



Review article

Appropriate use of positron emission tomography with [¹⁸F] fluorodeoxyglucose for staging of oncology patients

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ABSTRACT

Positron emission tomography (PET) was developed in the mid-1970, and its initial applications were for heart and brain imaging research. Nowadays, this technology is aimed mainly at staging or restaging tumours as it allows the assessment of biochemical processes that are either specific or associated with tumour biology.

The full appreciation of PET potentials and limitations among general practitioners and internists cannot be considered achieved and the appropriate use of PET especially when coupled to X-ray computed tomography (CT) is still suboptimal.

The majority of PET studies rely on the use of fluorodeoxyglucose labelled with fluorine-18 (FDG), which is a radiopharmaceutical specific for glucose transport and metabolism.

PET with FDG is amenable for studying most type of tumours, including those of the head and neck, lung, oesophagus, colo-rectal, gastrointestinal stromal tumours, pancreas, some types of lymphomas and melanoma, whereas in some tumours, including those of the reproductive system, brain, breast and bones, there is a limited role for PET and there is no substantial role for FDG-PET for the bronchoalveolar, hepatocellular, urinary system, testicular, neuroendocrine, carcinoids and adrenal tumours, differentiated thyroid cancers, and several subtypes of malignant lymphoma. Thus, the limits of FDG have stimulated the use and development of other radiopharmaceuticals. These tracers represent the opportunity for expanding the use of PET to other areas in oncology in the near future.

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1. Introduction

Positron emission tomography (PET) was developed in the mid-1970, and its initial applications were for heart and brain imaging research [1]. It was only in the year 2000, however that the widespread use of imaging with PET took off notably in clinical oncology, after two major events: the establishment of commercial production and distribution of the glucose analogue, 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG), and the invention of a device that combines PET with X-ray computed tomography (PET/CT) [2]. Nowadays, of the more than 2,000,000 PET studies performed worldwide per year, 98% of them are aimed at staging or restaging a tumour.

This technology is still in its rising phase, but whereas its use has become quite well known to physicians practicing nuclear medicine, radiologists and oncologists, i.e. among imaging specialists and referring physicians, the full appreciation of PET potentials and limitations among general practitioners and internists cannot be considered achieved. Thus, an appropriate use of PET is still far from being in the armamentarium of the investigational options fully appreciated by physicians other than imaging specialists and oncologists.

PET allows the assessment of biochemical processes, thus of dysfunctions that are either specific or associated with tumour biology, including the overexpression and up-regulation of various types of kinases and the increased transport of substrates, by measuring the accumulation of tailored radiopharmaceuticals. The majority of PET studies rely on the use of FDG, which is a radiopharmaceutical specific for glucose transport and metabolism. This review is aimed at providing an overview of the clinical use of FDG-PET and FDG-PET/CT, focusing on its main use, i.e. tumour staging.

2. Head and neck cancers (HNC)

The role of FDG-PET/CT scanning in HNC is somewhat controversial. There are a number of studies that have examined the value of PET in initial staging and have reported that the incidence of metastatic disease or secondary cancers is 11.1% to 12.9% [3]. The staging of lymph node status with PET has also been examined [4]; the sensitivity of PET in this regard ranges from 47 to 100%, while the specificity ranges from 87 to 100%.

In HNC the incidence of distant metastases is lower than in other primary malignancies, ranging from 4 to 25% [5]. Although loco-regional control of disease in HNC patients has improved, it is not matched by improvements in survival, due to an increase in deaths from distant

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metastases and the emergence of second primary tumours. Distant metastases usually occur late during the course of the disease, whereas second primary cancers are found even in patients with early-stage HNC [6]. Since second primary cancers and distant metastases are the leading causes of treatment failure and death in patients with HNC, early detection is essential for accurate tumour staging, optimal management and patient counselling.

