Imaging and PET — PET/CT imaging

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Résumé

Imagerie TEP — imagerie TEP scanner

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L'utilisation de la TEP-TDM a de beaucoup augmenté puisque la fusion des images TEP à l'imagerie anatomique des coupes de la TDM est très utile. L'addition de la TDM à la TEP augmente la sensibilité et la spécificité de la TEP, et l'addition de la TEP à la TDM augmente la sensibilité et la spécificité de la TDM pour l'imagerie oncologique. L'effet synergique de l'addition de la TDM à la TEP facilite la correction du coefficient d'atténuation requis par la TEP, puisque ce dernier peut être obtenu par l'analyse de l'information TDM. Cette combinaison réduit le temps d'acquisition de la TEP-TDM de 25-30 % comparé à l'acquisition TEP unique, permettant ainsi d'imager un plus grand nombre de patients, tout en leur assurant un plus grand confort avec une durée d'examen réduite à 20 minutes. L'acquisition combinée FDG-TEP et TDM fournit une information pertinente à la classification et au suivi de plusieurs tumeurs, dont le cancer du poumon, le cancer du colon, le lymphome, les cancers gynécologiques, le mélanome ainsi que plusieurs autres, avec cependant une exception notable, le cancer de la prostate. Pour ce dernier, les dérivés de la choline pourraient possiblement être utilisés comme traceurs. Les publications sur l'application de la TEP-TDM en oncologie demeurent encore peu nombreuses, mais plusieurs essais cliniques valables ont démontré les avantages de cette technique d'imagerie.

Mots-clés : TEP/TDM. Imagerie fonctionnelle. Oncologie. Tumeur maligne. FDG. Métabolisme.

Abstract

PET-CT has grown because the lack of anatomic landmarks in PET makes "hardware-fusion" to anatomic cross-sectional data extremely useful. Addition of CT to PET improves specificity, but also sensitivity, and adding PET to CT adds sensitivity and specificity in tumor imaging. The synergistic advantage of adding CT is that the attenuation correction needed for PET data can also be derived from the CT data. This makes PET-CT 25-30% faster than PET alone, leading to higher patient throughput and a more comfortable examination for patients typically lasting 20 minutes or less. FDG-PET-CT appears to provide relevant information in the staging and therapy monitoring of many tumors, such as lung carcinoma, colorectal cancer, lymphoma, gynaecological cancers, melanoma and many others, with the notable exception of prostatic cancer. For this cancer, choline derivatives may possibly become useful radiopharmaceuticals. The published literature on the applications of FDG-PET-CT in oncology is still limited but several well designed studies have demonstrated the benefits of PET-CT.

Key words: PET/CT. Functional imaging. Oncology. Malignant tumor. FDG. Metabolism.

Introduction

Since the first proof of concept PET/CT (Positron Emission Tomography/Computed Tomography) system devised by Townsend started to operate in 1998 and the first world-wide clinical PET/CT scanner came into operation in March 2001, PET/CT has developed into the fastest growing imaging modality world-wide (1, 2). The success of this combined modality is mainly due to the fact, that combined PET and CT data acquisition with F-18 fluorodeoxyglucose (FDG) is essentially synergistic in the diagnostic accuracy in oncological applications. The integration of both modalities provides precise localization of the lesions on the FDG-PET scans within the anatomic orientation provided by CT, thereby increasing specificity of the examination since "hardware-fused" PET/CT images are made available at the end of the examination. CT data of a PET/CT examination are also used to correct the PET emission images for photonic self attenuation by the human body (3-5). Only if attenuation correction

is performed, quantitative measurements of SUV (Standardized Uptake Values) in PET images can be obtained routinely. The use of the fast CT data acquisition in combination with fast 2D and 3D-emission data acquisition makes PET/CT approximately 50% faster than PET alone, which results in a more efficient use of the fast decaying PET radiopharmaceuticals (3); an examination lasts 20 minutes or less. In this article, the various applications of FDG-PET/CT in the evaluation of oncological as well as non-oncological disease will be discussed, as well the possible indications to perform a combined intra-venous contrast enhanced PET/CT.

