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PET/CT in oncology: for which tumours is it the reference standard?

Conor D. Collins

St. Vincent's University Hospital, Dublin, Ireland

Corresponding address: St. Vincent's University Hospital, Dublin 4, Ireland.
Email: c.collins@st-vincents.ie

Abstract

Positron emission tomography (PET)/computed tomography (CT) has a growing role in the imaging of many cancers. As our experience has grown over the past number of years so has our understanding for which cancers it is particularly useful. The value of PET/CT at each stage of the cancer journey is different for each cancer. This review attempts to tease out the role of PET/CT in the common cancers with particular emphasis on where it is the imaging investigation of choice.

Keywords: *PET/CT; Oncology.*

Introduction

The ability to visualise metabolic activity using the glucose analogue [^{18}F]fluorodeoxyglucose (FDG) and positron emission technology (PET) has revolutionised the imaging of cancer over the past 15 years. Combining computed tomography (CT) scan imaging with positron emission tomography (PET) imaging as an integrated examination (PET/CT) has brought extra benefits by way of accurate anatomical localisation, shorter examination time (average 30 min), improved patient comfort and convenience, higher patient throughout and lower cost per patient. Accurate registration of the anatomical and functional data has allowed an increasing role for PET/CT at different points of the cancer journey – diagnosis, staging, prognosis, treatment planning, assessment of treatment response and diagnosis of recurrence. Integrated PET/CT allows separation of physiological from pathological FDG uptake resulting in a reduction of false positive and false negative studies.

PET/CT protocols are still being evaluated and issues that require careful consideration include the necessity or otherwise for respiratory gating, use of intravenous and oral contrast media, CT operating parameters, PET scanning time and optimum injected dose of FDG[1,2]. In the absence of respiratory gating a good match is found if the CT image is acquired with partial or full expiration and the PET image with shallow breathing. Whilst dilute oral contrast material is now often administered routinely for PET/CT, this is not so with intravenous (IV) contrast agents. As FDG is much better for characterisation, the main reason to use IV contrast is improved vessel delineation. Preferably this should be administered in such a way as to visualise well the necessary area with the remainder of the PET/CT scan being acquired in the conventional manner. Use of IV contrast in PET/CT has only a minimum effect on attenuation but if contrast enhanced pixels are misidentified, artefacts may be generated on the PET image. Experience using IV contrast to date has shown that it does not generally cause a problem that could potentially interfere with the diagnostic value of PET/CT[3]. Oral contrast enables visualisation of the gastrointestinal tract although the distribution can be variable. Strategies have been developed to minimise or eliminate problems due to both IV and oral contrast[4]. Artefacts induced by CT based attenuation correction (contrast media, pacemakers, chemotherapy ports, prostheses, dental hardware, heavily calcified lymph nodes) can hinder image interpretation and the non-attenuated correction should be checked if this is suspected[5,6]. At present the majority of patients who undergo a PET/CT scan have already undergone an

1470-7330/07/000077 + 11

initial diagnostic CT scan – further advances in PET/CT using protocols incorporating IV contrast should make it possible to answer all pertinent questions in one examination.

A number of studies have been performed evaluating the general performance of PET/CT since 2001. A study comparing PET/CT with PET alone in 53 patients with various malignancies or possible malignancy found an improvement in accuracy from 90% to 98% with a decrease of 50% in equivocal abnormalities[7]. A study evaluating 204 patients with 586 suspicious sites of cancer found that PET/CT images offered extra information separate from PET and CT images in 49% of patients and 30% of sites with PET/CT contributing to improved patient care in 14% of patients[8]. A study of 91 patients and 190 suspected sites of disease found that combined PET/CT was of value in establishing the correct relationship between CT and FDG in 52% of sites[9]. A study comparing PET with PET/CT demonstrated a decrease in the level of uncertainty from 15.3% to 3.4%[10]. A prospective study comparing PET/CT with magnetic resonance imaging (MRI) in 98 patients showed PET/CT to be more accurate for overall TNM (99% vs 54%), T stage (80% vs 52%) and N stage (93% vs 73%), with both techniques equal for the assessment of M stage[11].

The most beneficial effect of having the CT data is that it frequently adds specificity to the PET data[7,12]. In some situations such as when disseminated pulmonary metastases are too small to be seen on PET, CT is also able to increase the sensitivity of the PET/CT examination. However, FDG-PET data also helps to specify CT findings such as lymph nodes with an equivocal appearance.