3. Lung cancers

3.1. Non-small cell lung cancers (NSCLC)

Chest CT is essential for staging purposes, however, whereas CT provides morphologic information on the extent of the disease, its role in the assessment of mediastinal lymph-node involvement is limited. Metastases have been found in up to 20% of small nodes (<1 cm) in patients with clinical stage cT1N0 and cT2N0, and only approximately 50% of the nodes with a diameter of 1.5 cm to 2 cm are found to be metastatic [7].

Mediastinoscopy remains the gold standard for invasive complete staging of the upper mediastinum in patients with potentially operable lung cancer. Several studies and meta-analyses have demonstrated that PET is superior to CT scanning for mediastinal staging in potentially operable non-small-cell lung cancer [8]. Due to the high negative predictive value of PET, invasive staging procedures like mediastinoscopy can generally be omitted in patients with negative mediastinal PET images. However, in case of patients with central tumours, central hilar N1-disease on CT scan, bronchoalveolar cell carcinoma or in all situations with weak FDG-uptake in the primary tumour [9], a more invasive mediastinal staging is recommended. It is estimated that the introduction of PET has reduced the number of mediastinoscopies by 65%.

It has been shown that integrated PET/CT is superior to all other imaging techniques in the evaluation of chest wall infiltration, mediastinal invasion, and in the exact localization of occult distant metastases, which are found in up to 15% of the patients with potentially operable NSCLC [10].

Because PET-assisted staging is proven to be significantly more accurate than conventional staging and because all studies have shown major differences between PET-assisted and conventional delineation of treatment volumes in NSCLC, the use of PET/CT for radiotherapy planning is highly recommended [11].

3.2. Small cell lung cancer (SCLC)

A two-tiered staging system divides SCLC into limited disease and extensive disease, based on suitability for radiotherapy. FDG-PET has been proposed as a non-invasive measurement of the biological aggressiveness of the tumour, as a prognostic indicator and for differentiating limited disease from extensive disease [12].

The routine staging of SCLC includes CT of the chest to assess loco-regional disease, as well as CT of the upper abdomen, CT or MRI of the brain, and bone scintigraphy to detect metastatic spread. Unfortunately approximately 60% to 70% of patients at the time of SCLC diagnosis have extensive-stage disease on one or more of the above procedures [13]. The most common metastatic sites at the time of diagnosis are bone (19% to 38%), liver (17% to 34%), adrenal glands (10% to 17%) and brain (up to 14%).

The addition of PET to conventional imaging for patients with limited disease detects distant metastases in up to 10% of patients. However, PET identifies cancer in regional lymph nodes that are negative on CT, altering the therapy in about 30% of patients. However false-positive results with PET are not infrequent. Accordingly, further evaluation with imaging or biopsy should be performed to clarify PET results before patient management is altered. PET interpretation is aided by the combined assessment of CT images of the area(s) in question [12].

PET/CT scanning with FDG represents a major advance in the imaging of lung cancer and has an especially high impact on the management of patients who are candidates for potentially curative or radical radiotherapy. The available literature is almost exclusively devoted to NSCLC with few relevant studies of SCLC. In prospective studies where PET imaging was used to stage radical radiotherapy candidates, 25–30% of patients were excluded from therapy because PET detected advanced disease. In all studies where PET-assisted and conventional target or treatment volumes were compared, major differences between PET and conventional volumes were found. In patients with limited disease SCLC staged with PET/CT and treated with definitive intensity-modulated radiotherapy, elective nodal irradiation can be safely omitted from the planning target volume, for the purposes of dose escalation and toxicity reduction [14].

3.3. Malignant pleural mesothelioma

Preoperative clinical staging of malignant pleural mesothelioma is currently limited by the inaccuracy of imaging modalities to detect nodal involvement and loco regional spread. PET has played a supplementary role in detecting distant metastatic disease and quantification of FDG uptake has been demonstrated to be a useful prognostic factor [15].

Since the introduction of PET, a higher number of patients with extra thoracic spread has been identified and excluded as potential surgical candidates. This is reflected by a trend towards improved survival for patients who underwent PET preoperatively [16].

