To PET or not to PET: what are the indications?

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Functional imaging with positron emission tomography (PET) is playing an increasingly important role in the management of cancer patients. The most frequently used tracer is ^{18}F-fluoro-2-deoxy-glucose (FDG), which is based upon the higher rate of glucose metabolism of cancer cells. The preferential accumulation of FDG in neoplastic cells permits differentiation between benign and malignant tissue. The ability to perform whole-body imaging within one examination makes it an ideal technique to "screen" patients for cancer deposits. Interpretation of PET is, however, hampered by the lack of anatomical detail, which makes it sometimes difficult to correctly localise hot spots or differentiate tumour tissue from benign structures with physiological high FDG uptake (e.g., brown fat, gut, inflammation). These challenges are largely resolved by the introduction of the combined PET/CT scanners. Modern scanners are equipped with the latest generation multi-detector row CT scanners making it the most comprehensive diagnostic tool in oncological imaging today (one-stop shop). Because of the high cost and radiation burden of the combined modality, appropriate selection of patients, in whom the addition of PET is likely to influence patient management is mandatory.

Value of PET in staging and restaging

The impact of PET on patient management is most obvious in the detection of distant metastasis (*M-stage*). Literature data on different tumour types shows that PET detected metastatic spread in up to one third of patients, with negative or equivocal conventional imaging. The likelihood of detecting additional metastasis is highly dependent on the FDG avidity of the primary tumour. PET staging is only recommended in tumour types that are known to be routinely FDG-avid, like most carcinomas (except for prostate cancer, renal cell cancer, neuro-endocrine tumours), lymphomas (except for SLL), high-grade sarcomas and melanoma. The additional metastases found on PET are mostly localised in regions difficult to assess with CT (e.g. bones, lymph node, peritoneal spread) or localised in unusual areas (e.g. soft tissue, extremities). Integrated PET/CT proved to be better than PET alone, mainly by reducing the risk of false-positive interpretations. FDG-PET has a low sensitivity for brain metastases owing to the high glucose uptake of normal surrounding brain tissue. MRI remains the method of choice to stage the brain. Sensitivity of PET is significantly lower in small lesions and therefore PET cannot be used to exclude metastatic disease in subcentrimetric nodules, which are increasingly detected in the lungs with MDCT. While some PET images can be considered definite proof of multi-focal metastatic disease, caution is always indicated in solitary PET findings that would alter treatment management.

PET also proved to be superior to CT for nodal staging (*N-stage*) and is explained by its ability to detect tumour involvement in normal-sized nodes and exclude disease in inflammatory enlarged ones. The clinical impact of PET is best documented in the mediastinal staging of NSCLC where the high negative predictive value creates the possibility of omitting invasive staging if PET suggests the absence of LN disease. However, PET is not able to detect microscopic involvement of lymph nodes. In tumour types where this is often present (head and neck cancer, oesophageal cancer, rectal cancer, breast cancer), PET is not sensitive enough to exclude nodal involvement. In clinical practice, the high PPV will be used to upstage patients. False-positive findings, however, do occur and are related to concomitant infectious or granulomatous diseases. Clinically relevant FDG-avid nodes that would alter treatment substantially (e.g. surgery or not) should therefore be confirmed with histology.

PET in itself does not add much to the assessment of the *T-stage*, because its inferior spatial resolution does not give more detail of the exact tumour extent compared with CT or MRI. In a minority of patients, PET/CT allows a better discrimination between the tumour and surrounding (inflammatory tissue) as seen in central lung tumours with retro-obstructive atelectasis or pneumonia). Since the amount of FDG uptake in a tumour is related to the proliferation rate and grade of hypoxia, which are factors associated with more aggressive behaviour, FDG uptake in

the primary tumour (often expressed as SUV) is reported to have additional prognostic information apart from pathological TNM stage in many tumour types. Whether baseline SUV uptake could be of use to guide further treatment remains to be proven. Translation of literature data into clinical practice is hampered by the fact that PET imaging is not yet standardised and using threshold values to define a more aggressive tumour type is centre-dependent.

Since PET is not hampered by anatomical distortions seen after surgery or radiotherapy, PET proved to be more accurate in detecting *residual or recurrent disease after treatment*. PET/CT is the modality of choice in evaluating residual disease at the end of treatment in high-grade non-Hodgkin's lymphoma and Hodgkin's disease, and this is incorporated into the new response criteria proposed by the International Harmonisation Project.

Most studies in recurrent disease focus on patients with suspected recurrence (rising tumour markers, residual masses). Literature data on the routine use of PET in follow-up is scarce. Most experience is gained in lymphoma and many of these studies report an unacceptable high false-positive rate. Therefore, it is recommended to perform PET only in high-risk patients.

Value of PET in radiotherapy planning

Improvements in radiotherapy techniques make it possible to deliver radiation therapy with a steep fall-off gradient and thus limit the volume of normal tissues irradiated. This could improve the therapeutic index and allow dose escalation or combined chemoradiation treatment to improve tumour control. Accurate target delineation is crucial in this setting. CT has been the most extensively used imaging modality in radiation therapy; however, the aforementioned limitations in the detection of tumours will also limit the efficacy of CT-based radiation therapy planning (RTP). Intrinsically co-registered anatomical and biological images obtained with PET/CT may provide ideal information for optimising RTP.

Current literature reports on theoretical RTP based on PET/CT data (only PET-positive nodes are included in GTV) compared with CT data. This strategy modifies radiation treatment fields in a substantial number of patients with reduction of geographical misses (in case the PET-based treatment field is larger than the CT-based one) and reduction of normal tissue irradiation (in cases of smaller fields). An additional significant benefit derived from the inclusion of functional images is a decrease in inter-observer variability in the definition of tumour contours by radiation oncologists. To use PET/CT images for RTP the patient must be imaged in the same position as was used for treatment delivery. This is done using a flat panel table top insert on which the immobilisation devices can be attached.

Value of PET for treatment response assessment

Response to cancer treatment is evaluated by subsequent assessments of target lesions and is defined as a significant decrease in measurable tumour dimensions (RECIST). The new targeted therapeutics that cause cytostasis rather than cytotoxicity, have challenged volume-based response criteria and tumour regression is increasingly recognised as an unreliable endpoint. New imaging modalities looking at tumour biology, like positron emission tomography (PET), are increasingly used to identify a subpopulation of patients most likely to respond.

Most experience is gained with FDG, which is closely related to the number of viable cells and their proliferation capacity. Data suggest that FDG-PET may be used as a sensitive test to assess the activity of new cytotoxic agents in phase II studies or identify non-responding tumours early and so provide the opportunity to adjust treatment regimens according to the individual chemosensitivity of the tumour tissue. However, further prospective and randomised validation of PET is still required before PET-controlled chemotherapy can be used in clinical practice. However, translating the PET literature on quantitative response evaluation into clinical practice is not trivial. Definition of standard response criteria for PET are still lacking. In part this relates to the prevailing heterogeneity of PET methodology and interpretations, but also to clinical interventions and endpoints applied in different trials. Therefore, there is a need for larger randomised trials providing more robust thresholds of responsiveness.

While FDG has paved the way for PET in clinical oncology, other radiopharmaceuticals are available to study processes such as blood flow (0–15 water), angiogenesis (integrins), proliferation (F18-FLT), apoptosis and hypoxia. Imaging of molecular pathway alterations will therefore become increasingly important in assessing the efficacy of these targeted drugs.

Conflict of interest statement

The author has no conflict of interest to report.