The value of positron emission tomography (PET) imaging in disease staging and therapy assessment

G. Jerusalem¹, R. Hustinx², Y. Beguin¹ & G. Fillet¹

¹Department of Medicine, Division of Medical Oncology and Hematology; ²Department of Medicine, Division of Nuclear Medicine, University of Liège, Liège, Belgium

Introduction

Computed tomography (CT) and magnetic resonance imaging (MRI) have had an immense impact on the practice of oncology. These techniques give information about structural or anatomical abnormalities helping to differentiate malignant from benign lesions and defining the stage of tumors. Based on the extent of tumor and the localization of normal structures, such as vessels and nerves, the surgical approach is planned as indicated. In contrast to these conventional radiological techniques, positron emission tomography (PET) is able to quantitatively assess biochemical and physiological processes in vivo. Biochemical processes are altered in virtually all stages of disease and these alterations usually precede anatomical changes. Radiolabeled agents can produce images and quantitative indexes of tumor blood flow and perfusion, metabolism, proliferative activity, hypoxia and tumor cell receptor characteristics. The use of fluorodeoxyglucose (FDG) for in vivo cancer imaging is based on the observation of enhanced glycolysis in tumor cells. Increased glycolysis is one of the most distinctive biochemical features of malignant cells, resulting from the amplification of the glucose transporter protein at the tumor cell surface as well as from activity of hexokinase [1]. Like glucose, fluorine-18-FDG (¹⁸F-FDG) is transported into cells by a glucose transporter protein and rapidly converted into ¹⁸F-FDG-6-phosphate. As the latter is not a substrate for glucose-6-phosphate isomerase, it is biochemically trapped in metabolizing tissues [2]. Other tracers designed to evaluate amino acid uptake (carbon-11 methionine), protein synthesis (carbon-11 tyrosine) or DNA synthesis and proliferation (carbon-11 thymidine and fluor-18 fluorodeoxyuridine) have been proposed as tumor imaging agents. While theoretically attractive, they are more difficult to produce and usually do not provide the same image contrast as ¹⁸F-FDG (with the notable exception of carbon-11 methionine for brain tumors). ¹⁸F-FDG can be efficiently radiolabeled by an automated method and its longer half-life (110 min compared to 20 min for carbon-11) allows distribution of the tracer to nuclear medicine departments without an on-site cyclotron.

The aim of this article is to examine whether whole body PET using ¹⁸F-FDG can already be considered as a necessary tool in the day-to-day practice of oncology. Based on current knowledge, we will define the important questions to be answered in the near future in diagnostic oncology. The value of PET in translational research is also very important but is beyond the scope of the present work.

Results of PET in diagnostic oncology

Diagnosis of pulmonary nodules and mass lesions

A recent meta-analysis that included 40 studies showed that PET using ¹⁸F-FDG is an accurate non-invasive imaging test for the diagnosis of pulmonary nodules and large mass lesions, although few data exist for nodules <1 cm in diameter [3]. The sensitivity and specificity of PET for the detection of 1474 focal pulmonary lesions of any size were 96.8% and 77.8%, respectively. However, the authors pointed out the poor quality of the methodology used in the majority of these studies. Sample sizes were small and blinding was often incomplete. Currently, PET is generally used after more easily obtainable tests, such as CT, have been carried out. Positron emission tomography is only indicated in patients who will have strategy planned according to PET results, i.e. either immediate thoracotomy or close follow-up. Lesions <0.6 cm are unlikely to be detected [4]. A false negative PET can be observed in some histological subtypes such as bronchoalveolar [5] and carcinoid [6] tumors (Figure 1). False-positive findings are frequently related to inflammatory or infectious processes (tuberculosis, cryptococcosis, histoplasmosis, aspergillosis, ...) [7]. Besides diagnostic accuracy, clinical outcomes and costs also have to be considered. Medicare reimbursement for PET imaging is more than three times higher than for CT-guided needle biopsy [3]. Using a decision tree sensitivity analysis, Gambhir et al. [8] suggested that the most cost-effective approach is combining CT and PET and proceeding to biopsy or surgery only for lesions that are positive on PET. Thereby, cost savings can be achieved through the avoidance of unnecessary thoracotomy.

