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GUIDELINES & RECOMMENDATIONS

Guidance on the use of PET for treatment planning in radiotherapy clinical trials

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ABSTRACT:

The aim of this article is to propose meaningful guidance covering the practical and technical issues involved when planning or conducting clinical trials involving positron emission tomography (PET)-guided radiotherapy. The complexity of imaging requirements will depend on the study aims, design and PET methods used. Where PET is used to adapt radiotherapy, a high level of accuracy and reproducibility is required to ensure effective and safe treatment delivery. The guidance in this document is intended to assist researchers designing clinical trials involving PET-guided radiotherapy to provide sufficient information about the appropriate methods to complete PET-CT imaging to a consistent standard at participating centres. The guidance is divided into six categories: application of PET in radiotherapy, resource requirements, quality assurance, imaging protocol design, data management and image processing. Each section provides an overview of the recent literature to support the specific recommendations. This guidance builds on previous recommendations from the National Cancer Research Institute PET Research Network and has been produced in collaboration with the National Radiotherapy Trials Quality Assurance Group.

APPLICATION OF PET IN RADIOTHERAPY

Positron emission tomography (PET) is an *in vivo* imaging technique used to explore biological processes at the cellular level to determine the extent of active disease and can often detect functional changes related to cancer treatment before anatomical imaging. PET-CT is a key investigative tool in cancer and is applied across a wide range of clinical indications determined by evidence-based guidelines.[1] PET-CT imaging has several important roles in radiotherapy clinical trials with differing levels of complexity:[2]

(1) To assist in diagnosis and/or staging to determine eligibility for entry into a clinical trial that involves radiotherapy.
(2) For response assessment to monitor the effectiveness of a new or modified treatment, usually comprising a baseline scan and one or more follow-up scans during or after a course of radiotherapy. Sometimes a PET imaging substudy may be performed to determine the usefulness of PET for response assessment in a particular tumour type and treatment, involving radiotherapy.
(3) For treatment modification, with PET performed prior to or during radiotherapy to guide dose and/or treatment volumes.
(4) In pilot/Phase I studies to evaluate the feasibility and safety of including PET in radiotherapy or the application of a new radiopharmaceutical to image relevant aspects of tumour biology, for example hypoxia, prior to a larger multicentre Phase II/III study.

The aim of this document is to present researchers with an overview of the technical and practical considerations in setting-up radiotherapy clinical trials involving PET with the key recommendations summarized in Table 1.

Table 1. Summary of recommendations

Summary of recommendations
1. Radiopharmaceutical selection may be dictated by availability and cost and researchers should explore this at an early stage in the study work-up.
2. PET-CT positioning needs to be optimized for radiotherapy planning in applications where accurate localization of PET uptake on the planning images is essential. This will require use of an indexed flat couch overlay and immobilization devices.
3. A dedicated radiotherapy planning PET-CT should be acquired with the patient in the radiotherapy position for direct planning in advanced delivery techniques, image-guided and adaptive radiotherapy and applications where the PET signal is used to define subvolumes or voxels within the tumour for dose escalation or "dose painting".
4. PET-CT scanners should be accredited to ensure quantitative results are consistent across centres.
5. For applications requiring the most accurate and reproducible positioning, the PET-CT should be commissioned for radiotherapy planning purposes and be included within the radiotherapy QA system.
6. A nuclear medicine physician/radiologist and MPE with experience in PET should be involved in the protocol development.
7. A standardized imaging protocol should be provided to centres identifying critical requirements to achieve the trial outcomes.
8. The CT parameters for the PET-CT will need to be optimized for delineation if replacing the radiotherapy planning CT for direct planning.
9. Experienced radiotherapy radiographers should position patients on the PET-CT scanner for applications requiring high accuracy and reproducibility.
10. Integrity of PET data should be tested throughout the anonymization and data transfer process to ensure quantitative values and volumes are preserved.
11. Registration techniques (rigid or non-rigid) should be validated for the intended application to assess the registration accuracy and registered images verified on a per patient basis.
12 . Volume delineation guidelines should be developed for the intended application to improve reproducibility across centres. For complex planning applications, a series of benchmark cases should be provided to individual centres for training.
13. Automated segmentation techniques should be validated for the intended application.
14. Volumes derived using automated segmentation algorithms must be visually inspected by the clinical oncologist on a per patient basis and manually edited where appropriate.

MPE, medical physics expert; PET, positron emission tomography; QA, quality assurance.

