^{18}FDG PET in oncology: The best and the worst (Review)

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Abstract. The clinical added-value of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG PET) in the management of oncology patients is increasingly documented. In the present review, we discuss both the benefits and the limitations of ^{18}FDG PET in different cancers. Considering the literature data and our own experience, we also indicate the best clinical approach to optimize the use of metabolic imaging in oncology.

Contents

1. Introduction

The incremental value of ^{18}F-fluoro-2-deoxy-D-glucose (^{18}FDG) positron emission tomography (PET) in the management of many patients suffering from cancer is well documented (1). Increasing data from prospective and retrospective studies highlights the advantages of ^{18}FDG PET in diagnosing, staging, re-staging, and monitoring various malignancies (2). To optimize the clinical use of metabolic imaging, however, ^{18}FDG PET has to be adequately incorporated into the patient's overall management from diagnosis to treatment and, thereafter, to follow-up (3). Accordingly, the role of metabolic imaging should be tailored to the specific clinical need in each kind of cancer.

In the present review, the clinical value of metabolic imaging is discussed for different cancers. We address the benefits as well as the limitations of ^{18}FDG PET in various types of non-central nervous system (non-CNS) cancers in terms of adequate staging, treatment impact, prognosis, and cost-effectiveness.

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2. Key-factors influencing the ^{18}FDG uptake

In physiological conditions, the ^{18}FDG tracer is avidly taken up by the cerebral grey matter and the heart in non-fasting patients. The tracer is slightly taken up by the liver, spleen, and colon. The glucose tracer is predominantly excreted by the urinary system through the kidneys, ureters, and bladder. Therefore, the sensitivity of metabolic imaging is most often suboptimal for the detection of ^{18}FDG-avid metastases within the brain and the urinary tract. Otherwise, the tumor:background ratio (T:B) within the lungs, pleura, mediastinum, liver, spleen, skeleton, peritoneum, and digestive system most often allows the adequate imaging of ^{18}FDG-avid tumors. In patients with high serum glucose levels, the T:B ratio may be suboptimal because of a possible competition between the ^{18}FDG tracer (as glucose analogue) and the natural circulating glucose.

In pathological conditions, the sensitivity of the metabolic technique is primarily based on the degree of tracer accumulation at the tumor site independent of its structural characteristics. So far, the histological types and subtypes of the primary tumor as well as of its metastases may influence the patterns of ^{18}FDG tumor uptake. As a marker of tumor viability, the ^{18}FDG uptake usually reflects the tumor aggressiveness. The intensity of glucose tracer uptake is also related to the tumor grade and the degree of differentiation. Overall, ^{18}FDG uptake appears to be a marker of high-grade and/or poorly-differentiated tumors, which means that ^{18}FDG-avid cancers probably present with a certain degree of aggressiveness, thereby expressing an inherent metastatic tendency. As such, ^{18}FDG PET has been used as a prognostic index prior to any therapy, and also to assess the tumor chemosensitivity after one or several courses of treatment.

Tumor size is another key parameter influencing the sensitivity of metabolic imaging. With most PET scanners used in practice, the spatial resolution is about 5-6 mm. As a rule, ^{18}FDG-avid tumors of >1 cm are clearly seen, while tumors of <0.5 cm are most often missed. Malignant lesions presenting with an intermediate size (0.5-1 cm) are inconstantly detected depending upon the intrinsic technical characteristics

Table I. Factors influencing the sensitivity and specificity of [18]FDG PET in oncology patients.

	Key-factors	Comments
Sensitivity	Histology	See Table III
	Size	FN: micrometastases - partial volume effect
	Background	FN: brain grey matter[a] - urinary tract[a]
	Physiology	FN: diabetes - hyperinsulinemia
Specificity	Infectious diseases	FP: pneumoniæ - aspergillosis - tuberculosis - abscess
	Inflammatory diseases	FP: sarcoidosis - asbestosis - granulomatosis
	Inflammatory changes	FP: radiation - surgery - talc pleurodesis - biopsy
	Physiology	FP: gastrointestinal tract[b] - ureters[b]

FN, false-negative results. FP, false-positive results. [a]Some tumors may be missed because the [18]FDG tracer is physiologically taken up by the brain and predominantly excreted through the urinary tract (kidney, ureters, bladder). [b]Normal [18]FDG uptakes within the gastrointestinal tract and the ureters may be falsely interpreted as tumors due to the lack of anatomical landmarks.

of the PET device and the tumor metabolism. Because [18]FDG PET is a form of molecular imaging, the suboptimal detection of small tumor lesions due to a partial volume effect may be neutralized by a much higher metabolic contrast between the target organ/lesion and the background ('candle-by-night' principle). The use of PET-CT devices may enhance the detection of metastases of <1 cm by using the high-resolution CT part of the combined device much more sensitively than [18]FDG PET imaging alone. On the other hand, the appropriate use of sentinel node biopsy (SNB), at an early stage of disease, has been shown to accurately detect microscopic nodal metastases. The key-factors influencing the sensitivity and specificity of [18]FDG PET in oncology are summarized in Table I.

3. Indications of [18]FDG PET in oncology

In the following section, the role of [18]FDG PET in various types of cancer is assessed from a clinical point of view by taking into account the most recent TNM classification of malignant tumors from the International Union Against Cancer (IUAC/UICC, 6th edition, 2002). In malignant melanoma, we chose to refer to the American Joint Committee on Cancer (AJCC) classification, which was recently incorporated into the TNM staging system. In lymphoma diseases, owing to the various classifications and their complexity, and because of the lack of a consensual staging system worldwide, we preferred to define the indications of [18]FDG PET from a practical point of view. Common indications for [18]FDG PET in US and Europe are summarized in Table II.

