INVITED SHORT COMMUNICATION

Recommendations for the use of PET and PET–CT for radiotherapy planning in research projects

E J SOMER, PhD, L C PIKE, MSc and P K MARSDEN, PhD

PET Imaging Centre, Division of Imaging Sciences and Biomedical Engineering, King's College London, London, UK

ABSTRACT. With the increasing use of positron emission tomography (PET) for disease staging, follow-up and therapy monitoring in a number of oncological indications there is growing interest in the use of PET and PET–CT for radiation treatment planning. In order to create a strong clinical evidence base for this, it is important to ensure that research data are clinically relevant and of a high quality. Therefore the National Cancer Research Institute PET Research Network make these recommendations to assist investigators in the development of radiotherapy clinical trials involving the use of PET and PET–CT. These recommendations provide an overview of the current literature in this rapidly evolving field, including standards for PET in clinical trials, disease staging, volume delineation, intensity modulated radiotherapy and PET-augmented planning techniques, and are targeted at a general audience. We conclude with specific recommendations for the use of PET in radiotherapy planning in research projects.

Received 21 April 2011
Revised 1 August 2011
Accepted 17 August 2011

DOI: 10.1259/bjr/46048428

General

An International Atomic Energy Agency (IAEA) expert panel concluded that there is a strong case for the routine clinical use of fluorine-18 (^{18}F) fludeoxyglucose (FDG) positron emission tomography (PET) in radiotherapy planning for non-small cell lung cancer, and cautious use should be considered in a variety of other tumour types [1]. However, the non-critical use of PET to reduce treatment volumes could impair rather than improve prognosis [2]. While recommendations as to the routine clinical use of PET in radiotherapy are beyond the scope of this document, such recommendations will require a solid evidence base only achievable through the early adoption of standards for clinical trials. Those requiring further information on either PET or radiotherapy are directed elsewhere [3, 4].

Standards and accreditation of positron emission tomography systems and scanning sites

Quantitative analysis of PET images can complement visual interpretation and provide an objective measure useful in prediction of response or response assessment [5]. The most widely accepted measure, standardised uptake value (SUV), is defined as the concentration of tracer in tissue divided by the injected activity normalised to patient weight [6]. In the case of FDG PET, SUV provides a simple, semi-quantitative index of glucose metabolism. There are numerous sources of variation and error that affect SUV [5] and it is recommended that PET protocols are standardised across scanning sites that comply with minimum standards, such as those published by the European Association of Nuclear Medicine [7]. The National Cancer Research Institute (NCRI) PET Research Network has implemented standards and a site accreditation procedure for UK sites participating in multicentre trials (www.ncri-pet.org.uk), and these are generally applicable to radiotherapy trials. The NCRI Radiotherapy Clinical Trials Quality Assurance Group sets the standard of quality control (QC) for radiotherapy clinical trials (www.rttrialsqa.org.uk). Through links with the NCRI Clinical and Translational Radiotherapy Research Working Group (CTRad) and the NCRI PET Research Network, further guidance for the use of PET in radiotherapy trials will be developed.

Disease staging

FDG PET is a whole-body scanning technique that has greater sensitivity and specificity for nodal staging than CT or MRI in many tumour types [8]. Pre-treatment staging with FDG PET can change therapeutic intent from curative to palliative in up to one-third of patients, and the up-staging of patients with a poorer prognosis following PET and their exclusion from ongoing radiotherapy trials can result in an artificial improvement in the outcome of the trial group (this is known as the ''Will Rogers effect'' [9]). Therefore, to avoid possible bias in trials evaluating the use of PET for volume

Address correspondence to: Professor Paul Marsden, Division of Imaging Sciences, King's College London, PET Imaging Centre, St Thomas' Hospital, London SE1 7EH, UK. E-mail: paul.marsden@kcl.ac.uk

delineation compared with conventional techniques, it is essential that patients in the control and experimental arms are staged in exactly the same way. Trials evaluating the value of PET staging against treatment outcome must pay particular attention to this aspect of the study design as it may be unethical not to include this additional information in the treatment plan.