RESOURCE REQUIREMENTS

Radiopharmaceuticals for oncology applications

The most commonly used radiopharmaceutical for PET imaging, and hence radiotherapy clinical trials, is ^{18}F-fluorodeoxyglucose (FDG). FDG is an analogue of glucose, which has higher uptake in areas with increased glucose transport and metabolism including many cancers. ^{18}F-FDG PET has high sensitivity in many cancer types;[3] however, it is not "specific" for malignant disease, being taken up in other processes with increased glucose turnover such as infection and inflammation.

Other radiopharmaceuticals have been developed to investigate specific biochemical processes for imaging in cancer, including hypoxia, protein and cell membrane synthesis, amino acid transport, somatostatin receptor and protein binding.[4,5] Table 2 provides a summary of the primary targets in current PET imaging of cancer that have potential applications in radiotherapy.

^{11}C, ^{18}F and $^{60/61/64}$Cu are produced in a cyclotron, while ^{68}Ga and ^{62}Cu are generator produced. The short half-life of ^{11}C (20 min) means that studies utilizing ^{11}C radiopharmaceuticals need to be carried out at centres with an onsite cyclotron. Radiopharmaceutical selection may be dictated by availability and cost, particularly for non-FDG radiotracers and researchers should explore this at an early stage in the study workup.

Equipment for PET-guided radiotherapy

All major radiotherapy centres in the UK have access to clinical PET-CT imaging services, however, they may not be in the same location nor have the same provider as the radiotherapy service. Most clinical PET-CT scanners have the capability to perform imaging to aid radiotherapy planning, however, access to specialist radiotherapy equipment (external lasers, flat bed and immobilization devices etc.) will vary between centres limiting the range of radiotherapy work that can be performed.

PET imaging for diagnosis and response assessment would generally incorporate standard clinical PET-CT imaging procedures into the trial protocol. However, patient positioning for clinical PET-CT is optimized for image quality whilst trying to maintain patient comfort and often this does not reflect positioning used for radiotherapy planning. Different arm positioning, the use of a curved couch and shallow or free breathing can result in significantly different patient positioning in the diagnostic PET-CT compared to radiotherapy planning images.

For some simple planning applications, such as deciding whether to include or exclude structures and for assisting in determining the disease extent alongside other imaging, standard PET-CT positioning and visual comparison of anatomy without registration may be acceptable if the clinician is able to adequately localize the PET uptake. However, where accurate localization of PET uptake on the planning images is essential, the PET-CT needs to be optimized for radiotherapy planning.

- For studies requiring high registration accuracy and reproducibility, the PET-CT should be performed in the radiotherapy position (or as close as possible) using an indexed

Table 2. A summary of some of the primary targets in current PET imaging of cancer with potential for radiotherapy applications

Target pathway	Potential radiopharmaceuticals
Tumour hypoxia	^{18}F-MISO ^{18}F-FAZA ^{18}F-HX4 $^{60/61/62/64}$Cu-ATSM
Protein and cell membrane synthesis	^{11}C or ^{18}F-choline ^{11}C-acetate
Transporter-targeted agents	^{11}C-MET ^{18}F-FET ^{18}F-FACBC
Receptor-targeted agents	^{68}Ga-DOTATOC/DOTANOC/DOTATATE ^{68}Ga-pentixafor
Protein-targeted agents	^{68}Ga-PSMA ^{18}F-FLT

^{11}C-MET, ^{11}C-L-methyl-methionine; $^{60/61/62/64}$Cu-ATSM, $^{60/61/62/64}$copper(II)-diacetyl-bis(N^4-methylthiosemicarbazone); ^{18}F-FACBC, anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid; ^{18}F-FAZA, ^{18}F-fluoroazomycin; ^{18}F-FET, ^{18}F-fluoroethyltyrosine; ^{18}F-FLT, ^{18}F-fluorothymidine; ^{18}F-HX4, ^{18}F-flortanidazole; ^{18}F-MISO, ^{18}F-fluoromisonidazole;^{68}Ga-PSMA, ^{68}Ga-prostate-specific membrane antigen.

flat couch overlay and immobilization devices as appropriate. The CT component of the PET-CT is then used to register the PET to the radiotherapy planning (RTP) CT to aid in delineation of the gross tumour volume. This is sometimes termed as "indirect" planning.[6]

- When the PET-CT is acquired with the patient in their radiotherapy position using a flat, indexed couch overlay and immobilization, the CT component of the PET-CT can be adapted to replace the RTP CT and used "directly" for delineation of target volumes and healthy tissues. This is often referred to as "direct" planning.

