

FUNCTIONAL IMAGING USING PET AND RADIOTHERAPY PLANNING

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Abstract

Functional imaging with PET allows new insights into the extent of a tumour. This information has been rapidly included into treatment protocols. There are some complications in the process, not least of which is how to define the edge of the tumour. This review outlines current uses of PET in radiotherapy treatment planning. Concepts of radiotherapy volumes are outlined and common applications explored. PET now has an established role in radiotherapy planning. It is hoped that in those areas where it has not shown benefit, the development of new PET tracers will allow further improvement. There is still much work to be done, especially in the area of standardisation of techniques.

Increasingly, radiotherapy planning is relying on functional imaging to assist with tumour delineation. This is re-writing the radiation oncology literature in a significant number of areas as we improve both our ability to choose patients for treatment and to adequately cover the target. Combined with image guided radiotherapy, we are likely to see continuous evolution in treatment protocols over the next few years.

The planning process involves defining the volume of tumour (gross tumour volume), volume which may contain microscopic tumour (clinical tumour volume), and a margin incorporating movement (planning treatment volume). Traditionally, a significant proportion of radiotherapy failures were felt to be due to missing the tumour, geographic miss, where the radiotherapy field fails to cover adequately the volume the tumour encompasses. The treating team is increasingly getting better at sculpting the irradiated volume to match the tumour volume plus a margin for movement. Decreasing the irradiated volume so much runs the risk of geographic miss increasing.

Functional imaging, utilising PET, has been developed from the late 1970s. However, the vast majority of the current PET workload is oncology. PET can be utilised to look at a number of functional characteristics of tumours. The most widely used PET tracer has been ¹⁸F-deoxyglucose (FDG). Because most tumour types overexpress glucose transporters compared with normal tissues, FDG is preferentially taken up into the tumour rather than normal tissues. The ¹⁸F isotope attached to the glucose subsequently undergoes radioactive decay releasing a positron, which quickly annihilates to give off two gamma rays at almost 180 degrees to each other. These two photons are detected by a PET scanner and the point of decay resolved. All modern PET scanners now incorporate a diagnostic CT scanner in the gantry. This allows generation of both PET and CT image sets which are fused together to give precise anatomical localisation, and PET image quality improvements by allowing attenuation correction of the PET image.

Although FDG is the workhorse tracer for PET imaging, there are a number of other PET tracers which can be used for clinical imaging or to shed insight into tumour biology.¹ Examples include imaging of cellular proliferation with ¹⁸F-thymidine (FLT) and tumour hypoxia using nitroimidazole based PET tracers (eg. ¹⁸F-misonidazole, FMISO). It is also possible to use positron emitters other than ¹⁸F, but many have other problems. Carbon based tracers have the complication of a short half-life, meaning that the PET camera has to be situated in close proximity to a cyclotron as the half-life is in the order of 20 minutes. ¹¹C-Choline has found application in prostate cancer. ⁶⁸Ga DOTATATE DOTA-(Tyr³)-octreotate) or DOTANOC, (⁶⁸Ga-labelled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-NaI³- which target somatostatin receptors, have become mainstream imaging for neuroendocrine tumours.

Relatively few PET scans are performed solely for the purpose of radiotherapy planning. Much more often they are performed in the process of staging or therapy response monitoring. The advent of PET/CT and improved fusion tools in radiotherapy planning systems have vastly simplified the process of importing PET data. This presents an opportunity for radiotherapy departments to request diagnostic PET scans be performed in a radiotherapy treatment position, or at least close to it, to minimise the necessity to transform the image.² A particular problem in using PET in radiation therapy planning is the problem of edge detection. The apparent edge of the tumour varies widely depending on the contrast/window settings used in displaying the PET images. A number of approaches have been used ranging from manual delineation of the tumour boundaries by experienced clinicians to fully automated edge detection algorithms, which frequently define the edge as the contour defined by a particular percentage, say 60%, of the maximal uptake in the tumour. Such automated methods must be adapted for tumour type, location, size and PET scanner resolution and may require manual correction where the contour is rendered

incorrectly. Whatever method is chosen, it is important to standardise the methodology so that consistent results are achieved. This is particularly important in clinical trials. In practice, when delineating treatment volumes, PET is just one part of the information used and the final contour is also informed by other imaging (such as MRI and CT), and sometimes other information such as biopsy results, which may clear an equivocal node seen on other imaging.

Tumour movement can be a problem. With FDG PET the PET image is acquired over about 20 minutes, but the CT is acquired over about a minute. This tends to blur the tumour volume on PET, thus incorporating some tumour movement. This can be useful in lung treatments as there is some in-built margin for respiratory motion. Increasingly, literature demonstrates that FDG PET has a significant impact on treatment volumes. The volume treated may be smaller using PET, but in practice it often increases in size. In some situations such as in lung cancer causing distal collapse, the volume is significantly decreased.¹ PET may also be useful in adaptive planning, whereby the radiotherapy treatment is altered in response to treatment induced changes in the tumour volume. This is particularly useful in decreasing normal tissue dose, such as in head and neck treatment, or to allow intensification of the dose to a smaller volume.