Digestive cancer. Esophageal carcinoma avidly accumulates [18]FDG except for some adenocarcinomas located at the caudal part of the gastro-esophageal junction (4). The major indication for whole-body [18]FDG is the detection of unsuspected distant metastasis (stage IV disease), which leads to a change in the treatment approach in approximately 10-20% of patients. The accuracy of PET for assessing local lymph-node involvement is low because these nodes are often located in close vicinity to the primary tumor. Regional lymph-node involvement is diagnosed with a lower sensitivity than endoscopy ultrasound, but with a superior specificity (5). The positive predictive value of a PET(CT) positive mediastinal lymph node is very high. False positive findings are located at the lung hilum (inflammation), thyroid bed (benign adenoma), parotid gland (Warthin's tumor, pleomorphic adenoma), and mediastinum (sarcoidosis; pneumoconiosis). Preliminary data indicate the potential utility of [18]FDG PET for the diagnosis and staging of recurrent disease. [18]FDG PET has the intrinsic advantage of its whole-body imaging capacity resulting in a high sensitivity. Focal false-positive PET has been reported at the anastomosis during several months following endoscopy dilatation of a stricture. [18]FDG PET can be used for early treatment response assessment (i.e. as soon as 2 weeks after 5FU-based polychemotherapy) as well as for the evaluation of residual viable tumor load after treatment (i.e. 4-6 weeks after chemo-radiotherapy). In these two settings, some reports indicate a strong link between the PET findings and the survival end-points (4,6). Further research should clarify the clinical implementation of these promising applications of metabolic imaging.

Cancer of the proximal stomach and gastroesophageal junction is thought to be more aggressive than esophageal tumors and more complex to treat. Even after curative gastrectomy, the disease may recur in both regional and distal sites in at least 80% of patients. Two distinct histopathological growth types of stomach adenocarcinoma have been described: intestinal and diffuse. Based upon presently available scientific data, there is no proven role for the routine use of [18]FDG PET in the initial staging or follow-up of gastric cancer (4,7). The major limitation of the technique is the recent observation that about one third of these tumors do not concentrate the tracer ([18]FDG non-avidity). Recent data indicate that the non-avidity for [18]FDG is related to the growth type (less uptake in diffusely growing tumors), the degree of differentiation (less uptake in poorly-differentiated tumors), and the mucus content of the tumor cells (less uptake in containing cells more mucus).

Unlike gastric cancers, most pancreatic carcinomas, especially ductal adenocarcinomas, demonstrate increased [18]FDG uptake due to the overexpression of glucose transporters

Table II. Common indications for ^{18}FDG PET imaging.

Reimbursed indications in EU and US	Comments
Non-small cell lung cancer[a]	Diagnosis - staging/restaging[d] - treatment monitoring[b] - prognosis[e]
Solitary lung nodule[a]	Metabolic characterisation of inconclusive nodule on CT scan
Colon cancer[a]	Diagnosis - staging/restaging[d] - treatment monitoring[b] - prognosis[e]
Malignant melanoma[a]	Diagnosis[f] - staging/restaging[d] - treatment monitoring[b]
Lymphoma[a]	Diagnosis[g] - staging/restaging[d] - treatment monitoring[b] - prognosis[e]
Breast cancer[a]	Staging/restaging[d] - treatment monitoring - prognosis[e]
Head and neck cancer[a]	Diagnosis - staging/restaging[d] - treatment monitoring[b] - prognosis[e]
Esophageal cancer[a]	Diagnosis - staging/restaging[d] - treatment monitoring[b] - prognosis[e]
Pancreatic cancer	Diagnosis - staging/restaging[d] - treatment monitoring[b] - prognosis[e]
Ovarian cancer	Staging/restaging[d] - treatment monitoring[b] - prognosis[e]
Thyroid cancer[a]	Staging - elevated Tg with negative I-131 whole-body scan - prognosis[e]
Cancer of unknown origin[c]	Diagnosis - staging - treatment choices - prognosis[e]

[a]Medicare covered indications in US; expanded coverage was recently proposed for cervical, ovarian, testicular, small cell lung, pancreatic, and brain cancers. [b]Implicitly accepted in clinical routine for evaluating the treatment efficacy in terms of complete or partial metabolic response versus stable disease versus progressive disease. [c]Implicitly accepted in clinical routine for localizing the primary tumor (PET-guided biopsy) and also for treatment-decision making. [d]Detection of loco-regional and distant metastases/recurrences or simple follow-up surveillance; excludes initial staging of axillary nodes in breast cancer. [e]Some studies highlighted the prognostic information derived from ^{18}FDG PET. [f]AJCC stage ≥IIc (Breslow >4 mm - Ulceration +); excludes evaluation of regional nodes in AJCC stage-I and -II disease. [g]Hodgkin's lymphoma and non-Hodgkin's lymphoma; intermediate and high-grade lymphomas. Tg, thyroglobulin.

(GLUTs) at their cell membrane and an increased hexokinase activity (8). The overall diagnostic accuracy of PET is approximately 80%. ^{18}FDG PET has no role in the initial staging or follow-up of islet cell tumors and other endocrine tumors because of the low ^{18}FDG avidity (9). The metabolic work-up of these cancers should be performed using Indium111-labeled Octreotide SPECT or, when available, whole-body F^{18}-dopa PET. Metabolic imaging can also play a role in the initial work-up of a pancreatic mass of unknown origin. PET provides an alternative in lesions of <2 cm because the differential diagnosis between focal pancreatitis and malignancy is often challenging for these lesions. False negative PET findings have been reported in small lesions (due to the limited spatial resolution), in the presence of elevated serum glucose levels and/or diabetes mellitus (due to a competition between the circulating glucose and the FDG), and in cystic or mucinous tumors. False positivity has been reported in cases of foci of active pancreatitis. The diagnostic accuracy of PET strongly depends on the use of correlative imaging, joining structural (CT/MRI) and metabolic (PET) findings. ^{18}FDG PET cannot be used to assess T-stage (local resectability) and has a low accuracy for N-staging (due to the proximity of regional lymph nodes to the primary tumor). However, ^{18}FDG PET has a higher sensitivity than CT for M-staging by detecting unsuspected metastatic lesions in the liver, lung and retroperitoneal space. Rare false positivity has been reported in the liver with dilated bile ducts and inflammatory granulomas. Only preliminary data are presently available on the promising use of serial ^{18}FDG PET (before, during, or after treatment) for assessing the efficacy of neoadjuvant chemoradiation therapy. PET plays a role in the follow-up of patients. The three major indications are: a) differentiation of postoperative fibrotic changes from recurrent tumors in cases of equivocal CT findings; b) metabolic characterization of new lesions seen on conventional work-up; and c) patients with rising serum tumor marker levels and a negative conventional work-up (10). A few data also highlighted the prognostic value of ^{18}FDG tumor uptake as an independent predictor of survival in pancreatic carcinomas (11,12).