Staging of non-small cell lung cancer (NSCLC)

The use of more accurate diagnostic techniques promises to reduce excess mortality, morbidity and cost associated with
futile procedures on the one hand, and missed therapeutic opportunities on the other. Based on the available literature, we can reasonably conclude that the use of PET leads to more accurate staging of lung cancer [9]. The meta-analysis performed by Dwamena et al. [10] showed sensitivities of 79% and 60%, and specificity of 91% and 77% for PET and CT, respectively. Models predict that the addition of 18F-FDG PET to the preoperative work-up of patients with negative mediastinal CT scans could prevent about one ‘futile’ thoracotomy for every 10 scans [9]. Using a decision tree sensitivity analysis, several groups suggested potential cost savings by adding PET to conventional staging procedures [11–14]. Unfortunately, the published data on the direct impact of PET on patient management and cost savings represent the potential rather than the actual clinical impact or cost-effectiveness of PET. Two small randomized controlled trials with thoracotomy as endpoint have now been reported at the ASCO annual meeting. In 2000, van Tinteren et al. [15] showed data on 188 patients with clinical stage I–III NSCLC randomized prior to mediastinoscopy or thoracotomy to undergo either conventional work-up or conventional work-up plus PET. The preliminary results indicate a reduction in the number of ‘futile’ thoracotomies from 41% (39/96) to 21% (19/92) when PET was performed. PET prevented about one ‘futile’ thoracotomy for every five scans. In contrast, Boyer et al. [16] reported a negative study at the 2001 ASCO meeting. Their preliminary results based on 164 of 179 patients with clinical stage I–II NSCLC showed that PET scanning when added to conventional staging did not alter the thoracotomy rate or the management of patients.

Head and neck cancer

The critical review of somewhat conflicting data done by Schecke et al. [17] indicated that FDG-PET had little additional value to physical examination and conventional imaging studies (supplemented by biopsy when appropriate) for the detection of subclinical nodal metastases, unknown primaries, or disease in the chest. However, FDG-PET may be useful in differentiating residual or recurrent disease from treatment-induced normal tissue changes. Positron emission tomography can contribute to the timely institution of salvage therapy or the prevention of unnecessary biopsies of irradiated tissues, which may aggravate injury [17]. Unfortunately, a high false positive rate is observed when patients are investigated earlier than 12 weeks after irradiation [18].

Colorectal cancer

Surgical reintervention can potentially cure a fraction of patients with recurrent colorectal cancer. Accurate staging of recurrence is necessary for the identification of patients who may benefit from surgical resection. The meta-analysis performed by Huebner et al. [19] indicated a sensitivity of 97% and a specificity of 76% for PET in detecting recurrent
disease. Patient management was modified in 29% of the cases as a result of PET. Unfortunately, as pointed out by Huebner et al. [19], the methodological quality of many of the studies included in the meta-analysis was suboptimal. Nevertheless, performing PET in addition to conventional staging procedures allowed selection of appropriate candidates for surgical resection and exclusion of those who were unlikely to benefit from this procedure [20, 21]. The low specificity (76%) reported in the meta-analysis has to be considered. In our opinion, a positive PET has to be confirmed by a conventional radiological study or a biopsy before starting systemic salvage therapy or excluding a patient for potential curative surgery. PET was also found to have a high sensitivity and specificity for detecting and estimating the extent of recurrence in patients with elevated carcinoembryonic antigen (CEA) but negative conventional imaging [22] (Figure 2). The timing of staging procedures (conventional staging followed by PET) may explain part of the superiority of PET over conventional staging procedures, in particular for rapidly growing, poorly differentiated tumors.

Pancreatic cancer

Differentiating mass-forming pancreatitis from malignancy has been suggested as a potential indication for PET. However, PET does not reliably prove or exclude malignancy in situations where conventional diagnostic procedures leave doubt as to the nature of a pancreatic mass [23, 24]. In particular, PET often missed pT1 cancers, the most amenable to surgical cure [24]. Even important tumor masses can be missed in patients with mucinous adenocarcinoma, indicating the importance of the tumor histology [23]. On the other hand, the question of technical unresectability for locally advanced disease can only be definitively answered by surgical exploration [24]. If the disease is metastatic, a biopsy is always indicated to exclude a curable disease such as lymphoma infiltrating the pancreas. Therefore, it is unlikely that the number of invasive procedures can be significantly reduced by using PET.

Esophageal cancer

Positron emission tomography is not useful for tumor-staging because of its limited spatial resolution. The sensitivity of PET to detect involved locoregional lymph nodes is low, due to the difficulty of differentiating locoregional nodes very near to the primary lesion from heterogeneous FDG uptake in the primary lesion itself, and to recognize the presence of microscopic disease in positive nodes. The only potential role of PET in staging esophageal cancer is for the detection of unknown distant lymph nodes or metastases, allowing the optimal selection of patients for curative surgery [25, 26].

Melanoma

Positron emission tomography has no role in the evaluation of early stage disease. Positron emission tomography is insensitive for detecting microscopic nodal invasion and sentinel lymph node biopsy is far superior in this indication [27, 28].