Response criteria are evolving. It has been appreciated that growth in the size of a mass may not of itself represent progression. Nor may a failure of the mass to shrink represent treatment failure. Metabolic imaging with FDG PET may provide more accurate response measurements than traditional anatomic criteria such as, RECIST (Response Evaluation Criteria In Solid Tumors). For example, persistently enlarged (>1cm) cervical lymph nodes in the neck post therapy for head and neck cancer which are FDG negative, are reliably found to be benign, whereas these would be abnormal on CT criteria. The traditional RECIST criteria are being modified to take into account functional imaging.³

Specific tumour sites

Head and neck cancer

Although CT and MRI are better for delineating the extent of local tumour due to the lower resolution of PET, FDG PET has higher accuracy in head and neck cancer for nodal staging and higher sensitivity for detecting the occasional patient with distant metastases at staging.^{4,5} PET may therefore modify the radiotherapy plan or change the treatment from a curative intent to palliative. In the setting of suspected recurrence, FDG PET may facilitate radiotherapy planning as the CT and MRI may be of limited utility in the setting of post-operative anatomical change. FDG PET can assist in finding the unknown primary site in squamous carcinoma of unknown primary. Fusion with the radiotherapy planning CT may be problematic if head positioning is different during the two scans. This can be minimised by reproducing the radiotherapy planning position during PET scanning using a flat palette, standard head holders or even a mask.

Central nervous system

FDG PET has only limited application in the setting of central nervous system malignancy, for example, detecting high grade transformation in a low grade glioma) due to the high background FDG uptake in normal gray matter. PET scanning using other tracers such as ¹⁸F-DOPA (3,4-dihydroxy-6-18F-fluoro-L-phenylalanine) and ¹¹C-Methionine (MET), have the advantage that the signal to background ratio is much higher, allowing the tumour to be delineated from background cortex. Current work is exploring the use of this in radiotherapy planning. This has been explored in low grade glioma and may image the residual tumour better than MRI alone.⁶ Other PET tracers are useful in specific situations such as ⁶⁸Ga DOTOTATE, which has high affinity for meningioma.⁷

Thoracic malignancies

PET has found extensive use in radiotherapy planning of non-small cell lung cancer and this has given rise to an extensive literature. MacManus et al showed that in 22/102 patients the target volume increased and in 16 patients the volume decreased. The prospective trial showed a significant impact on survival.⁸ Other series have shown that PET decreases the inter-observer variability.⁹ A number of papers have shown high benefit in terms of delineating the volume needing to be irradiated. There has also been significant work looking at radiation response assessment. Indeed, one paper has shown that the response to radiotherapy can be predicted by PET just two weeks into a six week course of radiotherapy.¹⁰

Gastrointestinal tumours

There has been some work investigating oesophageal PET in defining the radiotherapy treatment volume. However, the situation is complicated by significant intra-lymphatic spread.¹¹ Pre-op assessment of rectal cancer treatment with nodal assessment is helpful both with MRI and with PET. MRI has the additional benefit of demonstrating tumour extension through the wall of the rectum, which is a key discriminating factor in deciding whether radiotherapy is required. PET may be helpful in pelvic nodal assessment and radiotherapy field design, but the data is not conclusive.¹ In the treatment of anal carcinoma, PET can be helpful in defining inguinal nodal involvement, decreasing the volume that needs to be irradiated and possibly the dose.^{12,13}

Other malignancies

PET has been shown to influence the radiotherapy field design in Hodgkin's disease.¹⁴ This is particularly important in the paediatric population as these patients have a long survival. PET can also be very helpful in therapy response monitoring.

Melanoma takes up FDG very readily but there is debate as to whether this changes staging.^{15,16} There is interest in defining the role of FDG in Merkel cell carcinoma, but similar to squamous cell carcinoma, there is little published evidence. Current Trans-Tasman Radiation Oncology Group studies are incorporating PET.

In the treatment of carcinoma of the cervix,¹⁷ FDG PET is under investigation; PET has considerably greater accuracy for detecting para-aortic nodal involvement than MR and CT.¹⁷ It has been shown to be useful in adaptive brachytherapy planning, however the value in external beam planning over MRI imaging remains under investigation.¹⁸

The future

Increasingly, the approaches being looked at are more sophisticated. PET has moved from being solely an imaging modality to being able to probe the pathways driving tumour growth. It is hoped that with a combination of molecular markers it may be possible to define the events which are involved in a particular patient and continue to drive the cancer to divide. Such approaches may be extremely useful in terms of defining the benefit of biologic therapy, as traditional approaches have largely failed to assist us in planning treatment.

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