Correct staging and careful selection of subjects for inclusion will provide a homogeneous group that improves the statistical power of radiotherapy trials if rigorous and consistent imaging protocols are enforced.

Volume delineation

The first step in planning external beam radiotherapy is the accurate definition of a number of target volumes. These volumes, defined by the International Commission on Radiation Units and Measurements (ICRU) [10–12], are:

- Gross tumour volume (GTV) represents the confirmed tumour that is palpable or visible on physical or radiological examination. More specifically, the terms GTV-T (primary tumour), GTV-N (nodal disease) or GTV-M (metastatic disease) can be used.
- Clinical target volume (CTV) is the GTV plus margins that represent subclinical disease.
- Planning target volume (PTV) encloses the CTV within margins that account for physical uncertainty in shape measurement, motion and distortion during treatment, and errors in patient positioning and set-up [13]. Once established, the PTV should not be modified. The concept of a planning organ at risk volume (PRV) has been introduced to allow for positional and other uncertainties that also apply to organs at risk. However, the PRV is relevant only for serial architecture structures, particularly the spinal cord, brainstem or other neural structures, and its use is discouraged for parallel architecture structures. Where a conflict arises between the dose to the PTV and a critical normal structure, or its associated PRV, this should be controlled by altering the dose–volume planning constraints, in discussion with the prescribing clinician [14].
- Biological target volume (BTV) is a recent term introduced to define a treatment volume based upon information derived from functional imaging [15]. While the term is popular within nuclear medicine literature, the ICRU advises against its usage [12] in favour of GTV-T with a label to specify the imaging modality and treatment point. For example: GTV-T (MRI T_2, 0 Gy) would be a GTV evaluated with a T_2 weighted MRI scan before treatment, GTV-T (fluoromisonidazole PET, 30 Gy) could refer to the same tumour evaluated with fluoromisonidazole PET after an absorbed dose of 30 Gy. If the use of BTV persists the ''type'' should always be specified.

Conventional radiotherapy with its ''brick-shaped'' treatment field and significant irradiation of normal tissue was superseded in the 1990s by the introduction of CT-based conformal radiotherapy (3D-CRT). This uses a number of collimated external beams to tailor the irradiated field to the shape of the tumour volume as defined according to the appearance of anatomical structures on a CT scan acquired with the patient immobilised in the treatment position. Increased conformance of the delivered dose to the planned volume in this way allows the use of dose escalation; however, this cannot compensate for inadequacies in tumour imaging that result in an inaccurate plan [1].

Given PET and CT data, a conservative algorithm for the modification of the CT-based GTV runs as follows: draw tumour outlines according to established practice (*e.g.* along anatomical boundaries depicted on CT). If a lymph node is visualised with PET and PET is known to be more specific than CT, it might be legitimate to enlarge the treatment volume to include this node. If a lymph node is not visualised with PET and it is known that PET is more sensitive than CT, it might be legitimate to decrease the target volume to exclude this node [16], subject to circumspect recommendations of the treating clinician and established clinical protocols. Inclusion of small (<5 ml) structures (*i.e.* lymph nodes) should be based upon detectability rather than SUV [2]. This should be considered the elementary model of PET-augmented radiotherapy.

No attempt should be made to define volumes based solely upon segmented PET data [17] and threshold-based methods for PET volume delineation should be avoided [18]. There is no consensus as to which of the many available algorithms performs best and no automatic delineation technique should be regarded as a reliable standard. Expert manual delineation by a clinical oncologist working with a nuclear medicine physician is recommended [2]. Image display protocols may vary depending on the specific hardware and software used, and further work is required to standardise across systems. Settings (intensity threshold, colour table, fusion opacity, etc.) should be optimised and the acquisition of a small training cohort to be delineated at all participating sites is recommended.