Primary and recurrent colorectal cancers most often demonstrate a high concentration of ^{18}FDG allowing sensitive whole body staging of these patients by PET (13). Rare exceptions are mucinous adenocarcinomas which can be missed by ^{18}FDG PET probably because of their relatively low cellularity and abundant non-^{18}FDG accumulating mucin content (14). Interestingly, precancerous adenomateus polyps also demonstrate intense ^{18}FDG uptake. Based on the current data, ^{18}FDG PET is not sensitive enough for the diagnosis of local lymph-node involvement; a suboptimal sensitivity due to the close vicinity of these lymph nodes to the intensely active primary tumor, and also to their limited microscopic involvement. This limits the role of metabolic imaging in the preoperative primary staging of colorectal cancer. However, most centers accept two exceptions in which ^{18}FDG PET should be performed: a) co-existing resectable liver or lung metastasis (to exclude the presence of other non-resectable metastatic foci); and b) metabolic characterization of equivocal conventional imaging findings (15). A baseline PET study may be useful for post-treatment monitoring, especially in patients treated with chemoradiation (16). The preoperative re-staging of patients with suspected or proven recurrent disease is a common indication for whole-body ^{18}FDG PET imaging based on: a) an unexplained rising of CEA levels; b) equivocal lesions visualized by conventional staging techniques

(such as the presacral masses located behind the bladder, which are often seen on CT after resection of the rectum); and, c) re-staging prior to curative resection for a known metastasis. ^{18}FDG PET has been demonstrated to be more sensitive to CT in all sites except for the lung, where both modalities are equivalent. From the results of the literature data, it can be concluded that ^{18}FDG PET can effectively direct patients with recurrent colorectal cancer to the most appropriate treatment. The major limitations of the technique in this setting is its sub-optimal specificity; false positive ^{18}FDG accumulation due to physiological intestinal uptake, benign lesions (i.e. adenoma), and inflammation (ulcerative colitis; following adjuvant local radiotherapy) must be considered. In addition, peritoneal metastases, especially small implants, may be missed in ^{18}FDG PET imaging (sensitivity comparable to CT). Correlative PET-CT imaging should significantly increase the diagnostic accuracy. Preliminary data indicate the utility of ^{18}FDG PET to assess the treatment response after radiofrequency ablation for liver metastasis (17). Similarly, the metabolic response can be assessed as early as 2 weeks following either 5FU-based chemotherapy or concurrent radio-chemotherapy (16,18).

Only limited data are presently available on the use of ^{18}FDG PET in hepatocellular (HCC) and cholangiocellular carcinomas. A significant proportion (approximately 50%) of HCCs do not show increased ^{18}FDG uptake and cannot be distinguished from normal liver parenchyma (19). Some data indicate that the ^{18}FDG avidity is related to the degree of differentiation of the tumor with poorly-differentiated tumors demonstrating a higher uptake. The underlying biochemical mechanism is probably the high wash-out of the tracer due to a relatively high glucose-6-phosphatase activity. The available literature data on cholangiocarcinomas are controversial. Some reports indicate high ^{18}FDG avidity for this type of tumor, especially in peripheral cholangiocarcinomas. From our experience and others, false negative results are not infrequent, particularly in hilar cholangiocarcinomas (20). Therefore, a negative PET finding cannot exclude malignancy, while a positive PET is highly suspicious for malignancies. In conclusion, based upon the published data, the routine use of FDG-PET in the diagnosis, staging and follow-up of primary liver cancer is not justified.

Lung cancer. In pre-treatment staging, the CT scan remains the modality of choice for T-staging (21). However, in patients who are candidates for radiotherapy but present with a severely impaired lung function, atelectasis, and/or pleural effusion, PET appears particularly useful for the precise targeting of the tumor volume while minimizing the irradiation to non-tumoral tissue; clinical conditions where the CT scan is often less useful (22). Owing to its limited spatial resolution, PET may miss small tumors of <1 cm in size (i.e. *in situ* stage 0 cancer). Similarly, metabolic imaging cannot accurately determine the primary tumor invasion to the adjacent structures (pleura, oesophagus, and great vessels). In addition, pure bronchioloalveolar tumors and well-differentiated lung carcinoids are most often missed by metabolic imaging (23-26). Otherwise, for N-staging and M-staging, metabolic imaging is often superior to morphological imaging. ^{18}FDG PET has demonstrated its accuracy in differentiating N_0-N_1 stages from N_2-N_3 stages, which is determinant for the patient's management (27). Indeed, unlike N_2 stages, surgery is the first option in N_0-N_1 stages, while being contraindicated in N_3 stages. One should note the limitations of ^{18}FDG PET for the diagnosis of N_1 stages versus N_0 stages. Because of the intense ^{18}FDG uptake within the primary lung tumor, the detection of ipsilateral hilary nodes may be suboptimal. The best clinical impact of metabolic imaging appears to be for N_2-N_3 patients (stage IIIA-IIIB). In these cases, ^{18}FDG PET is superior to CT scan for the detection of mediastinal, ipsilateral, controlateral, and supraclavicular nodal metastases (28). Even though metabolic imaging may miss microscopic nodes, ^{18}FDG PET has a high negative predictive value, thereby sparing the patients unnecessary mediastinoscopies. As such, a negative PET result at the level of the mediastinum may indicate a thoracotomy with a high confidence. Conversely, the high sensitivity of ^{18}FDG PET should lead to a biopsy or a mediastinoscopy in cases of positive results suggestive of N_2 and N_3 stages. The use of metabolic imaging is also of clinical interest for the M-staging of lung cancers, especially when the disease is locally advanced (stages IIIA-IIIB). ^{18}FDG PET is particularly sensitive for the detection of bone, liver, and adrenal metastases (29,30). However, the staging of brain metastases is clearly insufficient because of the high physiological brain uptake (31). As a practical consequence, a complementary brain CT/MRI is always mandatory. Metabolic imaging may be used to non-invasively follow the patients during their treatments. The likelihood of tumor recurrence is low in patients with a negative PET scan 4-6 weeks after treatment. Conversely, PET is highly suggestive of recurrence in patients with a positive post-treatment scan (32,33). Soon after radiation or surgery (<1-2 months), or talc pleurodesis, the inflammatory changes may give an increased ^{18}FDG uptake (34). Recent data also indicate that metabolic imaging may yield prognostic information in lung cancer patients with stage-I or -II disease based on the primary tumor ^{18}FDG uptake (35,36).