Acquiring a dedicated planning PET-CT for direct planning removes the errors associated with acquisition and registration of images at different time points, which is the preferred option for applications requiring the highest levels of accuracy. This includes advanced delivery techniques, image-guided and adaptive radiotherapy and applications where the PET signal is used to define subvolumes or voxels within the tumour for dose escalation or "dose painting".[6] It is, however, the most complex option and requires access to specialist equipment and expertise that will not be available at all PET-CT centres. Whilst indirect planning is more accurate than using standard clinical PET-CT positioning, errors can still be introduced during patient set-up and/or registration and centres will still need access to specialist equipment and expertise.

Staffing requirements

A nuclear medicine physician/radiologist with experience in PET-CT should be part of the protocol development group and involved in ongoing trial management to provide advice and support for the imaging aspects of the study design and in applying for research approvals. Detailed information about licences and research authorizations required for the administration of radioactive substances can be found in the Administration of Radioactive Substances Advisory Committee (ARSAC) Notes for Guidance[7] and on the NHS Health Research Authority website.[8]

Medical physics experts (MPE) from the lead centre should be consulted at an early stage of trial design to provide advice on the scientific and technical aspects of the protocol, including quality control (QC) requirements, radiation dose assessments and safety considerations. It is unlikely a single MPE will have appropriate experience in both radiotherapy and PET therefore advice will be required from both PET and radiotherapy physics experts.

Individual roles and responsibilities for the provision of radiotherapy and PET imaging procedures at recruiting centres will vary depending on local arrangements and levels of expertise. For successful implementation of the protocol at the recruiting centres, there will need to be close collaboration between radiotherapy and nuclear medicine/PET staff. Existing levels of staff training will vary between centres and the lead investigator centre may need to provide support and advice for more complex study designs to ensure the required level of expertise in both PET and radiotherapy are achieved.

QUALITY ASSURANCE

Routine PET-CT quality control

The choice of acquisition and reconstruction parameters directly impacts on bias and variation in quantitative PET metrics which will in turn affect delineation for radiotherapy applications. To minimize bias and variation and achieve comparable quantitative results across scanning centres, it is important to implement standardized imaging protocols and regular QC procedures. Recommended minimum requirements for routine PET-CT QC are described in the Institute of Physics and Engineering in Medicine Report 108[9] and CT specific QC is covered in the Institute of Physics and Engineering in Medicine report 91.[10] Use of standard phantoms is an accepted method for matching PET image quality and quantitative performance between centres and can be achieved by ensuring participating PET-CT scanners have been accredited through national or international accreditation programmes such as that provided by the UK PET Core Lab[11] or European Association of Nuclear Medicine (EANM).[12]

Radiotherapy specific Quality Control

For applications requiring the most accurate and reproducible positioning, the PET-CT will require immobilization consistent with the radiotherapy set-up, external radiotherapy lasers and an indexed couch overlay. The PET-CT will also need commissioning for radiotherapy planning purposes and be included within the radiotherapy quality assurance system. Test procedures and tolerances should follow national and international guidance[13,14] with input from an experienced radiotherapy physicist (MPE) to ensure appropriate tests are defined and tolerances set for indirect and direct planning applications.

Commissioning and routine QC tests of the PET-CT should cover the couch, external lasers and set-up accuracy and should mirror that required for the radiotherapy CT simulator. For direct treatment planning, where the CT component of the PET-CT acquisition replaces the RTP CT, additional tests are required to ensure accuracy of dose calculation and delineation. Regular tests using point or line sources should be included as part of the routine QC schedule to assess the accuracy of the PET to CT alignment. This should be repeated after the gantries are separated for servicing and be performed with and without weight on the couch.[15]

IMAGING PROTOCOL DESIGN

PET protocol

There are several technical, physical and biological factors known to affect quantification in PET imaging.[16] To minimize variation in PET results between centres, it is recommended to provide centres with an imaging protocol based on the latest EANM guidelines.[17] Whilst these guidelines focus on ^{18}F-FDG PET, the general principles apply for non-FDG tracers. Additional advice should be sought from a nuclear medicine physician/radiologist with experience in PET-CT to determine trial specific requirements. Ideally the imaging protocol should identify the critical time points in the radiotherapy pathway and essential imaging requirements along with how much centres can deviate without compromising the trial outcomes. For studies using PET to monitor changes in uptake over time, subsequent PET-CT scans should be performed on the same scanner whenever possible with patient preparation, positioning and acquisition matched as closely as possible to the baseline scan to minimize variability. Consideration should also be given to any information to be collected at the time of imaging, such as patient preparation (*e.g.* fasting, blood glucose level), and a form provided with the imaging protocol for the local imaging staff to complete.