It is widely accepted that the use of PET–CT for volume definition increases reproducibility compared with CT alone [1], but is still subject to a degree of interobserver variability. Multicentre trials may consider the use of carefully validated automated delineation tools with the addition of manual contour editing, and these can reduce this variability still further [19]. However, adherence to a rigorous contouring protocol also promotes excellent conformity [20] and researchers are reminded that ''fully automated contouring can sometimes be 100% reproducible but 100% wrong'' [21].

Physiological motion will adversely affect accurate volume delineation. Time-averaged PET images that inherently account for periodic motion may be useful in determining tumour margins but are subject to CT attenuation correction artefacts. Potentially, four-dimensional (4D) PET–CT will provide quantitative PET data suitable for use in 4D radiotherapy, but these techniques are still at the experimental stage and it is unclear how corrected data should be integrated into the planning process.

However volumes are delineated it should be remembered that PET SUV is not an absolute property of a tumour but a broad reflection of tracer bio-distribution imaged on a single occasion with a specific scanner

following a particular protocol. Reproducible results can be achieved provided established protocols are rigorously adhered to.

Intensity-modulated and image-guided radiotherapy

Accurate target definition is a prerequisite of intensity-modulated radiotherapy (IMRT), which offers a major improvement over 3D-CRT in terms of conformance of treatment volume to planned volume and allows a consequent dose escalation within the tumour volume.

The use of IMRT for the treatment of tumour subvolumes with particular radio-characteristics delineated using PET, known as dose-painting, is an active area of research. Current research focuses on imaging of hypoxia with novel PET tracers, but there is no consensus on how best to define these subvolumes or how to integrate these subvolumes into treatment plans.

Image-guided radiotherapy (IGRT), which utilises imaging to monitor tumour motion and modify the treatment volume over the course of therapy, allows a reduction in planning margins (<5 mm versus 10 mm). This margin reduction makes the accurate alignment of PET and planning CT particularly important, but it should be noted that the delineation of 1 mm margins with an image resolution in PET of 7–9 mm is not expected to be successful [22].

Indirect planning

Indirect planning combines the PET (or PET–CT) data with a planning CT acquired on a separate occasion. Most modern planning systems support PET or MRI-augmented CT-guided planning [23], albeit to a limited extent. There are logistical and financial [3] reasons why indirect planning may be the preferred option. Often the PET data will have to serve for both disease staging and tumour delineation, and this places restriction upon the timing of the acquisition within the treatment pathway and the use of immobilisation devices which are not prepared until a decision to treat has been taken. It has been recommended that a dedicated planning PET–CT scan is acquired for fusion with a planning CT once custom-made immobilisation devices have been prepared [24].

Image registration techniques that align PET and planning CT require careful validation on a per application basis. The results of image registration depend upon the correct use of custom-made immobilisation devices, and rigid-body PET to planning CT registration errors of a few millimetres [25, 26] are to be expected. Non-rigid algorithms may be able to account for a degree of interscan motion, but these techniques have not been widely validated, particularly for PET data, and should be used with caution. If PET–CT is available, use of the CT component may provide a more accurate registration to the planning CT, but this assumes accurate alignment of the PET and CT gantries, synchronisation of respiratory phase and reproducible scanning couch motion. The alignment errors associated with indirect planning may make it unsuitable for advanced IMRT applications such as dose-painting.

Direct planning

If PET–CT data are available from a scanner that has passed the QC requirements for radiotherapy planning, the CT component of the PET–CT scan can replace the CT planning scan altogether. The QC requirements for radiotherapy planning PET–CT typically include provision of external lasers and careful assessment of scanner couch motion. This is termed direct planning.

In addition to the standard QC required for quantitative PET–CT and the adoption of radiotherapy CT-simulator QC protocols [27] for the scanner and room lasers, the PET–CT gantry alignment must be confirmed, and data transfer and display, including any Digital Imaging and Communications in Medicine (DICOM) radiotherapy objects, within the treatment planning system must be validated. CT acquisition parameters should be matched to established protocols, but the recent introduction of PET–CT scanning in many centres may mean that the CT hardware specification exceeds that available within the existing planning environment.