4. Digestive tract cancers

4.1. Oesophageal and stomach cancers

Cancer of the oesophagus and stomach can be effectively studied by PET both in staging and restaging. In patients with oesophageal carcinoma PET/CT is more specific than CT and ultrasounds in the identification of regional nodal metastases and evaluation of response to neoadjuvant chemotherapy, even though accurate staging of lymph node metastatic spread can be difficult due to the small volume of disease in some lymph nodes. Therefore PET can differentiate resectable and non-resectable diseases avoiding unnecessary surgery. In detecting gastric cancer recurrence, PET/CT is more accurate than CT and it has been reported that a change in management can occur in more than 20% of cases [17].

Most false positive results are due to the presence of inflammatory disease in the lower portion of oesophagus and/or in the stomach; sometimes inflammation can be associated with tumour and the endoscopic exploration of these organs is mandatory, especially in case of focal or intense uptakes.

Moreover false negative PET/TC can occur in evaluating lymph nodes close to the cancer, due to difficult distinction between cancer and proximal lymph node spread.

4.2. Colorectal carcinoma

PET/CT may be useful when inconclusive findings about metastatic lesions are reported on contrast enhanced CT. Thirty-two studies conducted up to 2004 have been analysed in three systematic reviews. For extra-hepatic lesions, the sensitivity and specificity of PET were 92% and 95%, and the sensitivity and specificity of CT were 61% and 91%, respectively. When data were pooled from the six studies that had the highest quality scores, the sensitivity and specificity of PET for extra hepatic lesions were 91% and 98%, respectively. For CT, sensitivity and specificity were 55% and 96%. PET resulted in a change in clinical management in 32% (range 20–58%) of the time in 13 studies. In the six studies with the highest quality scores, the mean change in management was 25% (range 20–32%) [18]. PET/CT with dedicated CT protocols such as contrast enhanced PET/CT and

PET/CT colonography may replace the diagnostic CT in pre-operative staging [19].

PET is found to be superior to CT for the identification of liver metastases. FDG-PET/CT, contrast enhanced CT and MRI were compared in a study for colorectal liver metastases in 65 patients. PET/CT was superior to contrast enhanced CT in detecting unexpected liver metastases and extra hepatic lesions. However, MRI was superior for small liver metastases [20].

4.3. Gastrointestinal stromal tumours (GIST)

Although FDG-PET has a limited use in staging GISTs some authors have shown a role of FDG uptake in predicting malignancy in GIST before surgery; in this setting the higher the uptake, the higher the malignancy and mitotic index [21].

4.4. Pancreatic cancer

PET/CT in pancreatic cancer is mainly indicated for staging, detecting CT-occult metastases, recurrence, monitoring therapy and for the diagnosis in patients with equivocal CT or non-diagnostic fine needle aspiration [22]. In detecting malignancy in cystic lesions, the accuracy of FDG-PET was 94% and was clearly superior to conventional CT (accuracy 80%). In this scenario, FDG-PET is considered as a complementary exam, especially when CT is non-diagnostic [23]. The evidence of unsuspected metastases in the liver, bones and lungs by FDG-PET/TC might thereby change the management protocol. PET/CT has been shown to be an effective imaging modality in detecting occult distant metastasis in patients with pancreatic cancer and thus changing patient management: in a recent study a sensitivity of 87% for metastatic lesion detection was shown and FDG-PET/TC changed management in 11% of the patients by detecting occult lesions not detected by CT alone. In a study, FDG-PET/CT and endoscopic ultrasound was compared for the diagnosis of primary pancreatic carcinoma and it was demonstrated that PET/CT was a high sensitive and endoscopic ultrasound was a high specific modality in diagnosing patients with complementary roles [24].