Local practice for injected activities varies across centres. The ARSAC Notes for Guidance[7] provide diagnostic reference levels (DRLs) for the majority of PET radiotracers and this should be used to determine dose constraints for clinical trials in accordance with the Ionizing Radiation (Medical Exposure) Regulations.[18,19] Some centres may have optimized local protocols using lower administered activities such as the weight-based regimes for adults and paediatrics suggested by the EANM.[17,20] To allow for variation across centres, the ARSAC DRL should be used in the research application and imaging protocol, but with allowance for centres to use lower injected activities where appropriate.

CT protocol

In clinical practice the CT acquired as part of a PET-CT scan is used for attenuation correction of PET data and to provide anatomical information for localization of the tracer uptake. The current national DRL for the CT acquired as part of a half-body PET-CT (base of brain to mid-thigh) is 60% lower than that for a diagnostic chest, abdomen and pelvis CT scan.[21,22] As a result, the image quality is not appropriate for direct delineation of radiotherapy volumes. For direct planning applications, the CT acquired as part of the PET-CT needs to be adapted to produce equivalent image quality to the radiotherapy planning CT it will replace.

Motion management techniques

A range of immobilization devices and positioning tools are available for optimal positioning of patients for radiotherapy planning, depending on the treatment site. This may include vacuum-bags, knee rests, foam mattresses, foot or head rests as well as indexed boards for different anatomical regions. PET centres will not have direct access to these devices and so a system must be established for transfer of devices to the imaging site on a per patient basis. Alternatively, funding may be required to purchase duplicates for the imaging site.

For direct and some indirect applications of PET-CT for treatment planning where accuracy and reproducibility of patient positioning is critical, experienced radiotherapy radiographers should position the patients on the PET-CT scanner as they would on a CT simulator.

For direct or indirect planning procedures involving thoracic lesions, it may be desirable to compensate for respiratory motion using software or hardware gating techniques (4D-PET-CT) to improve quantification accuracy and aid in tumour volume delineation.[23,24] Respiratory gating is not standard for PET-CT, so it should be determined whether respiratory gating equipment is available at the designated PET centres. Any respiratory gating method used for radiotherapy planning must be compatible with the treatment planning system (TPS) and the process validated with phantoms and/or patients prior to implementation in a radiotherapy planning application.

DATA MANAGEMENT

To reduce processing time and storage space on the PET-CT scanner, most PET studies are acquired in "frame mode". This mode stores PET data in sinograms and uses pre-defined computer storage and memory resources. This is known as "raw" data. Few centres routinely store raw PET data for clinical PET-CT studies, but this can be useful in the research setting if the incorrect reconstruction was used or if retrospective reconstructions are required. Most centres can store raw PET data as Digital Imaging and Communications in Medicine (DICOM) encapsulated files on a standard picture archiving and communication system. However, as the raw data are in proprietary

vendor-specific format it can only be reconstructed on the PET-CT scanner or using specialized research tools.

Once the PET and CT data have been acquired, the raw data are reconstructed into stacks of axial slices which are then used for clinical review or data analysis. Reconstructed images are routinely sent to a local picture archiving and communication system for long-term storage. As standard, centres should reconstruct the CT used for attenuation correction, the CT used for clinical review (which may have different parameters to the CT used for attenuation correction), the non-attenuation corrected PET (to aid in reviewing attenuation artefacts) and the attenuation corrected PET. For direct PET-CT, there will also be reconstructions designed specifically for the RTP CT.

Reconstructed PET-CT imaging data should be stored in a DICOM compliant format[25] to allow transfer of images across different storage media and reviewing/planning software. The choice of system for clinical review and volume delineation (nuclear medicine reporting workstation or TPS) may depend on the ability of the software to display fused PET-CT data in units of standardized uptake value and availability of the desired manual or automated tools for delineation. If volume delineation is performed on the PET/nuclear medicine software, volumes must be stored as DICOM compliant radiotherapy structure sets to ensure they can be read into the TPS. A tested and secure method[26,27] for transferring scans from the PET-CT scanner to the final location for reporting and/or delineation must be in place.