Against this background of published literature and based on clinical experience in a practice that has performed over 6000 examinations to date, the current role for PET/CT in the common cancers is outlined below.

Common cancers

Non small cell lung cancer (NSCLC)

Characterisation of the solitary pulmonary nodule using FDG-PET/CT has a high accuracy (90%) with visual interpretation sufficient for diagnosis and quantitative analysis adding little extra[13]. Focal chest wall infiltration, mediastinal invasion and differentiation of tumour from atelectasis are improved with PET/CT[14]. The most significant improvement in results with integrated PET/CT compared with PET alone relates to T staging where an accuracy rate of 97% compared with 67% has been demonstrated[15]. Whilst there is little difference between PET/CT and PET in accurately staging thoracic nodes, the overall benefit appears to lie in a moderate increase in specificity. PET/CT has a role in selecting patients for mediastinoscopy because of its high negative predictive value (80%) for nodal disease although it must be remembered that mediastinoscopy remains the gold standard[16]. Invasive procedures can be omitted in patients with peripheral tumours and negative PET scans. If the PET/CT scan is positive for mediastinal disease histological confirmation is required. For M staging an important role for PET/CT is the detection of unsuspected metastases. PET/CT appears to offer superior overall staging compared with CT and PET individually in the detection of extrathoracic metastases with the exact localisation provided by PET/CT being particularly advantageous[14].

The ability of FDG imaging to assess prognosis in NSCLC has been assessed in several studies[17–19]. In the largest published study involving 315 patients a maximum standardised uptake value (SUV_{max} of ≥ 10) was found to be a significant prognostic factor for disease free survival and overall survival ($p < 0.001$)[19]. The study by Sasaki evaluated 162 patients with Stage I–IIIB NSCLC. Each patient had a PET scan before either surgery or radical radiotherapy. The standardised uptake value (SUV) of the primary tumour was determined and a cut-off of 5.0 was found to be a significant prognostic factor for overall survival ($p = 0.03$) and disease free survival ($p = 0.001$)[18].

PET/CT also plays an important role in the planning of radiation treatment where a major problem exists distinguishing active tumour from atelectasis[20]. PET has a considerable effect on the decision making process prior to radiation therapy and in one study was responsible for a change in planning volumes in 14/24 patients[21]. Decreases in the target volumes in the patients with atelectasis led to decreases in tissue toxicity parameters. The treatment changes include alteration of the radiation dose, prevention of inappropriate radiation therapy and a change in intent in terms of curative versus palliative radiation therapy. Key questions remain regarding the influence of PET/CT on the planning treatment volume with regard to early recurrence and overall survival. The answers require outcome studies which are not yet currently available.

PET/CT is not without its pitfalls[22]. Physiological uptake can occur at multiple sites and active inflammation from sarcoid, infection, recent surgery and radiation. Although FDG is sensitive it lacks specificity after therapy because of its accumulation in irradiated tissues and post-surgical inflammatory changes. Timing of the examination and accurate clinical details are therefore important. In the treated patient particularly when there is distorted anatomy, PET/CT is extremely useful. In a study involving 42 patients with suspected recurrence, PET/CT demonstrated a sensitivity of 96%, specificity 82%, positive predictive value 89% and a negative predictive value 93% with a change in management in 15 patients (29%)[23]. Most of the post-surgical inflammatory FDG uptake resolves in 6–8 weeks. Evaluation of disease status is generally not possible in the setting of radiation pneumonitis. As a result patients are not

re-evaluated for 3 months after their last treatment. However, the inflammatory effects of radiation can last more than a year[24,25].

Despite the undoubted accuracy of PET/CT important underlying questions remain: is it cost-effective and what is its impact on patient survival? Several economic analyses have demonstrated its cost-effectiveness in reducing needless thoracotomies and in being selective regarding mediastinoscopy[26–29]. A recently published study using FDG-PET with advanced stage III NSCLC demonstrated significantly increased overall survival and disease-free survival in patients stratified by PET for neoadjuvant radiochemotherapy[30,31]. Another significant factor for survival was complete tumour resection[30]. Whilst not a perfect examination PET/CT will play an increasingly pivotal role in the non-invasive assessment of this tumour[32].