Pleural cancers. In patients presenting with pleural manifestations (pleural effusion, pleural thickening, thoracic pains), the use of ^{18}FDG PET was found particularly contributive to rule in primary malignancies, especially in cases of mesotheliomas; pleural cancers with a high ^{18}FDG avidity (37,38). Also interesting is the ability of metabolic imaging to detect pleural metastases, thereby allowing a more accurate staging and follow-up of the primary tumor (i.e. lung cancer). So far, the most important contribution of ^{18}FDG PET is its ability to rule out a pleural malignancy with a high accuracy and a high negative predictive value. As such, metabolic imaging may avoid a number of repeated and invasive studies. In patients suffering from undetermined pleural diseases, ^{18}FDG PET performed in a first-line strategy may be cost-effective either by guiding subsequent interventions or by withholding unnecessary interventions (39). In particular contexts, including pleural asbestosis, active infection (i.e. tuberculosis) or inflammation (i.e. talc pleurodesis, radiation, recent surgery), metabolic imaging may show a moderate to high ^{18}FDG uptake. Also, in these clinical circumstances, the confrontation with the CT findings is required and the pathological confirmation may be necessary (34).

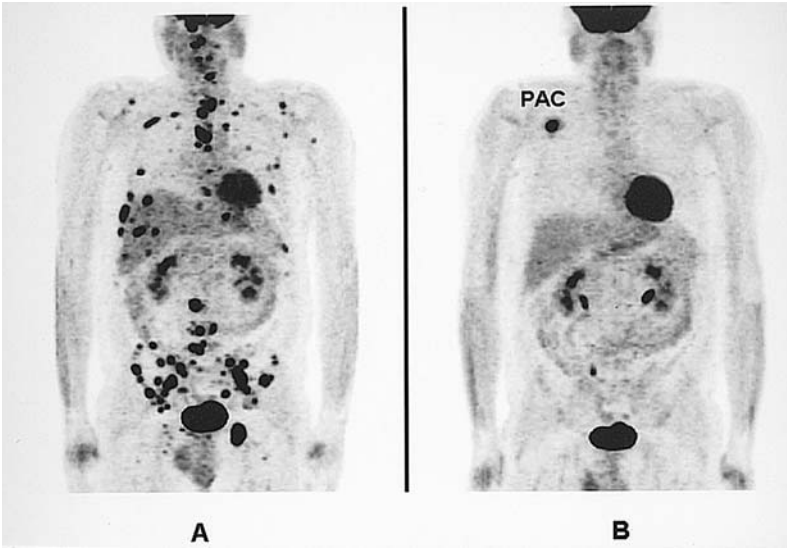

Figure 1. A case of multiple myeloma treated by chemotherapy. A, at baseline, whole-body ^{18}FDG PET showed multiple foci consistent with bone marrow tumor deposits. B, after 3 courses of chemotherapy, ^{18}FDG PET demonstrated a complete metabolic response. PAC, port-a-catheter.

Haematological cancers. In patients with lymphomas, many reports showed the superiority of ^{18}FDG PET to conventional work-up for initial staging, especially in the detection of nodal disease and occult splenic involvement (40,41). High ^{18}FDG uptake is roughly reported in Hodgkin's lymphoma (HL), large B-cell non-Hodgkin's lymphoma (NHL), follicular NHL, mantle cell lymphoma, and anaplastic large cell lymphoma. Conversely, low-grade lymphomas are common causes of false negative results with ^{18}FDG PET (42,43). Similarly, lymphocytic lymphoma, marginal zone lymphoma, mucosa-associated lymphoid tissue (MALT), and peripheral T-cell lymphoma have been shown to exhibit a low ^{18}FDG uptake. The value of metabolic imaging remains to be determined in T-cell NHL, Burkit-type NHL, lymphoplasmacytic NHL, and lymphocyte-predominance HL. So far, regardless of the type of lymphoma disease, metabolic imaging cannot replace a bone marrow biopsy for the detection of bone marrow involvement (43-45). In the follow-up, ^{18}FDG PET may yield determinant prognostic information in the sense that patients with a positive post-treatment scan are likely to relapse compared to the negative patients who have a favorable outcome (46). Also, a positive ^{18}FDG PET scan early during treatment as well as before autologous stem cell transplantation in relapsing patients would suggest that the installed treatments are probably ineffective, thereby re-orienting these patients to more experimental therapies (47). Optimal timing for assessing chemosensitivity is critical in order to avoid confusing results; transient ^{18}FDG uptake changes that may occur within the first two weeks post-treatment (from day 3 to day 15) (48). Hence, a duration of two weeks following therapy is commonly accepted as a minimum time period before performing the PET scan. So far, preliminary data show that a very early assessment (i.e. 1 day post chemotherapy) is also feasible in NHL (49). Although metabolic imaging may play an important role in various pathological forms of lymphomas, cost-effectiveness studies are still required in order to optimize the role of ^{18}FDG PET in the overall management of patients.

Other hematological malignant diseases, such as multiple myeloma and solitary plasmocytoma, may also derive clinical benefit from the appropriate use of ^{18}FDG PET (50). The staging of active intramedullary involvement may be efficiently achieved by using the metabolic technique, especially for detecting focal deposits and non-secretory disease (51,52). The use of ^{99m}Tc-MIBI and MRI may complement metabolic imaging for the detection of diffuse disease and small lesions, respectively (53). Of note, increased bone marrow and splenic ^{18}FDG uptake may be seen following treatment either with chemotherapy or growth factor stimulation (G-CSF), which renders it difficult to make an optimal assessment of residual disease (45,54). Therefore, the bone marrow biopsy remains the gold standard. Unlike conventional imaging, ^{18}FDG PET may be of particular value for assessing, at the same time, extramedullar tumor involvement as well as comorbid infectious and inflammatory diseases in the entire body. In the follow-up, metabolic imaging may be useful either for the detection of early relapse or for treatment monitoring (55). More data from large series remain necessary in order to precisely establish the added-value of ^{18}FDG PET in patients with multiple myeloma and solitary plasmocytoma (Fig. 1).