Information about the patient and the image acquisition and reconstruction is stored within the DICOM header of the images. For research studies, the PET-CT data need to be anonymized to remove patient identifiable information from these header fields for centralized storage. During anonymization and post-processing of images, some software may delete or modify DICOM fields required for quantification. As part of ongoing quality control of image data, it is important that these DICOM fields are checked to ensure that data integrity is maintained after anonymization and transfer.[28]

IMAGE PROCESSING

Image registration

For indirect planning applications, the PET-CT images are registered to the RTP CT to aid in the delineation of target volumes and normal tissues.[6] This involves applying a registration algorithm to register the CT component of the PET-CT to the RTP CT, then applying the transformation matrix to the PET data. As the spatial resolution of the PET is much lower than the RTP CT, registration will result in resampling of the PET voxels to match the CT thus affecting the voxel values.

Local and global registration accuracy will depend on the anatomical site, extent of deformation, image quality and registration algorithm used. The impact of registration errors on the treatment delivery depends on the accuracy required for the intended application and whether the errors will be propagated throughout the treatment plan.[29] An application- and anatomical site-specific evaluation of the registration accuracy should be performed as described in the American Association of Physicists in Medicine (AAPM) Report 132 and registered images should be verified on a per-patient basis.[29]

There are three categories of registration techniques:

- Rigid registration is a linear transformation that includes translation and rotation only, preserving the distances between all points in the image.
- Affine registration is also linear, but in addition to translation and rotation, includes scaling, shearing and plane reflection. Distances between points in the image are not preserved but parallel lines remain parallel.
- Deformable registration is a non-linear transformation and maps points from one image to another

If the patient positioning for the PET-CT closely matches the RTP CT and there has not been significant anatomical changes, rigid registration or rigid registration over a limited field of view may be sufficient to assist in visualizing tissues for volume delineation.[29,30] Deformable registration techniques may be suitable where patient positioning is not well matched, or the anatomy has changed, however, has some limitations.[29] In particular, application of the transformation matrix from the CT to the PET can provide accurate registration of tissue boundaries, however, due to lack of structural information, accurate registration of the interior tissue structure can be variable and may result in large voxel-to-voxel differences.[31] Deformable registration techniques are therefore unsuitable for applications utilizing PET voxel values or gradients for response assessment to adapt the radiotherapy plan. In these cases, the recommended procedure is to acquire a dedicated PET-CT in the radiotherapy position for direct planning. Many centres do not have access to multimodality deformable registration algorithms and the implementation will be software dependent requiring each to be validated for the intended trial application.

Volume delineation

In radiotherapy planning applications, the PET may be used alongside other imaging to help guide the oncologist in delineating the primary gross tumour volume on the RTP CT. Where PET is known to be more sensitive than CT, it may also be used in the decision to include or exclude lymph nodes within the planning target volume based on tracer uptake.[6] In this case, volumes will usually be delineated on the RTP CT following established practice and a margin added to account for microscopic disease. Manual or automatic segmentation techniques can also be used for delineation of tracer-avid subvolumes for dose painting or biologically conformal radiotherapy applications.[30]

The use of PET to aid in manual volume delineation can improve reproducibility compared to CT alone, however, can be subject to interobserver variability.[32,33] To improve consistency of volume delineation across centres, outlining guidelines should be included in the trial protocol.[34] The guidelines should include standardized colour scale and windowing settings for visualization of PET uptake as these can influence the lesion margins.[35] Volume delineation should be performed by a clinical

oncologist and nuclear medicine physician/radiologist together to ensure accurate interpretation of the PET uptake. For more complex planning applications, the use of benchmark cases is recommended. These can be accessed by centres prior to the trial opening to monitor delineation consistency and provide a consensus on the use of PET across recruiting centres.

Automated segmentation algorithms can be classified into two broad groups: simple threshold-based techniques (fixed or adaptive) and more advanced algorithms.[36] Threshold-based techniques are computationally simple to implement, however, do not perform well with smaller lesions or complex structures (non-spherical or non-uniform uptake) making them unsuitable for accurate volume delineation in many radiotherapy applications.[37] The chosen threshold is also dependent on the characteristics of the scanner and the reconstructed images so requires prior knowledge of each scanner along with strict adherence to imaging protocols at all participating centres.

To overcome the limitations of manual and threshold segmentation techniques, several advanced automated segmentation algorithms have been developed for delineation of PET volumes. The AAPM have published a review of these proposed algorithms including the advantages and limitations of each type.[36] It is important to note however, that few are widely available and most are not fully validated, therefore no single method is recommended.[30] Where automated segmentation methods are to be used in a trial, they should be validated for the intended application and critically verified by a physician. No current automated segmentation algorithm is accurate across all patients and anatomical sites, therefore volumes derived using automated segmentation algorithms must be visually inspected by the clinical oncologist and manually edited where appropriate.

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