Colorectal cancer

Established roles of FDG-PET and PET/CT in patients with colorectal cancer are restaging of patients with locally recurrent disease, exclusion of disease elsewhere in patients undergoing surgical resection of hepatic or pulmonary metastases, characterisation of equivocal lesions detected by conventional imaging and identification of the site of recurrence in patients with elevated serum carcinoembryonic antigen (CEA)[33–35].

Physiological uptake can sometimes cause difficulties with scan interpretation though this is much less of a problem with PET/CT when oral contrast has been administered. Nonetheless, it has to be remembered that inflammatory bowel disease, diverticulitis, physiological uptake in colonic mucosa, lymphoid tissue and smooth muscle are all non-malignant causes of increased FDG uptake in the bowel. The CT component is very useful in confirming the presence of FDG within the ureter, urinary bladder abnormalities, physiologically active ovaries and muscle such as the anal sphincter. Often the pattern of uptake with such benign causes is widespread or segmental, unlike the focal uptake of FDG present in malignancy[36].

A large study assessing 3210 aymptomatic individuals using FDG-PET (as a screening technique) found a premalignant or malignant colorectal tumour in 20 patients[37]. Despite the high reported sensitivity, lesions <0.7 cm could not be accurately detected. As a result PET/CT is not recommended for routine screening or diagnosis as it neither efficacious nor cost-effective.

If the primary tumour mass is bulky small adjacent lymph nodes may not be resolved as separate structures on PET images[38]. A particular advantage of CT is that it can often identify small lymph nodes adjacent to the primary tumour even though it is unable to identify any micrometastases. MRI is the preferred technique for identification of mesorectal infiltration[39,40].

In a study comparing PET/CT with PET alone in 45 patients, it was found that PET/CT resulted in a 50% reduction in equivocal or probable lesions and increases in definite locations by 25%[41]. Overall correct staging increased from 78% to 89%. More recently, a prospective study using PET/CT colongraphy in 14 patients demonstrated accurate identification of the primary tumour in 13/14 patients and accurate lymph node staging in 9/11 patients with six extracolonic sites of disease also detected[42].

Approximately one-third of patients with newly diagnosed colorectal cancer will develop hepatic metastases. A meta-analysis comparing CT, MRI and FDG-PET ($>$3000 patients, 61 studies) concluded that PET had a significantly higher sensitivity than both other modalities on a per patient basis[43]. A study comparing contrast enhanced CT and PET/CT in 76 patients concluded that there was little difference with sensitivities of 95% and 91% respectively[44]. A recently published paper indicates that the routine use of FDG-PET (and by inference PET/CT) in preoperative assessment of liver metastases from colorectal cancer can be justified using evidence based methods[45].

Following surgery and radiation therapy it can be very difficult to differentiate post-treatment changes from residual or recurrent tumour. Local recurrence of rectal cancer develops in approximately one-third of patients undergoing curative resection and early diagnosis is essential. In a study of 51 patients PET/CT was able to exclude active disease by its ability to accurately localise foci of increased FDG uptake to displaced normal organs[46]. PET/CT had an accuracy of 88% for the diagnosis of recurrent colorectal cancer compared with 71% for PET. In an additional study, PET/CT demonstrated a sensitivity of 89%, specificity 92% and accuracy of 90% for recurrent colorectal cancer in the abdomen, liver and extra-abdominal sites[47]. For patients with previous hepatic surgery, PET/CT proved superior to contrast enhanced CT at the site of surgery or in close proximity with a specificity of 100% (compared with 50% for contrast enhanced CT)[44]. PET/CT was also superior for the detection of extrahepatic dissemination with a sensitivity of 89% compared with 64% for CT with a 21% change in therapeutic strategy on the basis of the additional PET/CT findings[44].

PET and PET/CT have also proved to be helpful in patients who have undergone radiofrequency ablation for hepatic metastases[48,49]. These patients often have serial anatomical imaging whereas metabolic imaging has proved to be helpful in detecting recurrence earlier. One small study examining 16 hepatic metastases reported a sensitivity of 65% for both PET and PET/CT compared with CT alone (44%) in patients who had undergone radiofrequency ablation[50].

Lymphoma

Detailed discussions on the role of PET and PET/CT in lymphoma are published elsewhere[51,52]. Lymphomas are

a group of diseases broadly subdivided into Hodgkin's (HL) and non-Hodgkin's lymphomas (NHL), each of which is associated with different presentations, outcomes and therapies. NHL is more common than HL by a ratio of approximately 6:1 and has been increasing in incidence over the past 40 years[53,54]. HL tends to spread in a contiguous fashion from one lymph node group to the next adjacent group. NHL is a disseminated disease involving lymph node groups haphazardly and multiple organs may be involved as well as the bone marrow. Identification of disease in extranodal sites has an adverse effect on prognosis[55]. Whole body imaging is therefore important for accurate staging as this determines management.