Direct planning assumes that the patient has received a previous staging scan with a dedicated planning scan acquired following the preparation of immobilisation devices. Within IGRT there is a move towards ''reproducible patient positioning'' rather than strict immobilisation, but this will still require a degree of pre-planning preparation. Radiotherapy-trained radiographers should be involved throughout and their workflow should be tailored to minimise staff radiation dose [28]. Despite the increased logistical challenges, direct planning remains the preferred option.

Specific recommendations

(1) PET data should only be acquired at scanning sites that comply with defined standards for quantitative PET studies. Strict scanning protocol adherence must be enforced and routine scanner QC (including PET–CT gantry alignment checks) performed.
(2) Subjects should be accurately staged, preferably with PET, before entering any radiotherapy trial that assesses PET treatment volume delineation with respect to patient outcome.
(3) An approach that uses PET findings to include or exclude structures defined on the CT-based plan is preferred for clinical (non-technical) studies. Lymph nodes should be included according to detectability rather than SUV.
(4) Automated delineation techniques (particularly those based upon fixed intensity thresholds) should be avoided, but may be assessed as part of a parallel trial. Pre-validated algorithms may be appropriate, subject to manual editing and visual confirmation, where the reduction of interobserver variability is particularly important.

(5) Treatment volumes should be delineated by a clinical oncologist working in cooperation with an experienced nuclear medicine physician or radiologist trained in PET. Image display and contour delineation protocols should be standardised across centres on a per-trial basis and the acquisition of a small training cohort is advised.
(6) Indirect planning should be performed on a PET scan acquired for that specific purpose while the patient is immobilised in the treatment position. Scanner adaptations, including a flat couch top, are essential.
(7) Registration algorithms used for indirect planning should be validated on a per-application basis. Non-rigid algorithms should be used with caution.
(8) If PET–CT is used for direct planning, the scanner, software and protocols, patient couch and external lasers should be integrated into the local oncology quality management system to ensure that there is an agreed understanding of QC requirements.
(9) Transfer of PET, CT and radiotherapy (DICOM-RT) data and subsequent display within the treatment planning system should be validated with phantom measurements.
(10) Direct planning is preferred for ''higher accuracy'' applications such as IMRT, IGRT and dose-painting.

Acknowledgments

This document has been prepared with input from the NCRI PET Scanning Methodology Expert Panel, the NCRI CTRad and the British Institute for Radiology, and the recommendations are made on behalf of the NCRI PET Research Network. The authors wish to thank the NCRI PET Scanning Methodology Expert Panel and CTRad for their invaluable advice during the preparation of this guidance document.