Malignant melanoma. In malignant melanoma, ^{18}FDG PET has a limited value in AJCC stage-I and -II melanoma, where the disease may have already reached microscopic lymph-node metastases (56,57). In early-stage disease, SNB should be indicated in a first-line strategy to detect unsuspected nodal metastases (58). In this clinical setting, the use of PET in malignant melanoma should be limited to particular situations (high-risk melanoma) where a treatment choice (i.e. extensive loco-regional lymphadenectomy) could be influenced by the presence of unsuspected distant metastases (59). Conversely, metabolic imaging appears to be more useful in advanced stages (AJCC stages III-IV). Similarly, ^{18}FDG PET may be indicated at first for the detection of recurrences (60,61). However, no clear scheme exists with

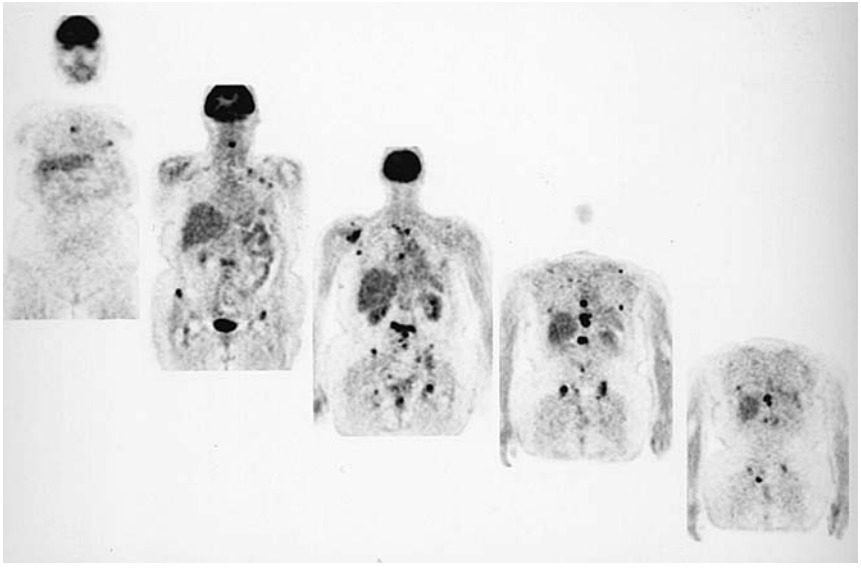

Figure 2. A case of ductal breast carcinoma treated by chemotherapy. The rise of tumor marker (CA15.3) suggested the recurrence of disease. MRI of the spine concluded in bone fractures. ^{18}FDG PET revealed multiple foci consistent with bone dissemination.

regard to the frequency of ^{18}FDG PET scans in follow-up (62). Additionally, the sensitivity of ^{18}FDG PET for the detection of brain metastases and small lung metastases remains dramatically low (63,64). Also, brain MRI and chest CT should complement whole-body PET for staging and re-staging purposes, especially in advanced stages (65). In addition to ^{18}FDG PET, the overall management of melanoma patients stresses the need for cost-effectiveness studies including other diagnostic modalities such as SNB, brain MRI, thoracic CT and, more recently, combined PET-CT devices.

Gynaecological cancers. The value of ^{18}FDG PET in the management of breast cancer is well documented, considering that mammography and ultrasonography are the modalities of choice for screening purposes and T-staging (66). In pre-treatment staging, ^{18}FDG PET may yield metabolic information on the primary tumor (67). Of note, lobular breast cancers are inherently less ^{18}FDG-avid than ductal carcinomas (68). Also, dynamic contrast-enhanced MRI is more sensitive for the detection of small primary tumors (i.e. <1 cm) (69,70). ^{18}FDG PET may be useful in cases of inconclusive MRI, fatty breasts, and fibrotic tissue after initial surgery/ radiation, especially to guide a biopsy (67,71). For the purpose of loco-regional staging, SNB is the modality of choice for the detection of occult nodal involvement (i.e. axillary lymph nodes), especially in early-stage disease (T1-2N0M0) (72,73). On the other hand, ^{18}FDG PET appears particularly useful for staging distant metastases (67,71). In particular, ^{18}FDG PET is indicated in loco-regionally advanced disease (i.e. SNB positive) as well as in patients scheduled for neoadjuvant chemotherapy or chemoradiation (74). Of note, the detection of brain metastases and osteoblastic metastases is often suboptimal in ^{18}FDG PET imaging (75,76). In these clinical circumstances, conventional imaging (brain MRI) and bone scans should be performed. After treatment, ^{18}FDG PET is useful for assessing the metabolic response to conventional treatments, thereby eventually re-orienting the patient toward experimental therapies (67,77,78). Of particular clinical interest is the potential of whole-body ^{18}FDG PET for the detection of recurrences (Fig. 2) in patients with elevated tumor markers and/or equivocal conventional imaging (79).

In cervical cancer, increasing data indicate the usefulness of ^{18}FDG PET for whole-body staging with a potential impact on treatment choices and patient prognosis (80-83). In particular, ^{18}FDG PET was more sensitive than CT/MRI in the detection of nodal metastases, thereby influencing the treatment options in terms of fields of irradiation (i.e. pelvic plus para-aortic chains) and combined therapy modality (i.e. platinum-based chemotherapy plus radiotherapy). However, at an early stage of disease (FIGO IA-IIA), the detection of pelvic micrometastases may be suboptimal by using metabolic imaging; SNB as a minimally invasive procedure may play a role in this clinical setting (84). The use of ^{18}FDG PET appears to be particularly warranted in the post-treatment surveillance of cervical cancer for the detection of symptomatic and asymptomatic recurrences in the entire body (85). The recent introduction of PET-CT should improve the diagnostic accuracy of ^{18}FDG PET by using the anatomic information from the CT part (86). More studies are needed to define the role of ^{18}FDG PET in the management of cervical cancer.

In endometrial cancer, very few data from the literature are available with regard to the value of ^{18}FDG PET in pre-treatment staging. In a recent prospective study, metabolic imaging was moderately sensitive in predicting lymph-node metastases from endometrial cancer. Therefore, ^{18}FDG PET should not replace lymphadenectomy (87). On the other hand, two retrospective studies highlighted the usefulness of metabolic imaging in the post-therapy surveillance of patients with treated endometrial cancer (88,89). In both studies, similar conclusions showed the added-value of ^{18}FDG PET for the detection of symptomatic and asymptomatic recurrences with a potential impact on treatment choices in nearly one third of patients. Further studies are necessary in order to assess the prognostic value and cost-effectiveness of metabolic imaging (90).

