a given threshold, creating a “compartment” for receipt of a uniform increased dose that is limited by the tolerance of adjacent normal tissue. A similar strategy involves redistribution of the tumour dose, by increasing the dose to radio-resistant sub-volumes while keeping the

mean tumour dose equal to the standard uniform dose and constant. Alternatively, sub-volumes may be defined according to individual voxel signal strength, and a mathematical methodology may be used to determine prescribed dose on a voxel-by-voxel basis—so-called dose painting by numbers (DPN).

It is important to recognise that these concepts and strategies have been made possible only by the development of highly conformal RT techniques, such as IMRT, which has allowed the delivery of RT to complex shapes at varying intensities. Notably, a recent phantom study has demonstrated that even better conformation to target volumes may be achieved for intensity-modulated proton RT than for intensity-modulated X-ray therapy [60]. Nevertheless, the problems previously outlined for the use of PET for TVD (relating to time, motion, coregistration and interpretation of PET images) are also valid when using PET for BTV definition; they are even more pertinent when escalating the dose applied to a small target. Motion is a particular concern when applying voxel-based high-dose IMRT prescriptions to certain sites, such that uniform sub-volume dose escalation, with the application of margins to the BTV to account for motion, has been proposed as a more appropriate strategy than DPN for moving tumours. Safer dose escalation may be achievable with particle therapy because of the reduced integral dose, although its application for PET-defined BTV (particularly for small or moving targets or sub-volumes) requires further investigation.

Figure 4. Comparative isodose distributions for matched CT-directed (left image) and fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET)-directed (right image) intensity-modulated radiotherapy (RT) plans for a patient with T3N2b disease of the right oral tongue at the level of the parotid glands (light blue). The CT-defined target volumes to receive high-dose RT (magenta) and prophylactic dose RT (yellow) are shown in the left image. The corresponding ^{18}F -FDG-PET-defined clinical target volume (magenta) is illustrated on the right. Gross tumour volume is shown in light green. Reprinted from Schwartz et al [55] with permission from John Wiley and Sons.

Figure 5. Positron emission tomography (PET)-defined prostate tumour biological target volume (BTV) for dose escalation using intensity-modulated radiotherapy (IMRT). Images of dose-planning CT with isodose distributions and ^{11}C -acetate PET/CT for two treatment plans: (a) standard IMRT plan with a 77.9 Gy dose to planning target volume (PTV) (*i.e.* prostate gland with a 6 mm margin); (b) theoretical simultaneous integrated boost IMRT plan to deliver 77.9, 81, 84, 87 and 90 Gy to the BTV and 72 Gy to the rest of the PTV. Reprinted from Seppala et al [56] with permission from Elsevier.

There are a number of further important concerns with the use of many current markers of cell metabolism and hypoxia (F-FDG/F-MISO/F-FAZA etc.) to define biological sub-volumes for dose escalation. These are similar to those described in the previous section on GTV definition. First, although it may be very tempting to use the gradation of ^{18}F -FDG across a tumour as a dose-painting medium, clinical and pre-clinical data have cast doubts on the correlation of the microscopic biology with the ^{18}F -FDG signal [35, 46, 52]. Second, the methodology used to segment and quantitatively model ^{18}F -FDG uptake can also affect TVD [27, 46]. Third, awareness of the spatial resolution of PET is important, for example a recent animal tumour model study compared threshold segmented PET volumes with autoradiographic images. Discrepancies between the PET image and microscopic appearances occurred which were attributed to the finite resolution of PET [61]. This is particularly important when considering small and highly active regions of the tumour, and the authors concluded that these limitations should be taken into account when dose painting. Fourth, single-time-point BTV assessment may be unreliable as the basis for creating sub-volumes for escalated dose, for example spatial and temporal variation of BTVs have been shown to occur within individual tumours. Nehmeh et al [62] examined the reproducibility of detecting hypoxic sub-volumes in head and neck tumours. Patients underwent ^{18}F -FMISO PET scans 3 days apart, with no intervention. When the images were compared, only 6/13 (46%) patients exhibited a strong correlation of hypoxic zones between their two scans. Several methods have been proposed to overcome BTV spatial and

temporal variability, including delivering the boost volume early in the RT course to avoid later biological variation. An adaptive RT approach may also be taken, in which repeated PET images are acquired throughout RT, and the treatment plan can be adjusted according to changes in the BTV. Alternatively, modelling approaches that are based on population-based re-oxygenation dynamics derived from kinetic analysis of serial scans have also been proposed.