5. Genitourinary cancers

Prostate cancer has a relative low FDG uptake due to its low metabolic rate, thus there is no clinical role for this radiopharmaceutical. On the contrary, N-[¹¹C]methyl-choline and N-[¹⁸F]methyl-choline (¹¹C-choline and ¹⁸F-choline), two markers of the up-regulation of choline kinase in prostate cancer cells, are useful in the detection of loco-regional and distant metastases [25].

Moreover, because of urinary excretion of FDG through kidneys FDG-PET has a limited role, compared with CT and bone scan in detecting soft-tissue metastasis to pelvic lymph nodes and bone metastasis [26,27]. However, it can be useful if special delayed views are obtained. In a recent prospective study, 43 patients were studied for initial staging before cystectomy with PET/CT: all had negative CT and bone scintigraphy. PET/CT demonstrated a positive predictive value of 78%, a negative predictive value of 91%, sensitivity of 70%, and specificity of 94%. Recurrence-free survival, disease-free survival and overall survival were all significantly poorer in the patients with positive PET/CT than in those with a negative scan [28].

A large variability in diagnosis of renal cell cancer by PET/CT has been reported; due to urinary elimination of FDG a role can be argued in staging renal cell carcinoma in sites other than kidney. Sensitivities ranging from 40% to 100% are reported in staging of the disease [29], whereas a sensitivity of 60% and a specificity of 100% for primary tumour have been shown [30]. Studies have reported a complementary role of FDG-PET to the conventional imaging methods, in detecting distant metastasis [31].

In testicular cancers, PET can play a role, especially in defining recurrent and residual masses and in patients with raised markers.

Moreover results from many studies about the role of PET/CT in initial staging of testicular cancer are variable [32]. Although FDG-PET seems to be superior to contrast enhanced CT in evaluating infra diaphragmatic and supra diaphragmatic lesions, this finding doesn't reach a statistic level of evidence [33]. PET has been shown to have sensitivity, specificity, accuracy, negative predictive value and positive predictive value of 70%, 100%, 93%, 92% and 100% respectively, in patients with non-seminomatous germ cell tumours in Stage I, with normal findings on conventional imaging. Thus PET/CT may play a complementary role in staging and restaging of these tumours.

6. Breast cancer

In patients with cancer not larger than 2 cm (T1) biopsy of sentinel node remains the most important and sensitive diagnostic procedure to evaluate axillary node involvement [34]. However, a clearly positive FDG-PET scan in patients with a high risk of nodal metastases carries high positive predictive value and may identify patients with nodal metastases. This could indicate the need for standard axillary nodal dissection and more aggressive therapeutic approaches. The use of PET/CT may be suggested in patients with stage at presentation other than T1 (primitive tumours larger than 2 cm).

7. Gynecologic cancers

7.1. Ovarian cancer

It has been shown that PET/CT in staging provides additional value to transvaginal ultrasound for differentiating between benign and malignant lesions and is superior in staging providing evidence of additional lesion sites, compared to contrast enhanced CT [35].

7.2. Cervical cancer

Assessing metabolic tumour activity, evaluating possible endometrial diffusion, pelvic nodal involvement (even in cases with negative CT or MRI studies) and detection of distant metastases represent applications of FDG-PET/CT in cervical cancer patients. A recent meta-analysis demonstrated a combined pooled sensitivity and specificity of 84% and 95%, respectively, for aortic node metastases, while similar values for pelvic node metastases were 79% and 99%, respectively [36].

8. Bone tumours

FDG-PET/CT shows a significant correlation with grading and tumour aggressiveness [37], but a recent meta-analysis has demonstrated that sodium [¹⁸F]fluoride PET or PET/CT allows to predict the outcome in patients with bone sarcomas better than conventional grading systems [38].

FDG-PET/CT may be used to identify the metabolically most active site for biopsy and may play an important role in determining the metabolic rates of osteosarcoma, guiding biopsy, detecting local recurrence in amputation stumps, evaluating patients with suspected metastatic disease, monitoring response to therapy and assessing for prognosis and differentiating viable sarcoma from post treatment changes [39].