In ovarian cancer, the value of ^{18}FDG PET is more controversial. Metabolic imaging is probably not indicated for the initial diagnosis of ovarian cancer. However, ^{18}FDG PET is a valuable tool for staging loco-regional and distant metastases (91,92). In particular, metabolic imaging may detect diffuse or macroscopic peritoneal deposits within the entire abdomen from the sub-diaphragmatic spaces to the pelvis; ^{18}FDG patterns of peritoneal involvement are often missed by conventional imaging. However, metabolic imaging cannot localize microscopic implants within the peritoneum (93). Similarly, well-differentiated serous/mucinous cystadenocarcinoma, borderline tumors, and pT1 adenocarcinomas are common causes of false negative results. In addition to physiological bowel retention or ureteral stasis, a number of benign gynecological diseases, such as mucinous cystadenomas, endometrial and follicular cysts, functional corpus luteum cysts, salpingo-oophoritis, fibromas, cystadenofibromas, teratomas, dermoid cysts, endometriosis, tubo-ovarial abscesses, benign thecoma, and schwanoma, may lead to false positive results (94). In the follow-up, ^{18}FDG PET appears clearly warranted for the detection of recurrent disease, especially in cases of elevated tumor markers and negative CT/MRI. Metabolic imaging may also be of clinical interest in monitoring the treatment, especially for optimizing neoadjuvant chemotherapy protocols (95,96). A positive PET post-treatment is strongly suggestive of recurrent/residual disease, which may avoid the need for invasive interventions. Although a negative PET following the primary therapy cannot exclude the presence of microscopic residual disease, recent data suggest that a negative PET in high-risk ovarian cancer treated by chemotherapy has a similar prognostic value to second-look laparotomy (97). The recent introduction of PET-CT devices should significantly enhance the diagnostic accuracy of metabolic imaging by reducing the number of false positive results as well as by improving the anatomic localization of ^{18}FDG-avid pathological sites (87,98).

Cancers of the male genital system. ^{18}FDG PET is clearly of limited value for the staging of patients with prostate carcinoma (99). At an early stage of its natural evolution, when the disease is still locally confined, metabolic imaging cannot detect microscopic tumor deposits within the prostate or adjacent structures. In more advanced stages, ^{18}FDG PET has a poor sensitivity for the detection of nodal involvement as well as for the localization of predominantly osteoblastic metastases. Because of their low proliferative activity, prostate tumors are most often poorly ^{18}FDG-avid. The proximity of the urinary tractus and the partial volume effect are additional causes that hamper the detection of such tumors. Thus, prostate carcinomas should not be explored by metabolic imaging for staging purposes. During the follow-up, ^{18}FDG PET may play a role in patients with elevated PSA, especially in those who escape hormonal dependence, thereby, presenting with a more aggressive tumor behavior. Unlike prostate cancers, ^{18}FDG PET may be of clinical interest in testicular cancers either for staging the disease prior to any treatment or for detecting a recurrence in follow-up. Metabolic imaging also appears useful for treatment decision-making. In a subset of patients treated by neoadjuvant chemotherapy, ^{18}FDG PET may detect residual viable masses for complementary surgery (100). So far, the sensitivity of metabolic imaging is low in cases of differentiated teratomas, necrotic or fibrotic tumors (quasi-complete response). Early after treatment (<2 weeks), false-negative results have been reported in patients with germ-cell carcinoma, which requires caution when assessing chemosensitivity with metabolic imaging (101). On the other hand, ^{18}FDG PET may be indicated for localizing late relapse (>2 years), especially following a rise of α-FP or ß-HCG; in this clinical setting, morphological imaging is often equivocal or falsely negative (102).

Cancers of the urinary system. In renal cell carcinoma (RCC), the role of ^{18}FDG PET is limited for localizing the primary tumor site owing to the physiological excretion of the glucose tracer through the urinary tract. The sensitivity of metabolic imaging was particularly insufficient in RCC of <5 cm (103). The weak to moderate expression of glucose transporter-1 (GLUT-1) observed in most RCC may also explain the lack of ^{18}FDG uptake even in large tumors (>5 cm). Hence, morphological imaging is indicated in a first-line imaging strategy for diagnosis purposes, especially for the accurate measurement of primary tumor dimensions. Similarly, MRI and CT are better than ^{18}FDG PET for assessing the renal architecture as well as for evaluating the tumor extent locally and beyond the calyces. In particular, key-invasive criteria, such as renal capsule disrupture, adrenal involvement, and renal veins and/or vena cava infiltration may be more accurately assessed by using high-resolution MRI. In advanced stages, metabolic imaging may be of clinical interest for the detection of regional nodal involvement and the staging of visceral metastases on the entire body. During follow-up, ^{18}FDG PET is also useful for the detection of recurrences or for evaluating the treatment efficacy (104). However, the sensitivity of metabolic imaging for staging and re-staging distant metastases from RCC may be insufficient; low or no ^{18}FDG uptake has been reported in patients with documented lesions from renal adenocarcinomas (105,106). This emphasizes the confrontation to conventional imaging when ^{18}FDG PET shows no abnormality. In bladder cancer, the role of ^{18}FDG PET is clearly limited when evaluating the depth of disease according to the TNM/UICC classification. Whether or not the cancer invades the sub-epithelial connective tissue, the superficial (inner half) or deep muscle (outer half) cannot be objectively assessed by PET imaging. This limits the value of metabolic imaging when the tumor is still confined within the bladder wall, especially in cases of microscopic lesions. Besides, the urine stasis most often prevents the localization of the bladder tumor. As a consequence, biopsy-guided cystoscopy and contrast-enhanced MRI are primarily indicated in early-stage disease. Otherwise, in advanced stages (>T3), metabolic imaging is of particular interest in detecting loco-regional involvement and distant metastases. Similarly, ^{18}FDG PET is useful for the detection of extravesical recurrences. Nonetheless, microscopic nodal metastases are most often missed in PET imaging. After surgery, the accurate interpretation of local recurrence may be particularly difficult because the normal anatomy is often modified. The recent introduction of combined PET-CT should significantly improve the diagnostic accuracy in cancers derived from the urinary tract (107).