The staging system for HL is based on the Cotswold classification[56]. This is of less value in NHL as the prognosis is more dependent on histological grade and other parameters such as tumour bulk and specific organ involvement than on stage[57]. On the basis of encouraging initial studies FDG-PET has been evaluated extensively in staging, therapy monitoring and surveillance in patients with lymphoma. PET/CT is replacing conventional CT for staging and therapy monitoring except in those where PET is suboptimal (e.g. diabetes). Results to date using PET/CT indicate that it is superior to PET or CT alone[58–61]. In the study by Schaefer *et al.*[58] involving 60 patients (42 HL, 18 high-grade NHL) the sensitivity and specificity for lymph node involvement was 94% and 100% for PET/CT compared with 88% and 86% for contrast enhanced CT. For organ involvement, the sensitivity and specificity was 88% and 100% for PET/CT compared with 50% and 90% for contrast enhanced CT[58]. Although PET/CT performed well for exclusion of disease, histological verification was available in only a small number of patients. Other studies with 73 patients and 27 patients demonstrated a significant improvement for PET/CT ($p = 0.03$ and 0.02 respectively)[4,59]. The study by Hutchings *et al.* (99 patients) also confirmed the superiority of PET/CT but is the first to demonstrate that caution is required if treatment is to be based exclusively on PET/CT. This study demonstrated upstaging by PET/CT in 10 patients but only disease progression in one (median follow-up 24 months) indicating that more intensive therapy would not have been necessary[61].

Studies using semi-quantitative measures such as standardised uptake value (SUV) or differential uptake ratio (DUR) have demonstrated that aggressive lymphomas tend to have higher FDG uptake than indolent histologies. Okada *et al.*[62] showed in a study of 34 patients that lymphomas which were aggressive and resistant to treatment tended to show high uptake of FDG and decreased survival. More recently, Schoder *et al.*[63] demonstrated that patients with SUV >10 have a high likelihood of aggressive NHL. However, it is worth noting that considerable overlap in SUVs exists in indolent and aggressive NHL in many of the studies with the SUV being determined from the site with the most intense uptake rather than all sites of disease[63–65]. Nonetheless, it is possible to conclude that patients with an SUV ≥ 13 at the site of most intense uptake indicates a high probability of aggressive histology while an SUV ≤ 6 is very likely associated with indolent histology[63,66].

FDG-PET is the best non-invasive imaging technique for assessing treatment response[67]. However, FDG is not a perfect indicator of response as it can be influenced by tumour biology, tumour burden at diagnosis, dose and type of chemotherapy regime in addition to the timing of the scan post-therapy[68,69]. In the largest study comprising 90 patients the probability of complete remission at the end of treatment was 58% if PET remained positive compared with 83% if PET was negative[70]. Analysing the data from 17 end-of-treatment studies revealed a sensitivity for PET imaging for the detection of residual disease of 76%, specificity 94%, a positive predictive value of 82%, negative predictive value of 92% and an overall accuracy of 89%[68]. Zijlstra *et al.*[71] performed a meta-analysis of the reported sensitivity and specificity of relevant studies up to 2004. They reported a pooled sensitivity and specificity for detection of residual disease in Hodgkin's disease of 84% and 90% respectively. For NHL, pooled sensitivity and specificity were 72% and 100% respectively. A negative PET scan does not exclude minimal residual disease leading later to a clinical relapse[72].

Several studies have shown that FDG-PET during or after reinduction chemotherapy has an important prognostic role in the pretransplanation evaluation of patients with lymphoma[73–77]. For patients undergoing allogeneic stem cell transplantation PET has been shown to have a role in monitoring response to adoptive immunotherapy and deciding on further donor lymphocyte infusions[78].

There are five categories in the standardised criteria for response assessment proposed by Cheson *et al.*[79]. Juweid *et al.*[66] showed that a response classification based on integration of FDG-PET with International Workshop Classification (IWC) would provide a more accurate response assessment than IWC alone. Combining IWC and PET provided a statistically significant indicator for progression free survival ($p = 0.008$). The use of PET imaging in this manner is likely to make the CRu category redundant.