9. Lymphomas

FDG-PET/CT is emerging as a powerful imaging modality for diagnosis, staging, and treatment monitoring of lymphoma patients [40]. Both Hodgkin's disease (HD) and aggressive non-Hodgkin's lymphoma (NHL) normally show a high FDG uptake without any significant difference among subtypes and sites of disease. Because NHL is a group of disease constituted by a wide range of manifestation, heterogeneity in glucose metabolism can be observed; for this reason low grade

lymphomas can present a low metabolic rate and the routine use of PET is still debated and needs further evaluations.

Normally FDG-PET/CT allows to detect more lesions than CT leading to a change in the stage of up to 15% of patients [41]. A number of studies have assessed the value of PET in the diagnosis of bone and bone marrow, gastrointestinal tract and spleen, which may occur in 10–25% of newly diagnosed patients with lymphoma [42].

10. Malignant melanoma

Malignant melanoma metastasizes very widely. FDG shows a high tumour-to-background ratio and can highlight metastases at unusual sites that are easily missed with conventional imaging modalities [43]. The accuracy of PET in detecting melanoma metastases ranges between 81 and 100% [44]. PET/CT is also more accurate than conventional imaging in restaging and follow-up, with 89% sensitivity and 88% specificity for melanoma lesion detection during restaging, especially in high-risk patients [45].

11. Adrenocortical tumours

FDG-PET/CT has been shown to have excellent diagnostic performance (sensitivity 93% and specificity 90%) in differentiating adrenal lesions detected on CT or MRI in patients with known malignancies.

Meta-analysis of combination PET-computed tomography (CT) reports revealed that FDG PET was highly sensitive and specific for differentiating malignant from benign adrenal disease. Diagnostic accuracy was not influenced by the type of imaging device (PET vs PET/CT), but specificity was dependent on the clinical status (cancer vs no cancer) [46].

12. Brain tumours

Studies have demonstrated that FDG-PET can identify the elevated glucose consumption in brain tumours and is now accepted that the uptake correlates with the grade of malignancy in astrocytic tumours and survival, but its role is limited by the high cerebral glucose uptake of the normal brain tissue [47]. However FDG can be used to distinguish between radiation necrosis and tumour recurrence. Other tracers such as

[¹⁸F]fluoroethyltyrosine, an artificial amino acid that accumulates into cells, or [¹⁸F]fluorothymidine, an imaging biomarker of cell proliferation, may provide better diagnostic performances [48,49].

13. Thyroid cancer

FDG-PET or PET/CT seems to be useful in staging of invasive and metastatic Hurtle cell thyroid carcinoma and anaplastic thyroid carcinoma, while more studies are needed in staging of poorly differentiated thyroid carcinoma. In patients with aggressive histological subtypes of differentiated thyroid carcinoma, presenting as radioiodine refractory, FDG uptake confirms the high tumour aggressiveness [50].

14. Neuroendocrine tumours

FDG has limited clinical role, as the uptake in well-differentiated tumours is generally low. At present, 3,4-dihydroxy-6-([¹⁸F]fluoro)-L-phenylalanine (¹⁸F-DOPA) PET/CT is the most widely used PET tracer [51]. Also somatostatin receptor PET tracers such as [⁶⁸Ga]-DOTA,1-Nal(3)]-octreotide (⁶⁸Ga-DOTANOC) and [⁶⁸Ga]-DOTA,Tyr(3)]-octreotate (⁶⁸Ga-DOTATATE) have shown promising results in patients with neuroendocrine tumours, with a higher lesion detection rate than is achieved with ¹⁸F-DOPA. In particular, ⁶⁸Ga-DOTANOC may allow to detect more lesions than ⁶⁸Ga-DOTATATE in patients with gastro intestinal pancreatic neuroendocrine tumours [52] (Table 1).