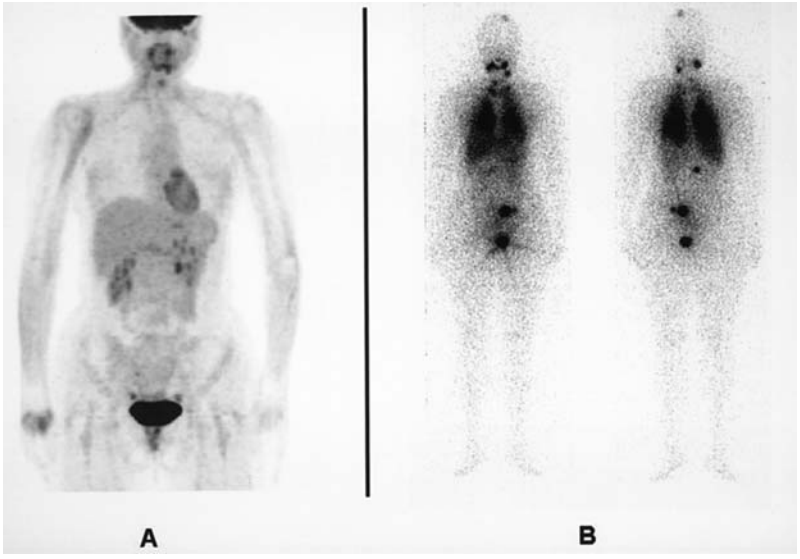

Figure 3. A case of well-differentiated thyroid cancer (follicular type) previously treated by total thyroidectomy and ^{131}I-iodine therapy. The rise of tumor marker (thyroglobuline) indicated a complete work-up. A, whole-body ^{18}FDG PET showed normal distribution. B, whole-body scan following a therapeutic dose of ^{131}I-iodine revealed a 'flip-flop' imaging pattern with multiple ^{131}I-avid but ^{18}FDG-non-avid metastatic sites (skull, lungs, nodes, skeleton).

Head and neck cancer. In malignancies affecting the oral cavity, the pharyngeal or laryngeal sphere, metabolic imaging cannot accurately detect small tumors and most infracentimetric nodes because of its limited spatial resolution (108). Also, for the purpose of initial staging, ^{18}FDG PET is proving of limited value for stage 0 (*in situ*) tumors, and early stage-I and -II disease. Similarly, metabolic imaging alone cannot precisely assess the tumor involvement in adjacent structures (i.e. vessels, nerves, muscles, and fat tissue). As such, enhanced-MRI remains the modality of choice for loco-regional staging. Also, the role of SNB is increasingly documented in N0 patients either to detect occult nodal metastases or to avoid unnecessary lymphadenectomies (109,110). In patients with oral and oropharyngeal cancers with no ^{18}FDG uptake (i.e. cN0), the combination of PET (high specificity) plus SNB (high sensitivity) was cost-effective for staging regional lymph-node metastases while reducing the rate of elective neck dissections (111). In head and neck cancer patients scheduled either for (chemo)radiation or surgery, recent data also indicate the potential of pre-treatment ^{18}FDG tumor uptake to predict outcome in terms of local control and disease-free survival (112). In patients with advanced head and neck tumors, ^{18}FDG PET may significantly impact the tumor staging and, thus, the treatment choices by the detection of distant metastasis, especially at the lung or mediastinum (113). Whole-body ^{18}FDG PET is of clinical interest for the detection of a second primary tumor as well as for the localization of occult primaries in patients presenting with cervical nodal metastasis (114). After treatment, ^{18}FDG PET can help in the differentiation between residual/recurrent tumors and normal tissue sequelae, especially when the physical examination and CT scan are equivocal. Preliminary studies report some potential of ^{18}FDG PET for the detection of recurrent disease in T1 and T2 stages (i.e. laryngeal carcinoma). In advanced stages, the diagnostic accuracy of ^{18}FDG PET is well established compared to conventional imaging mainly because of its higher specificity. In the process of post-therapy monitoring, a positive PET scan at a primary or nodal site 1 month after radiotherapy is highly suggestive of residual disease, while a negative scan at 4 months post radiation can confidently rule out recurrent tumor (115). ^{18}FDG PET may improve the patient's management in terms of adequate treatment and reduced cost by avoiding futile interventions (i.e. surgery or panendoscopy for non-resectable tumors and benign lesions detected by CT); this is particularly true for patients with advanced tumors and recurrent laryngeal carcinoma (116). The recent introduction of combined PET-CT should significantly improve the management of patients with head and neck cancer but the exact role of this emerging technique is yet to be defined (117).

Soft tissue and bone sarcomas. In sarcomas of the bone and soft tissue, ^{18}FDG PET may play a useful role in pre-treatment staging, considering that the primary diagnosis remains biopsy-proven (118). Osteosarcomas, Ewing sarcomas, chondrosarcomas, and high-grade tumors in general, have been shown to exhibit high ^{18}FDG uptake (119). Conversely, low-grade sarcomas, especially low-grade liposarcomas and chondrosarcomas, often express low ^{18}FDG avidity (120). On the other hand, besides infectious and inflammatory lesions, a number of benign soft tissue and bone tumors may be ^{18}FDG-avid. False positive results include giant cell tumors, chondroblastoma, fibroma, fibrolipoma, Langerhans cell histiocytosis, non-ossifying fibroma, eosinophilic granuloma, and fibrous dysplasia (118,121). In patients with histologically confirmed sarcomas, the ^{18}FDG tumor uptake has been shown to be correlated to the tumor grade as well as to end-point survival (119). Also, metabolic imaging may be of interest for evaluating the efficacy of treatment (122). So far, in early stages, when the disease is locally limited, MRI is preferred for a better delineation of soft tissue involvement from the contiguous bone (123). The use of PET-CT may significantly

Table III. Potential causes of false negative results in ^{18}FDG PET imaging: tumors presenting with variable or low ^{18}FDG-avidity.