To avoid the problematic issues associated with ^{18}F -FDG and the currently used hypoxia markers, novel approaches and alternative PET ligands that have higher specificity for biological indicators and less variability are being sought. For example, recent PET research on liver metastases using ^{15}O -radiolabelled water has shown that those with higher plasma tissue perfusion variables (*i.e.* improved blood flow or perfusion) were associated with better patient RT outcome and improved survival [63–65]. This suggests that assessment of indicators of tumour perfusion, such as exchangeable tissue volume of distribution using PET, may be useful as BTV markers.

Summary

The use of PET for imaging tumour phenotype plays to its strengths. Individualised treatment with PET-guided dose escalation has promise as a concept to improve treatment efficacy, particularly if combined with refined particle therapy. Studies have demonstrated the feasibility of biological image-guided dose escalation for

photon therapy. However, the value of the concept in clinical practice still needs to be explored further and ultimately verified by randomised trials.

PET to evaluate radiotherapy response

^{18}F -FDG-PET has been used to assess the response to treatment: monitor early response, to determine whether a patient should continue or change treatment, or for restaging on treatment completion. Although this application of PET plays to one of its strengths, *i.e.* monitoring change, it has proved to be more complex than assessment following chemotherapy. This is largely because of the non-specific avidity of ^{18}F -FDG-PET and the biological effects of RT over time. For example, the timing of cell kill following RT can vary, and the ^{18}F -FDG uptake in inflammatory cells and thymic or bone marrow hyperplasia that can appear following treatment can also affect the interpretation of PET results [66, 67]. The development of alternative and/or more specific PET ligands for monitoring RT response may enable circumvention of some of the problems encountered when using ^{18}F -FDG-PET. One example is the use of probes that are specific for apoptosis, as previously used in single-photon emission CT studies of lymphoma (Figure 6 from [68]). The future use of probes that are specific for other cell-death mechanisms following therapeutic radiation, such as cell cycle arrest or intramitotic cell death, may prove to have even greater use for response assessment.

The methodological considerations and the technical and clinical challenges of measuring therapy response using ^{18}F -FDG-PET have been reviewed [69, 70]. Two key points are highlighted, which are in line with the European Organisation for Research and Treatment of Cancer recommendations [71]. First, it is important to use a pre-treatment scan as a baseline of "FDG avidity" for comparison with the post-treatment scan. This should be acquired close with the beginning of treatment, even if ^{18}F -FDG-PET is not expected to contribute to diagnosis or staging. This will reduce both false-negative (*i.e.* it will help to distinguish tumours with low baseline ^{18}F -FDG-uptake) and false-positive findings (*i.e.* it will help to distinguish tumour *vs* therapy-induced inflammation) [66, 70] (Figure 7 from [70]). Second, patients need to be imaged post-RT at an appropriate and optimised time point tailored to the end point under assessment. Delays as long as 6 months have been suggested to avoid false-positive ^{18}F -FDG-PET findings caused by acute inflammatory changes although, for restaging, the timing generally depends on when recurrence is suspected on the basis of clinical, biochemical or imaging indications. A further consideration is the radiation burden from serial PET/CT imaging, which would have to be assessed on an individual-patient risk-benefit basis.

In relation to early therapy response, the available literature concedes that a rapid decline in ^{18}F -FDG-PET SUV within a tumour correlates well with ultimate treatment response on therapy completion (as assessed

Figure 6. $^{99\text{m}}\text{Tc}$ -annexin-V scintigraphy to monitor radiation-induced apoptotic cell death in follicular lymphoma patients. (a) Total body, partially shown; (b) single-positron emission CT (SPECT) transverse; (c) sagittal; and (d) coronal images of pre-treatment scans of a 42-year-old male demonstrating physiological uptake in bones and salivary glands and weak uptake in right-sided high neck nodes; (e) Total body, partially shown; (f) SPECT transverse; (g) sagittal; and (h) coronal imaging performed 4 days after irradiation (4 Gy in two fractions of 2 Gy with 48 h interval) showing intense tumour uptake (arrows) in the irradiated right-sided high neck nodes. Reprinted from Haas et al [68] with permission from Elsevier.

Figure 7. Pre- and post-therapy fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) scans of an oesophageal cancer patient. Comparison of scans shows that findings obtained 3 weeks after chemoradiotherapy are related to oesophagitis, with tumour ^{18}F -FDG uptake markedly decreased. Reprinted from Weber [70] with permission from Society of Nuclear Medicine. SUV, standard uptake value.

by clinical pathology and radiography findings) and with better progression-free and overall survival. One further benefit may be a potentially lower dose burden than with conventional X-ray imaging plans, notably as reported for paediatric cancers [72]. The advantages of ^{18}F -FDG-PET for restaging are similar to those for initial diagnostic staging, with the added important ability to distinguish necrosis or fibrosis in residual masses. The difficulty with these applications is the anticipated requirement for a pre-treatment PET scan to document baseline FDG avidity [69], which many patients would not ordinarily have undergone.