15. Conclusions and future outlook

PET is amenable for studying most type of tumours, including those of the head and neck, lung, oesophagus, colo-rectal, gastrointestinal stromal tumours, pancreas, adrenal tumours, some types of lymphomas and melanoma. This is not, however a constant paradigm of all cancers as some tumours, including those of the reproductive system, brain, breast and bones, have variable uptake, whereas there is no substantial role for FDG-PET for the bronchoalveolar, hepatocellular, urinary system, neuroendocrine, carcinoid, differentiated thyroid cancers, and several subtypes of malignant lymphoma (Table 1). Thus, the limits of FDG have stimulated the use and development of

Table 1

Types of cancer in which PET and PET/CT with FDG may improve staging.

Adrenocortical tumours	To differentiate lesions detected with CT or MRI
Bladder cancer	Image degradation due to urinary excretion of FDG
Bone sarcomas	To identify metabolically most active sites to guide biopsy and to assess distant metastases additional radiopharmaceuticals F-18 fluoride
Brain tumours	For grading and to differentiate radiation necrosis from recurrence Additional for guiding biopsy [¹⁸ F]fluoroethyltyrosine, [¹⁸ F]fluorothymidine are recommended
Breast cancer	Patients in stage other than T1 (primitive tumours larger than 2 cm)
Brochoalveolar cancer	Not detected with FDG; no other radiopharmaceuticals available
Cervical cancer	To assess endometrial diffusion, pelvic nodal involvement and distant metastases
Colorectal carcinoma	PET/CT is useful in case of inconclusive findings about metastatic lesions following contrast enhanced CT and for detecting unexpected liver metastases and extraepatic lesions
Oesophageal cancer	PET/CT is more specific than CT and ultrasound in the identification of regional nodal metastases
Gastric cancer	PET/CT is more accurate than CT and changes management in 20% of patients
Gastrointestinal stromal tumours	Indicates grade of malignancy before surgery
Head and neck	Distant metastases and the emergence of second primary tumours
Lymphomas (Hodgkin and aggressive non-Hodgkin)	Detection of additional site as compared to CT
Malignant melanoma	Detection of metastases at unusual sites missed with conventional imaging modalities
Malignant mesothelioma	Detection of extratoracic spread excludes patients from useless surgery
Neuroendocrine tumours	Variable FDG uptake; [¹⁸ F]fluorodopa and somatostatin analogues labelled with [⁶⁸ Ga] are preferred
Non-small cell lung cancer	Superior to CT evaluation of chest wall infiltration, mediastinal invasion and the localization occult distant metastases
Ovarian cancer	Additional value to transvaginal ultrasound for differentiating benign vs. malignant lesions and to detect additional lesion sites
Pancreatic cancer	Complementary to CT when the latter is non-diagnostic. Detects metastases in the liver bones and lungs
Renal cancer	Large variability of results
Small cell lung cancer	PET identifies cancer in regional lymph nodes that are negative on CT. Staging with PET/CT treated with intensity modulated radiotherapy allows to avoid elective nodal irradiation
Testicular cancer (non-seminomatous germ cell)	To detect recurrent and residual masses and in patients with raised markers
Thyroid cancer	In patients with aggressive tumours refractory to radioiodine

other radiopharmaceuticals. These tracers represent the opportunity for expanding the use of PET to other areas in oncology in the near future.

More recently a new type of device has been developed that couples PET and magnetic resonance imaging (MRI) [53,54]. PET/MRI has already found applications in oncology [55] and appears very promising for a number of future applications also in neurology [56] and cardiology [57]. This approach may change the future developments of PET imaging.

Learning points

- The appropriate use of PET with FDG requires the knowledge of its potentials and limitations as for some cancers results may be key for staging whereas in other cases PET findings may be misleading.
- PET is not appropriate for diagnosis whereas it is key for staging and restaging especially when associated with CT scanning.
- Tracers more appropriate than FDG may be available for specific types of tumours.
- A clear question should be addressed to the nuclear medicine physician when requiring a PET study and all complementary available data sent along with the prescription of PET scanning.

Conflicts of interest

The authors state that they have no conflicts of interest.

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