The desire to instigate an early change in therapy in non-responders arose from a belief that this improved outcome. Spaepen *et al.*[80] evaluated 70 patients with aggressive NHL after 3–4 cycles of therapy and demonstrated that none of 33 patients with abnormal PET imaging achieved a durable complete response whereas 31/37 with a normal PET scan remained in complete response (median follow-up 1107 days). There was a statistically significant association between PET and progression free survival and overall survival ($p < 0.00001$). A recent study evaluated 90 patients with aggressive

NHL prospectively prior to chemotherapy, at the end of the second cycle and following completion. After completion 83% of patients who were PET negative after two cycles achieved a complete response compared with only 58% of PET positive patients. Outcome also differed significantly with the two year estimates of event free survival being 83% compared with 43% ($p<0.001$) and an overall survival of 90% compared with 61% ($p=0.006$) [70]. In the largest prospective multicentre evaluation to date PET was able to predict treatment outcome correctly after only two cycles of chemo in 103/108 (95%) patients with Hodgkin's disease[81]. A further study using 77 patients with Hodgkin's disease (median follow-up 23 months) showed that a positive PET after two cycles of chemotherapy was associated with reduced progression free survival ($p<0.001$) and overall survival ($p<0.01$)[82]. However, despite these encouraging results the most recently issued guidelines recommended that use of PET in this manner should only be done in a clinical trial or as part of a prospective registry[83].

A pilot study by Jerusalem *et al.*[67] involving 36 patients with treated HL underwent PET imaging every 4–6 months for 2–3 years. Identification of active residual or relapsed disease was possible up to 9 months prior to confirmation by conventional imaging or biopsy. This allows early commencement of salvage therapy but a high incidence of false positive results was also recorded (17%). A more recent analysis of data from this group concerning patients with NHL have proved disappointing. Careful attention to patient's history and physical examination with particular regard to those at high risk of relapse remain the best course of action[66,84].

Oesophagus

PET/CT has resolved many of the interpretation difficulties formerly associated with PET: paraoesophageal brown fat, asymmetric uptake in the vocal cords and atherosclerotic disease in the aorta and great vessels[85–88]. Reflux and radiation-induced oesophagitis have been described in the PET and PET/CT literature[89–91]. Well differentiated adenocarcinoma may result in little or no FDG uptake (approx. 20% of cases)[92,93].

The role of PET/CT in the staging of disease is to assess for the presence of distant metatases. Kato *et al.*[94] evaluated 149 patients for the potential incremental value of PET over CT and found that with regard to staging, PET had an overall 14% incremental value over CT[94]. They also reported a low sensitivity for regional lymph node detection (32%) confirming results from earlier studies which demonstrated sensitivities in the order of 41–45%[92,93]. A prospective study of 74 patients showed PET having a sensitivity of only 33% compared with 81% for endoscopic ultrasound[95]. Despite the reported low sensitivities, uptake within visualised loco-regional nodes is likely to represent malignant disease[93–95]. PET/CT has a reported incremental value over PET alone in 25/115 sites (22%) and offered increased confidence and improved lesion localisation in 15% patients[96]. This resulted in a change of management in 10% of patients. PET/CT also demonstrated improved specificity and accuracy over PET alone for the detection of sites of oesophageal cancer. PET has been shown to be the most accurate method of detecting distant metastatic disease[93,97].

The ability of PET/CT to accurately define the craniocaudal extent of disease indicates that it has a role in radiotherapy planning. One study analysing the effect of PET on CT planning of oesophageal tumours demonstrated that PET upstaged 8/21 patients by revealing metastatic or nodal disease[98]. Other studies have indicated that PET and endoscopic ultrasound may be beneficial in determining gross tumour volume[99]. Another study, however, demonstrated mismatch between a negative PET scan and visible tumour on CT or endoscopic ultrasound introducing a cautionary note that treatment volume should not be determined on the basis of PET imaging alone[100].

The role of PET/CT in the assessment of response to neoadjuvant chemotherapy was recently reported to be equal to endoscopic ultrasound with fine needle aspiration (80% for both) and superior to that of CT[101]. PET/CT was also more accurate than both CT and endoscopic ultrasound (with FNA) (93% vs 78% and 78% respectively) with regard to differentiating T4 from T1–T3 status as well as more accurate in predicting complete response to therapy. Earlier work had shown that a reduction in FDG uptake correlated with tumour response histologically. In addition, patients with no response on PET imaging had a significantly worse survival than responders[102].