Despite persuasive results supporting the potential use of ^{18}F -FDG-PET for monitoring early treatment response and restaging post-RT, there is only limited evidence that a beneficial effect can actually be achieved by altering treatment options, reducing the costs and side effects of ineffective therapy or improving patient outcome. The general picture that seems to be emerging is that a positive ^{18}F -FDG scan following RT indicates a worse prognosis than a negative ^{18}F -FDG scan. For example, a retrospective study of 188 patients with H+N cancer reported that patients with a positive post-treatment ^{18}F -FDG scan within 12 months of treatment had significantly worse 3 year overall survival and disease-free survival [73]. This appears to be telling us simply that “responders” to RT do better because ^{18}F -FDG-PET findings determine only tumour metabolic glucose consumption changes, and do not provide biological tumour information on cell growth rate, radiation sensitivity or repopulation for further interpretation. This type of information may, however, be important in the management of certain cancer types after definitive treatment, especially when an effective treatment is available and may

be appropriate. For example, response monitoring by ^{18}F -FDG-PET might facilitate the early administration of salvage or consolidation therapy or when determining resectability of persistent tumours. The role of ^{18}F -FDG-PET in informing the controversial decision of neck dissection after primary RT was examined in a retrospective study of 53 H+N cancer patients [74]. The authors found that the negative predictive value of PET was 100%, *i.e.* for patients who had no evidence of residual lymphadenopathy and a negative ^{18}F -FDG-PET scan 12 weeks after definitive radiation, potentially disfiguring neck dissection can probably be safely withheld. For advanced-stage Hodgkin’s lymphoma patients after first-line chemotherapy, a negative ^{18}F -FDG-PET scan post-treatment has a high negative predictive value for progression or early relapse for patients with residual disease [75], indicating that consolidation RT can probably be omitted in ^{18}F -FDG-PET-negative patients. This type of PET-guided response-adapted therapy is one of the most promising uses of PET. It will probably become routine practice for certain tumour types or particular clinical circumstances in the near future, although definitive outcome studies with longer follow-up periods are awaited to confirm the benefits.

PET for in-beam radiation therapy monitoring

Ionising damage to cells from therapeutic radiation using very high-energy photons, protons or heavier charged particles produces positron emitters as nuclear fragmentation reactions occur between the projectile and the atomic nuclei of the irradiated target tissue. In principle, therefore, PET could be used as an effective

and useful tool for the *in situ* monitoring of actual radiation dose deposition within RT target volumes.

In theory, the measurement of actual dose deposition during treatment can be achieved by comparing the measured positron emission distribution with an expected pattern calculated on the basis of the treatment plan, the patient's anatomical information and the time course of the irradiation. Using feedback mechanisms, this information could then be used to fine-adjust the treatment beams, either *post hoc* or in real time. Importantly, this strategy has the capacity to correct for major sources of error, including organ motion, treatment-planning errors, patient set-up errors and dose delivery problems caused by gantry, multileaf or scanning beam errors [57]. In practice, however, the relationship between dose received and positron activity measured is not straightforward. It is dependent on the fundamental physics of the radiation used and its subsequent radiobiological interaction with tissue *in vivo*, with many unknowns involved.

The feasibility of in-beam PET monitoring has been demonstrated for all types of therapeutic radiation, including high-energy photons [76–80]. However, this application is less evolved in conventional photon therapy, partly because the capture of data and the nature of radiation emitted from positrons are less straightforward following the interaction of photons with tissue [76]. Recent interest has also focused on proton and heavier charged particles, as they are highly desirable for therapy because of their superior biophysical and radiobiological properties, such as their increased RBE and more precise dose localisation capability (reviewed in [57–59]). This makes them highly attractive for treating “difficult” tumour sites, radio-resistant tumours and paediatric cancers because radiation to normal tissue may be minimised but the risk for treating moving tumour tissue is assumed to be greater. There are, however, limitations on the claimed “sub-millimetre” accuracy of particle therapy dose distribution for RT in human tissues [81] owing to the complexity of beam delivery and treatment planning. These limitations include the inherent inaccuracies of the physical beam model, density distribution changes that may occur

within the patient over the course of the treatment (including those from tumour motion) and positioning error. The first two points relate to our limited knowledge of beam “stopping powers”, whereby anatomical structures and tissue inhomogeneities modify the beam range, causing a “blurring” of the energy depth distribution (Bragg peak) in spread and depth. Experiments using in-beam PET have shown that the energy depth distribution of measured positron activity and the calculated Bragg peak depth distribution are more similar for ^{12}C or ^{16}O than for protons or ^3He ions in phantom targets (Figure 8 from [82]). The actual dose deposition therefore depends on the energy of the beam, the nature of the particle and the “basic physics uncertainty” of the tissue itself [81].