Figure 2. A 54-year-old patient with rectal carcinoma diagnosed in October 2000 and treated by radiotherapy, surgery and chemotherapy. During follow-up carcinoembryonic antigen (CEA) levels (9.7 ng/ml) increased in September 2001. Conventional imaging techniques (chest X-ray, liver ultrasound) were negative. (A) Whole-body positron emission tomography 1 month later showed an isolated liver metastasis. (B) Confirmatory computed tomography (CT) illustrated a 6-cm liver metastasis.
Positron emission tomography is sensitive in detecting metastatic disease and can thus identify unsuspected disease [29, 30]. Unfortunately, high false-positive rates have been reported [28, 29]. More importantly, the early diagnosis of metastatic disease has probably no impact on outcome as systemic treatment for melanoma remains extremely disappointing.

**Lymphoma**

Positron emission tomography has been used for staging of non-Hodgkin’s (NHL) or Hodgkin’s (HD) lymphoma. However, all published data [31–39] suffer from methodological problems because the studies compared CT and PET imaging but biopsies were performed in a low number of suspect lesions. For ethical reasons, multiple biopsies were only obtained in selected patients when the results were likely to influence staging and treatment. Although PET provides complementary information to conventional radiological techniques, further studies are warranted to confirm its accuracy and cost-effectiveness [40]. On the other hand, PET may be useful for monitoring treatment efficacy after a few cycles of chemotherapy [41, 42] but it is too early to use PET in this indication outside of a clinical trial. In addition, differentiating residual disease from fibrotic masses is not possible with CT. Positron emission tomography has a very high positive predictive value at the end of treatment evaluation (Figure 3) but recent publications indicate that this value may be lower for the evaluation of patients suffering from HD [43, 44] compared with previous reports [45–47] which included mostly or exclusively NHL patients. A histological confirmation of residual disease should be obtained before the start of salvage therapy [40]. The impact of an early diagnosis by PET of residual disease on long-term outcome remains unknown. In general, although there are few direct comparative studies, the performance of PET seems to be superior to gallium scintigraphy for the staging or restaging of lymphoma [48].

**Figure 3.** (A) Diffuse large B-cell lymphoma in a 53-year-old patient with a bulky abdominal mass at diagnosis. (B) After the end of anthracycline-based polychemotherapy a residual mass was shown by CT. (C) The 18F-FDG PET study was negative after treatment. The patient remained in clinical complete remission after a follow-up of >5 years.
**Thyroid cancer**

FDG-PET may be useful if radioiodine scintigraphy is negative and recurrence or metastases are suspected on the basis of elevated thyroglobulin levels or equivocal morphological imaging results [49]. Indeed, patients with a localized non-radioiodine-avid recurrence are candidates for surgical resection.

**Breast cancer**

Positron emission tomography may be useful in carefully selected situations, such as breast implants, dense breasts (younger patients) or after surgery and irradiation. However, the reported sensitivity (between 64% and 80% depending on interpretation criteria [50]) is insufficient to use PET outside of a clinical trial. Its sensitivity is also insufficient to replace surgical dissection or sentinel lymph node biopsy of the axilla for lymph node staging [50]. Positron emission tomography is able to assess early response of locally advanced or metastatic breast cancer to chemotherapy but the impact on patient management remains unknown [51–53].

**Carcinoma of unknown primary**

Positron emission tomography has been suggested as a useful test for the detection of an unknown primary site. Although PET is able to identify the primary tumor in some patients [54–56], the treatment is chosen based on histology obtained by biopsy (most frequently of a metastatic lesion) and the treatment goal remains palliation in almost all patients. Positron emission tomography thus has probably no impact on outcome.

**Discussion**

Many studies have documented the high accuracy of 18F-FDG PET for the detection and staging of malignant tumors. 18F-FDG PET has proven to be superior to morphological imaging techniques for differentiating tumor recurrence from scar tissue. However, the limitations of PET have to be pointed out. 18F-FDG is not a tumor-specific agent. Even within tumors, the totality of FDG uptake is not completely within the tumor cells themselves. Up to 24% of the 18F-FDG concentration in a tumor mass is actually in macrophages and other inflammatory cells within the tumor. As for other imaging modalities, it is important to be aware of normal variants and benign diseases that may mimic more serious pathology. Physiological uptake of 18F-FDG may be seen in the skeletal muscle after exercise or under tension, in the myocardium, in parts of the gastrointestinal tract (especially the stomach and caecum) and in the urinary tract [57]. Thymic uptake can be observed in the anterior mediastinum after treatment of lymphoma [58, 59]. Malignant processes may also be simulated by other benign diseases. In the thorax, active tuberculosis, sarcoidosis, histoplasmosis or aspergillosis may mimic tumors. Increased metabolic activity in bones, for instance due to a hyperplastic marrow (for any reason including stimulation by growth factors) or Paget’s disease, leads to increased 18F-FDG uptake. Inflammation in any tissue including the operative site may cause an increase in 18F-FDG accumulation [57]. Appropriate selection, referral and timing of scans in defined clinical situations, along with knowledge of the potential pitfalls, will lead to a reduction in the interpretation errors. Positron emission tomography scans also need to be interpreted in conjunction with a pertinent clinical history to help minimize the number of false-positive studies. Finally, brain metastases cannot be detected by whole-body PET because of high 18F-FDG uptake in the normal brain.