General aspects of PET/CT

1. Technical issues

Not only different crystal materials used for photon detection, but also two different data acquisition modes for emission scanning followed by various image reconstruction algorithms do complicate the comparison of the available PET/CT scanner systems. Lutetium (LSO, LYSO) — Germanium (GSO) as well as Bismutgermanate (BGO)-based crystals are used in different scanner types (6-8). PET-emission data is acquired in 2D- as well

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as in 3D-mode, whereas 3D-mode seems to be the preferential method. Additionally, different new reconstruction algorithms are used to improve image quality (9, 10). As seen in CT alone imaging, multi-row CT scanners with increased scan coverage up to 64-rows are implemented into PET/CT systems. Even though, CT scans are used for attenuation correction, multi-slice capabilities are getting more attractive, since additional contrast-enhanced studies are getting included into the standard PET/CT routine protocols. CT data is foremost used for attenuation correction and as anatomic reference frame in PET/CT. The measured attenuation maps in PET/CT are the CT images obtained from polychromatic X-rays of around 100 keV. These are transformed to μ -maps at the spatial resolution corresponding to the PET images, and correspond to attenuation images at 511 keV, the photon energy relevant in PET. It turns out that this transformation is relatively simple and can be achieved by a bi-linear lookup table with its inflection point at 0 Hounsfield units (5).

The artefacts, which can be generated in PET images due to the use of CT data transformed into μ -maps, are related to the use of concentrated CT contrast agents, CT beam hardening artefacts due to metallic implants and physiologic motion. It is currently advised to use imaging protocols in PET/CT which make use of dilute oral contrast agents for bowel opacification in PET/CT, and not to use i. v. bolus contrast CT data for attenuation correction. As the latter can be quickly acquired at the end of a PET/CT examination with a state-of-the-art CT, this poses no major limitation to develop “one-stop-shop” imaging protocols in PET/CT (11, 12). Additionally, major artefacts occur in the regions adjacent to the heart and the diaphragm. Specifically, PET data are acquired most frequently during free breathing, which corresponds largely to an end-expiratory position of the diaphragm, while CT is normally acquired at maximum inspiration. This leads to an anatomic mismatch between the two data sets with the lungs more expanded in CT. An analysis of this problem has shown that with the modern fast CT scanners it is probably best to also acquire the CT data during tidal breathing. Ideally, the CT data are acquired during end expiration, but frequently patient cooperation is problematic to achieve this (13).

2. Issues relevant in clinical imaging protocols

Patients have to be fasting for at least 4 hours prior to the FDG injection. Blood glucose measurements are performed routinely to detect patients with a possibly previously undetected diabetes. If patients were truly fasting, blood glucose levels in non-diabetic patients are normally below 8 mmol/l. However, in diabetic patients fasting more than 4 hours, an elevated blood glucose level above 8 mmol/l can be detected. Even though, routine injection of standard dose of 370 MBq of FDG can be injected without decrease in image quality. Therefore, the most important procedure is to ensure that the fasting time has been at least 4 hours. In diabetic patients with elevated glucose levels even though patients have been fasting, injection of fast acting insulin should not be performed, since the insulin will move the FDG into the muscles, due to insulin dependent transport. Routinely, oral contrast (e.g. Micropaque Scanner, Guerbet AG, Aulnay-sous-Bois, France) is administered 15 to 30 minutes prior to FDG injection, since adequate distribution in the intestinal structures is achieved typically after 60 minutes. The application of barium-sulphate containing oral contrast agents is a safe procedure and mostly

used for out-patient imaging. It has been shown that the use of CT data for transmission correction does not alter the size of the lesion significantly and that the SUV (Standardized Uptake Value) values measured do not differ significantly from those obtained with radioactive source transmission correction, except when the lesion is in body regions fraught with one of the problems discussed above (14). As a result of this basic information and data showing that PET lesion specification by CT does not improve when the tube current is increased above 20-60 mAs in normally sized patients (3). Bladder voiding just prior to scanning to eliminate the renally excreted FDG is mandatory. The average whole body patient dose at 40 mAs is approximately 3 mSv and adds up to the approximately 8 mSv for a standard dose of 370 MBq FDG. Obviously, the main contraindication is to perform PET/CT in pregnant women.