Until the development of in-beam PET, there was no other feasible method for non-invasive, *in situ* monitoring of radiation deposition during particle therapy. This system is currently under investigation at the Heavy Ion Medical Accelerator at Chiba, Japan, and at the Gesellschaft für Schwerionenforschung centre in Darmstadt, Germany. Dedicated PET scanners have been integrated into scanners at these treatment centres to make in-beam PET imaging a reality (Figure 9 from [83]). The clinical implementation of this imaging technology has resulted in intense study and a wealth of research from these centres. However, it is currently not clear how useful the positron trajectory information is for quality assurance: the limited spatial resolution of PET may not determine Bragg peak variations or treated volume with adequate accuracy. Furthermore, positron emitters are produced at shallower depths rather than in the Bragg peak, which needs to be accounted for. Currently, in-beam PET enables the detection of undesired range deviations and anatomical modifications during fractionated irradiation treatments. It helps to verify the accuracy of the beam portal position and provides the radiotherapist with an estimation of the difference in the dose if the delivered distribution differs from the planned one. Further research is needed to expand our knowledge of beam penetration and stopping powers. Reconstruction algorithms need to be developed to account for “basic physics uncertainty”,

Figure 8. Depth distributions of calculated dose (blue, dashed) and measured positron activity (red, solid) induced by beams of protons, ^3He , ^{12}C and ^{16}O ions in thick targets of polymethyl methacrylate. Reproduced from Enghardt et al [82] with kind permission from Forschungszentrum Dresden-Rossendorf.

Figure 9. Beam on-line positron emission tomography system mounted on a rotating gantry port (BOLPs-RGp). This system is used in the treatment room immediately following proton therapy to detect the position and intensity of resulting positron activity. Reprinted from Nishio et al [83] with permission from Elsevier.

tissue composition and radiobiological interaction. These last points are particularly challenging and addressing them will require multidisciplinary research in radiobiology and biophysics to determine the relationship between dose delivered, fragmentation reactions within atomic nuclei, biological damage [e.g. DNA (deoxyribonucleic acid) strand breaks and RBE] and resulting positron emission or activity. Perhaps this relationship could be used to define a new effective dose by relating the quantitative PET signal to the radiobiological damage.

Overall, in-beam PET may be considered at worse a basic quality assurance tool, but through technical development and meeting the challenges regarding biophysical and radiobiological interactions, in-beam PET could provide *in vivo* dosimetry information and, importantly, a powerful *in vivo* radiobiological tool. Thus, research in this area is speculative but potentially highly beneficial.

Conclusion

Research to date has shown that PET is a useful aid for diagnosis and staging in many tumour types; its substantial clinical use could impact an estimated one-third of cancer patients [9]. For GTV delineation, the situation is less clear. PET may assist GTV delineation in areas of uncertainty in some tumour types, but it is constrained by spatial resolution, specificity and sensitivity. The definition of tumour volumes is also significantly affected by technical and methodological variations in PET modelling techniques, which may be improved by additional research. Greater awareness of these limitations is required in the clinic, and further

research is necessary to examine whether or not the use of PET in defining GTV has clinical benefits. In assessments of RT response, PET is poised as a potentially useful tool that is effective in monitoring change.

Nevertheless, for the therapeutic clinician, the real “value” of PET in tumour diagnosis and staging, GTV delineation and assessing RT response is often limited or obscure, especially when other modalities are sufficient. For example, by implication, two-thirds of cancer patients are not affected by PET for tumour diagnostic purposes [9]; and using PET may not aid GTV delineation, for example, owing to false-negative PET findings in oesophageal cancer [39]. This can lead the clinician who is aware of PET’s limitations to conclude that, in many instances, it only adds time and complexity to clinical processes rather than adding utility to therapy planning decisions. For PET-determined RT response in particular, the value of PET scanning is restricted by the availability of efficacious alternative or salvage treatment options, with the result that the managing radiation oncologist is unable to act on PET information for the patients benefit. This highlights two important conclusions: there is a need to recognise the advantages and drawbacks of PET for current clinical applications and apply it more judiciously; and there is a requirement for more effective treatments.

Ongoing and future multidisciplinary research advances that use PET’s greatest strengths—in BTV or phenotype definition, in RT response and in-beam PET for true *in vivo* dose monitoring—promise to improve external beam RT, particularly for particle therapies. This may well lead to the development of truly 3D, radiobiologically optimised adaptive radiation therapy, in which treatment may be selected, optimised,

monitored and adapted by using PET for biological and functional imaging, prior to and during irradiation [57]. In this respect, PET may also be regarded as a powerful tool for the *in vivo* investigation of radiobiology, with great potential to advance therapeutic irradiation.

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