Care must be taken regarding the timing of the examination post-therapy in order to keep false positives to a minimum[91,90]. In one study, PET has been shown to have 100% sensitivity and 57% specificity for detection of local recurrence, 92% sensitivity and 83% specificity for detection of regional disease recurrence and 95% sensitivity and 80% specificity for detection of distant disease[103]. FDG also has prognostic value. Swisher *et al.*[104] found a standardised uptake value >4 to be an independent predictor of survival in a study of 103 patients.

Head and neck

Head and neck tumours are FDG avid, particularly squamous cell tumours (SCC) which make up the majority of cancers in this region. The use of PET/CT has reduced many of the difficulties encountered previously with PET making uptake in brown fat, neck muscles and physiological uptake elsewhere more confidently identified.

A recent study highlighted the value of PET/CT in 65 patients by demonstrating an overall sensitivity of 98%, specificity of 92% and accuracy of 94% ($p < 0.05$)[105]. That study also confirmed the improved confidence associated with PET/CT by the low number of equivocal abnormalities compared with CT and PET separately. In another study involving 157 sites of disease, PET/CT was more accurate than PET alone (96% vs 90%) and enabled 53% of equivocal abnormalities to be classified more confidently[106].

PET/CT substantially increases interobserver agreement and confidence levels in localisation of malignant disease for staging of SCC[107]. It may also be helpful in delineating perineural spread of disease and can show osseous extension of the primary tumour both of which influence management[108]. In addition, PET/CT allows for accurate characterisation and localisation of abnormalities identified elsewhere[109,110]. Some studies have suggested an important role for PET/CT in radiotherapy planning[111–114].

PET/CT has a high sensitivity and specificity in the detection of residual or recurrent disease. Various studies have reported a sensitivity range of 88–100% and specificity range of 75–100% at the primary site and for nodal recurrence[115–118]. The accurate anatomical localisation available with PET/CT is particularly advantageous in this clinical scenario. Accuracy is greatest if the examination is performed 12 weeks or more following completion of radiotherapy[119]. No formal study regarding prognosis has been published using PET/CT but in a study comprising 143 patients the relapse free survival was directly related to the SUV value[116].

Patients with SCC with no mucosal primary tumour identified represent 1–5% of all patients in whom SCC is diagnosed. Preliminary results with PET/CT suggest it may offer a slight increase in overall sensitivity for detection of unknown primary tumours but may be more useful in identifying a site suitable for biopsy[120]. Previous work using FDG-PET in this clinical scenario resulted in the identification of a primary site in 47% of patients with involved cervical nodes and no evidence of a primary tumour on conventional imaging[121]. False positive results may arise due to active infection and/or prior surgical interventions (including biopsy).

Breast

Despite some promising early data with FDG, a study involving 144 patients found that almost 40% of primary breast tumours <2 cm were not visualised on PET imaging[122]. However, FDG has a high positive predictive value so incidental focal increased uptake should be considered suspicious for malignant disease[123]. A recent study showed that MRI is more sensitive than PET/CT in the detection of breast cancer but PET/CT changed management in 6/21 patients by revealing metastatic disease[124].

Prognosis in breast cancer is determined by nodal status and the inability of FDG-PET to identify micrometastases within axillary nodes means that it acts as a complementary investigation to sentinel node imaging[125,126]. In a study comprising 167 patients the overall accuracy of FDG-PET for nodal staging was 90%[127]. In the largest prospective multi-centre study involving 360 patients, a sensitivity of 61% and specificity of 80% was reported[128]. Another study involving 165 patients reported a sensitivity of 28% and specificity of 86%[78]. To date, only one small study (15 patients) has been reported using PET/CT for axillary nodal staging which demonstrated a sensitivity of 80%, specificity of 90% and accuracy of 87%[129]. There is no published paper on PET/CT in assessing prognosis but earlier work using FDG-PET suggested that relapse-free survival was directly related to the SUV[130].

FDG-PET has been shown to be very useful in helping to identify unsuspected metastases in internal mammary nodes and distant sites. One early study demonstrated that FDG-PET identified extra-axillary metastases in 29% of patients[131]. Various groups have reported on the ability of PET to demonstrate unsuspected disease or help confirm equivocal lesions[123,132]. In a study involving 73 patients, ten had unsuspected disease in the mediastinum or internal mammary lymph nodes[133]. Assessment of internal mammary nodal status is controversial but up to 25% of patients with breast cancer may have involved internal mammary nodes at the time of presentation resulting in impaired survival[134].