While most PET/CT users consistently give dilute oral CT contrast agent for the examination, things are not as clear with I. V. contrast agents. I. V. contrast in CT is used for two purposes: lesion characterization and vessel delineation. FDG is frequently much better in characterizing a lesion than i. v. contrast involving tumor imaging; hence the main reason for giving I. V. contrast agent during the CT examination part is a better delineation of vessels. PET/CT in tumor staging is typically run as a head to pelvic floor examination, but the contrast enhanced study may be relevant only in a sub-region (i. e. CT contrast enhancement in the head & neck region in a head and neck tumor patient). The use of i. v. contrast agent will have to be further explored in the coming years and protocols have to be specified for the various imaging questions to be answered with PET/CT.

As a general rule for the interval between the end of treatment and PET/CT imaging, PET/CT can be performed 2 weeks after the end of chemotherapy treatment to assess the therapy response. For certain special indications like in gastro-intestinal stroma tumors (GIST), imaging can be performed even after 7 days to evaluate the successful treatment (15). In radiation treatment, a minimum interval of 6 weeks should be used after end of treatment, to reduce FDG-uptake due to inflammatory changes especially in the ENT region (16).

PET/CT in chest tumors

Integrated PET/CT adds significant clinical information in comparison to PET alone, CT alone or image comparison of separate PET and CT, due to better lesion identification and localization and fewer overlooked lesions in tumors not consistently accumulating FDG (17-19). In carcinoid tumors, bronchiolo-alveolar lung carcinoma and malignant effusions, diagnosis can sometimes only be based on the CT findings.

The advantage of PET/CT over PET in characterizing pulmonary nodules has not been defined yet. In tumor staging, conventional PET is unsuitable for T staging as it cannot help to anatomically define the tumor extent. Matters with PET/CT are somewhat different. It has been shown that in T staging of patients with lung cancer analysis of integrated PET/CT images is superior to CT alone, PET alone, and PET and CT viewed side by side (17). Due to the exact correlation of the extent of FDG uptake to anatomy, focal chest wall infiltration, mediastinal invasion and differentiation of tumor from atelectasis is improved. The latter is particularly important for the planning of radiotherapy in

patients with lung cancer associated with an atelectasis (20). However, PET/CT imaging with unenhanced CT is unable to distinguish contiguity of tumor with the mediastinum from the direct invasion of the walls of mediastinal structures and still must rely on contrast enhanced (ce) CT to define mediastinal vascular invasion.

PET/CT has proven to be a very effective for mediastinal nodal staging. Nevertheless, mediastinoscopy remains the gold standard for mediastinal staging, even if not all mediastinal lymph nodes can be accessed by mediastinoscopy, particularly in the paraaortic region and in aorto-pulmonic window. Most centers will still perform mediastinoscopy, if a lymph node is identified on PET/CT as pathological, which would preclude a surgical approach. In patients with bulky mediastinal disease or multi-level nodal involvement, the assessment of N stage is easy. However, exact localization of a solitary lymph node metastasis in the hilus and thus classification as N1 or N2 disease is difficult, but important (21). The anatomic information of CT in PET/CT may be useful here. Whole-body FDG PET is an excellent method to screen for extrathoracic metastases. The advantage of integrated PET/CT imaging is the exact localization of a focal abnormality on PET. This was the case in 20% of all patients with extrathoracic metastases in our study on the value of integrated PET/CT (17).