Uptake of 18F-FDG is related to both the grade and proliferative status of the tumor. Lower 18F-FDG uptake is more frequently observed in low-grade, slowly proliferating tumors than in poorly differentiated, rapidly growing tumors. The relationship between tumor characteristics and glucose utilization can be explained by differences in hexokinase, glucose-6-phosphatase and glucose transporter membrane protein levels. False-negative PET studies can be observed in well-differentiated tumors, such as prostate cancer, even when metastatic [60], or low-grade non-Hodgkin’s lymphoma [36]. 18F-FDG PET may be useful for early treatment evaluation after a few cycles of chemotherapy [42, 61]. Positron emission tomography may provide additional clinical information to conventional radiological techniques such as assessing subclinical response. However, methodological developments in this area are still required before PET can be considered a standard technique. The EORTC PET study group has recently produced guidelines for the use of 18F-FDG PET to assess response [62]. Decreased uptake of 18F-FDG after chemotherapy and/or radiotherapy compared with pretreatment is generally considered to be an early indicator of tumor response. Unchanged or increased 18F-FDG uptake suggests stable disease or progression of the tumor. However, the presence of inflammatory cells after therapy may result in persistently high 18F-FDG uptake despite tumor response to treatment. It has even been demonstrated that those cells show a higher 18F-FDG uptake than do viable tumor cells. The optimal timing of post-therapy 18F-FDG scans has yet to be determined in order to reduce the rate of false-positive scans related to uptake by host inflammatory cells. Another potential problem for PET interpretation is that some tumors are nonhomogenous: clusters of normal cells alternate with clusters of malignant cells. This phenomenon occurs on a microscopic scale far beyond the resolution of PET. Necrosis may also be present in parts of the tumor. Consequently, 18F-FDG uptake does not fully reflect the metabolic status of the tumoral tissue. False-negative PET studies can also be due to a partial volume effect leading to underestimation of uptake in small residual tumors (<1 cm).

Clinical PET facilities are rapidly increasing in number all over the world. Positron emission tomography has a wide variety of potential uses in oncology. Positron emission
tomography is now routinely used for disease staging and monitoring during or after treatment. Anatomic and functional images provide complementary information and, in many circumstances, registration of both sets of images are necessary for correct interpretation. It has to be proven that PET is more than an adjunct to the more standard conventional imaging techniques. The place of PET has to be defined in carefully designed algorithms adapted to each clinical situation. In some indications, such as early treatment evaluation or routine follow-up, PET may replace conventional imaging techniques in the future. Further clinical studies with analysis of cost-effectiveness are warranted to identify areas in clinical oncology where it may be most usefully employed. Positron emission tomography has not only to be more accurate than existing imaging modalities but PET has also to improve patient management and outcome (i.e. longer life, less morbidity). The benefit obtained has to be more important than extra expenditure. Providing this kind of evidence is difficult, time consuming and costly. Improved patient outcome may only be apparent months to years after a diagnostic test is performed. In a financially restricted healthcare system, it is unlikely that PET will achieve general acceptance unless it results in net savings in cost of patient management or in better outcome. Unfortunately, nearly all published data present only a retrospective evaluation of management and cost impact and the accuracy that can be achieved retrospectively is questionable. Elimination of interpretation bias is only possible with a study design that includes prospective definition of potential management plans and comparison of plans to subsequent actual management. Prospective studies of cost-effectiveness are clearly needed that would permit the optimal use of limited resources available for technology assessment [63].

Conclusion

The cost-effectiveness and clinical impact of PET has not yet been definitively proven by prospective studies. Positron emission tomography is very promising in many clinical situations, such as diagnosis of pulmonary nodules, staging of lung cancer, end of treatment evaluation in lymphoma and restaging of a suspected relapse of colon cancer, but prospective multicenter trials are needed before we can conclude that PET is an absolute necessary tool in clinical oncology. 18F-FDG does not replace other imaging modalities such as CT but seems to be very helpful in specific situations in which CT has known limitations, such as differentiation of benign from malignant lesions, differentiation of post-treatment changes from recurrent tumors, differentiation of benign from malignant lymph nodes, detection of unsuspected distant metastases and monitoring of therapy results. We do not need further data indicating that 18F-FDG PET is complementary to conventional radiological imaging. Time has come for large multicenter trials analyzing the real clinical impact of 18F-FDG PET on patient outcome.

References