For restaging, various studies have demonstrated a very high sensitivity (92–100%) but a lower specificity (72–82%)[135–137]. Some of the decreased specificity is related to the timing of the examination, others due to false positive uptake at various sites[138]. A study using PET/CT in 46 patients with recurrent disease showed higher sensitivity (85 vs 70%), specificity (76 vs 47%) and accuracy (81 vs 59%) for PET/CT compared with contrast enhanced CT[139]. This study also demonstrated an impact in management occurring in 51% supporting earlier work with FDG-PET[140,141]. There is as yet no report on the role of PET/CT in brachial plexopathy but earlier work demonstrated the value of combining FDG-PET with MRI[142].

No study has yet been published using PET/CT to assess response to therapy although the data from FDG-PET studies is encouraging. In one study, all patients who were found to have a pathological response had a marked reduction in FDG uptake at the time of the second scan[143]. A more recent study demonstrated that for the pathological responders the reduction in SUV was significantly different between complete, partial and non-responders[144]. Likewise, there has been no published data yet on the role of PET/CT in planning radiation treatment although this is likely to show similar advantages as in other tumours[20].

Melanoma

Although the primary tumours are often seen on FDG-PET and PET/CT images, this examination is not routinely used to evaluate the T stage of primary melanoma.

Patients with depth of melanoma <1.5 mm are not routinely imaged due to a low risk of metastatic disease and inability of PET and PET/CT to depict micrometastases. A study in which patients with lower stage disease were evaluated showed the sensitivity of PET to be only 17% indicating that such patients are more appropriately assessed with sentinel node imaging[145]. Due to the resolution of PET scanners, nodal metastases <5 mm are unlikely to be visualised. A recent study involving 83 patients does not support the use of PET/CT in patients undergoing sentinel lymph node biopsy with a reported positive predictive value of 24% and negative predictive value of 76% for nodal metastases[146].

For melanoma patients with a high risk of disease (stage III, IV), PET has been shown to be useful with a sensitivity of 94%, specificity 83% compared with 55% and 84% for CT[147,148]. A literature review demonstrated a sensitivity of 92% and specificity of 90% for the detection of metastatic disease[149]. A prospective study comparing PET/CT with whole-body MRI in advanced malignant melanoma in 420 lesions demonstrated an overall accuracy of 87% for PET/CT versus 79% for whole-body MRI[150]. PET/CT was significantly better in nodal staging, skin and subcutaneous metastases. Whole-body MRI was more sensitive in detecting hepatic, bone and brain metastases. They proposed that whole body staging in advanced malignant melanoma is most accurate when PET/CT is used in conjunction with whole body MRI. Integrated PET/CT offers a significant benefit in lesion localisation and an improvement in lesion characterisation compared with PET alone or side by side PET and CT. Another recently published study involving 127 consecutive patients demonstrated that PET/CT had a sensitivity of 91%, specificity of 94%, positive predictive value of 96% and negative predictive value of 87%[151].

Patients with stage III and stage IV disease require routine follow-up with PET or PET/CT. Various studies have shown sensitivities of 85–92% and specificities of 90–94% for PET compared with 57–81% ad 45–87% for conventional imaging[152,153]. No large studies have yet been published on the utility or added benefit of PET/CT although there are reports of PET/CT aiding in the localisation and diagnosis of disease[110,154,155]. In the diagnosis of relapsed melanoma, several studies have shown FDG-PET to have sensitivity, specificity and accuracy of 70–100%[156]. FDG-PET is particularly useful for detecting soft tissue and lymph node metastases. Most lesions missed by PET are usually <1 cm in diameter and are either pulmonary, hepatic or brain metastases (which are better visualised by CT or MRI).

Conclusion

There is a growing body of literature confirming the pivotal role of PET/CT at various points in the cancer journey although its influence is not the same at each point in every cancer. Integrated PET/CT is superior to both PET and CT acquired separately, whether viewed together side by side or alone. Protocols regarding the use of intravenous contrast remain to be clarified. A particular challenge for the future is the development of readily available tracers which are more specific than FDG. Progress in this area will further consolidate the role of PET/CT as the reference standard in oncoradiology.

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