References

1. MacManus M, Nestle U, Rosenzweig KE, Carrio I, Messa C, Belohlavek O, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006–2007. Radiother Oncol 2009;91:85–94.
2. Nestle U, Kremp S, Grosu A-L. Practical integration of [18F]-FDG-PET and PET-CT in the planning of radiotherapy for non-small cell lung cancer (NSCLC): the technical basis, ICRU-target volumes, problems, perspectives. Radiother Oncol 2006;81:209–25.
3. Barrington SF, Maisey MN, Wahl RL. Atlas of clinical positron emission tomography. 2nd edn. London, UK: Hodder Arnold; 2006.
4. Barrett A, Dobbs J, Morris SL, Roques T. Practical radiotherapy planning. 4th edn. London, UK: Hodder Arnold; 2009.
5. Vriens D, Visser EP, de Geus-Oei LF, Oyen WJ. Methodological considerations in quantification of oncological FDG PET studies. Eur J Nucl Med Mol Imaging 2009;37:1408–25.
6. Huang S. Anatomy of SUV. Standardized uptake value. Nucl Med Biol 2000;27:643–6.
7. Boellaard R, O'Doherty MJ, Wolfgang AW, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging 2010;37:181–200.
8. Gambhir SS, Czernin J, Schwimmer J, Silverman DHS, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. J Nucl Med 2001;42(suppl. 5):1S–93S.
9. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Eng J Med 1985;312:1604–8.
10. The International Commission on Radiation Units and Measurements. Prescribing recording and reporting photon beam therapy (ICRU Report 50). Bethesda, MD: International Commission on Radiation Units and Measurements; 1993.
11. The International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy (ICRU Report 62, supplement to ICRU Report 50). Bethesda, MD: International Commission on Radiation Units and Measurements; 1999.
12. The International Commission on Radiation Units and Measurements. ICRU report 83 chapter 4: definition of volumes. J ICRU 2010;10:41–53.
13. Antolak JA, Rosen II. Planning target volumes for radiotherapy: how much margin is needed? Int J Radiat Oncol Biol Phys 1999;44:1165–70.
14. British Institute of Radiology. Geometric uncertainties in radiotherapy: defining the planning target volume. London, UK: British Institute of Radiology; 2003.
15. Ling CC, Humm J, Larson S, Amols H, Fuks Z, Leibel S, et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. Int J Radiat Oncol Biol Phys 2000;47:551–60.
16. Gregoire V. Is there any future in radiotherapy planning without the use of PET: unraveling the myth. Radiother Oncol 2004;73:261–3.
17. Jarritt PH, Carson KJ, Hounsell AR, Visvikis D. The role of PET/CT scanning in radiotherapy planning. Br J Radiol 2006;79:S27–35.
18. Zaidi H, El Naqa I. PET-guided delineation of radiation therapy treatment volumes: a survey of image segmentation techniques. Eur J Nucl Med Mol Imaging 2010;37:2165–87.
19. van Baardwijk A, Bosmans G, Boersma L, Buijsen J, Wanders S, Hochstenbag M, et al. PET-CT-Based auto-contouring in non-small-cell lung cancer correlates with pathology and reduces interobserver variability in the delineation of the primary tumor and involved nodal volumes. Int J Radiat Oncol Biol Phys 2007;68:771–8.
20. Bayne M, Hicks RJ, Everitt S, Fimmell N, Ball D, Reynolds J, et al. Reproducibility of "intelligent" contouring of gross tumor volume in non-small-cell lung cancer on PET/CT images using a standardized visual method. Int J Radiat Oncol Biol Phys 2010;77:1151–7.
21. MacManus MP, Hicks RJ. Where do we draw the line? Contouring tumors on positron emission tomography/computed tomography. Int J Radiat Oncol Biol Phys 2008;71:2–4.
22. Ford EC, Herman J, Yorke E, Wahl RL. 18F-FDG PET/CT for image-guided and intensity-modulated radiotherapy. J Nucl Med 2009;50:1655–65.
23. Sharpe M, Brock KK. Quality assurance of Serial 3D image registration, fusion, and segmentation. Int J Radiat Oncol Biol Phys 2008;71(suppl. 1):S33–7.
24. Grgic A, Nestle U, Schaefer-Schuler A, Kremp S, Kirsch CM, Hellwig D. FDG-PET-based radiotherapy planning in lung cancer: optimum breathing protocol and patient positioning—an intraindividual comparison. Int J Radiat Oncol Biol Phys 2009;73:103–11.
25. Kessler ML. Image registration and data fusion in radiation therapy. Br J Radiol 2006;79:S99–108.

26. Ireland RH, Dyker KE, Barber DC, Wood SM, Hanney MB, Tindale WB, et al. Nonrigid image registration for head and neck cancer radiotherapy treatment planning with PET/CT. Int J Radiat Oncol Biol Phys 2007;68:952–7.
27. Institute of Physics and Engineering in Medicine. Physics aspects of quality control in radiotherapy 1998. Report no. 81. York, UK: Institute of Physics and Engineering in Medicine.
28. Carson KJ, Young VAL, Cosgrove VP, Jarritt PH, Hounsell AR. Personnel radiation dose considerations in the use of an integrated PET-CT scanner for radiotherapy treatment planning. Br J Radiol 2009;82:946–9.