Non-CNS tumors	Comments	Refs.
Low-grade lymphomas	FN: lymphocytic lymphoma - marginal zone lymphoma - peripheral T-cell lymphoma - mucosa-associated lymphoid tissue (MALT).	(42-45)
Neuroendocrine tumors	FN: well-differentiated and typical neuroendocrine tumors (i.e. carcinoids).	(125)
Differentiated thyroid carcinomas	'Flip-flop' phenomenon[a] (i.e. follicular and papillary thyroid carcinomas).	(127)
Prostate carcinomas	Not indicated: low or no ^{18}FDG uptake.	(99)
Lobular breast carcinomas	Lower ^{18}FDG uptake in lobular carcinomas than ductal carcinomas.	(68,72,73)
Osteoblastic metastases	Lower ^{18}FDG uptake in osteoblastic metastases versus osteolytic lesions; CT/MRI and bone scan required, especially in prostate and breast cancers.	(76)
Ovarian cystadenocarcinomas	FN: well-differentiated serous/mucinous tumors; morphological imaging required.	(91,92)
Bronchoalveolar lung carcinoma (BAC)	FN: no significant ^{18}FDG uptake in most BAC (>50%), especially in those with no invasive features.	(25,26)
Gastro-esophageal junction carcinomas (GEJ)	No significant ^{18}FDG uptake in nearly 30% of GEJ.	(4,5,7)
Gastric carcinomas	Low ^{18}FDG uptake related to diffuse growth, poor differentiation, and high mucus content.	(4,5,7)
Hepatocellular carcinomas (HCC)	No significant ^{18}FDG uptake in nearly 50% of HCC. ^{18}FDG avidity related to the degree of differentiation.	(19)
Cholangiocarcinomas (CC)	Controversial data; lower ^{18}FDG uptake in hilar CC than peripheral CC.	(20)
Renal cell carcinoma (RCC)	No significant ^{18}FDG uptake in most RCC (>50%) related to weak expression of GLUT-1, size (≤5 cm) and high background (urine stasis). FN also reported in distant metastases/recurrences. Morphological imaging required.	(103,104)
Mucinous/cystic GI cancers	FN: low or no ^{18}FDG uptake. Morphological imaging required.	(14)
Low-grade sarcomas	FN: early-stage sarcomas (stages I and II); low-grade liposarcomas and chondrosarcomas.	(118,119)

FN, false-negative results. [a]'Flip-flop' phenomenon, mismatched imaging patterns with either ^{131}I-avid/^{18}FDG non-avid or ^{18}FDG-avid/^{131}I non-avid tumor sites respectively. Alterations of the mechanisms of uptake involving the iodine-pump may explain the shift to ^{18}FDG-avid tumors. GLUT-1, glucose transporter 1 as early marker of malignant transformation is overexpressed in most FDG-avid cancers.

improve the definition of tumor extent (i.e. bone versus soft tissue lesions, and intramedullary versus extramedullary invasion).

Endocrine cancers. Evidence-based medicine showed that ^{18}FDG PET is likely not to be indicated in the first-line imaging strategy of most endocrine cancers (124). From thyroid cancers (papillary and follicular tumors) to neuroendocrine tumors (carcinoid, pheochromocytoma, paraganglioma), this kind of malignancy primarily includes well-differentiated cancers (Fig. 3). As such, metabolic imaging using the glucose analogue as a marker of tumor growth and proliferation appears to be less sensitive than conventional imaging tracers using radioiodine, $^{131/123}$I-MIBG, and Octreotide-DTPA-In^{111}. On the other hand, ^{18}FDG PET is the best imaging modality in cases of atypical tumors and less-differentiated tumors; malignancies that express a more aggressive behaviour with a propensity to disseminate (125). Accordingly, ^{18}FDG PET may yield prognostic information in differentiated thyroid cancer by differentiating high-risk patients with ^{18}FDG-avid metastases from low-risk subjects with ^{18}FDG-non-avid metastases (126). Additionally, alterations of the mechanisms of uptake involving the iodine-pump or the noradrenaline analogues, and the de-differentiation of somatostatin receptors may explain the shift to ^{18}FDG-avid tumors (127). Also, the histological type and grading of endocrine tumors should be taken into account for the most appropriate indication of ^{18}FDG PET in the staging of endocrine tumors. For instance, in undifferentiated/anaplastic thyroid cancer, and Hürtle cell carcinomas, metabolic imaging is proving efficient when ^{131}I-iodine uptake is low or absent (128,129). In this kind of thyroid cancer, ^{18}FDG PET may be included in the initial work-up as

well as in follow-up surveillance. Last but not least, metabolic imaging may also play a useful role for the documentation of recurrent/ persistent disease in patients with elevated tumor markers (i.e. TG, NSE, TCT, Chromogranin-A) while the conventional work-up is non-contributive (124,127,129,130).

Cancers of unknown origin. In approximately 5% of cancers, the primary site is unknown. This often leads to repeated, cost-prohibitive, and fruitless biological and radiological studies. In cancers of unknown origin (CUO), the type of metastases (carcinoma, lymphoma, well-differentiated, undifferentiated, or neuroendocrine) as well as the site of metastases (brain, liver, nodal, lung, peritoneal), probably impact the sensitivity of metabolic imaging for the detection of the primary malignancy. As a rule, ^{18}FDG PET appears to be particularly useful in CUP syndromes for localizing the primary tumor and, at the same time, staging the extent of disease in the entire body (131). Metabolic imaging may also significantly influence the treatment options with a potential impact on survival (132). As a practical consequence, ^{18}FDG PET should be indicated in a first-line imaging strategy for cost-effective management of CUP syndromes. Morphological imaging (CT/MRI) may be used as a second step for a guided-biopsy or for a targeted treatment (133,134). Table III highlights the main causes of false negative results in ^{18}FDG PET imaging as observed in various types of cancers.

4. Conclusion

The introduction of ^{18}FDG PET in the clinical setting has revolutionised the management of oncology patients. In many circumstances, metabolic imaging provided the best information for an accurate staging of disease, a more precise prognosis, and an appropriate treatment. However, in well-differentiated cancers, low-grade malignancies, and poorly aggressive tumors, the use of ^{18}FDG PET has been shown to reach its clinical limitations. The lack of anatomical landmarks and the limited spatial resolution of PET devices may be considered as the worst aspect of metabolic imaging. The development of combined PET-CT devices as well as the availability of more specific PET tracers will help overcome the technical and biochemical limitations of ^{18}FDG PET. Interactive exchanges between nuclear medicine physicians, radiologists, and oncologists are continuously needed to rationalize the clinical use of metabolic imaging.

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