FDG PET has been shown clinically useful in the evaluation of suspected lung cancer recurrence. Although FDG PET is a sensitive metabolic imaging modality, it lacks specificity after therapy, due to FDG accumulation in irradiated tissues and postsurgical inflammatory changes.

PET/CT in colorectal cancer and other abdominal tumors

1. Initial staging

The effectiveness of FDG PET/CT at initial diagnosis has been evaluated to date only in few studies, but the usefulness of PET suggests that its use is indicated (*fig. 1*). Whole body PET/CT with integrated colonography is technically feasible for whole body staging in patients with colorectal cancer. Further, compared with optimized abdominal CT staging alone, PET/CT colonography was significantly more accurate in defining TNM stage, which was mainly based on a more accurate definition of the T-stage. Differences were not detected for defining N-stage between PET/CT colonography and CT alone with a threshold of 0.7 cm for malignant nodes but were detected with a threshold of 1 cm (22, 23).

Fig. 1 : 49-year-old male patient with a known colon cancer of the right colonic flexure. Contrast-enhanced FDG — PET/CT performed for staging purpose.
a-d Maximum intensity projection (MIP) (a) demonstrates uptake in the right upper abdomen. Transaxial PET (b), contrast-enhanced CT (c) and fused PET/ceCT (d) at the level of the tumor demonstrates infiltration of pericolic fatty tissue and possible infiltration of the pancreatic head, proven at surgical exploration. Note the advantage of fused contrast-enhanced CT images with PET information as a single-step exam.

Further, management in treatment was changed due to the PET/CT findings compared to dedicated ceCT in 9% of the cases (24).

2. Recurrent disease

In recurrent disease, the morphology based information in CT does not permit distinction between post surgical changes and tumor recurrence nor can it detect tumor involvement of normal sized lymph nodes (25). In a study by Cohade et al., a direct comparison of PET and non-contrast enhanced PET/CT in 45 patients with known colorectal cancer demonstrated an improvement in diagnostic accuracy from 78% to 89% using PET/CT compared to PET alone (26). Not only did PET/CT improve the localization of lesions, but also the certainty in interpreting lesions as normal or definitively abnormal. A considerable limitation of this study was retrospective analysis and the missing comparison to contrast-enhanced CT studies. In the study by Selzner et al., the diagnostic value of contrast-enhanced CT (ceCT) and non-enhanced PET/CT were prospectively evaluated against each other in 76 patients referred for preoperative evaluation for liver resection for metastatic colorectal cancer (27). Detection of intrahepatic tumor load, extra/hepatic metastases, and local recurrence at the colorectal site were evaluated. The main end-point of the study was the assessment of the impact of the PET/CT findings on the therapeutic strategy. ceCT and PET/CT provided comparable findings for the detection of intra-hepatic metastases with a sensitivity of 95% and 91%, respectively. However, PET/CT was superior in establishing the diagnosis of intra-hepatic recurrence in patients with prior hepatectomy (spe-

cificity 50% vs. 100%, $p=0.04$). Local recurrences at the primary colo-rectal resection site were detected by ceCT and PET/CT with a sensitivity of 53% and 93%, respectively ($p=0.03$). Extra-hepatic disease was missed in the ceCT in one-third of the cases (sensitivity 64%), while PET/CT failed to detect extrahepatic lesions in only 11% of the cases (sensitivity 89%) ($p=0.02$). New findings on PET/CT resulted in a change in the therapeutic strategy in 21% of the patients. This study also demonstrated the well known limitation in spatial resolution of around 4-6mm of PET imaging since small tumors (e.g. < 5mm) were often not detected. Also the use of chemotherapy within the month prior to PET/CT resulted in a high incidence of false negative results. On the other hand, this effect might be used as a predictor of success in neo-adjuvant chemotherapy before resection.

From a logistical and clinical point of view, an intravenous contrast-enhanced study is essential to define exact localization of intra- as well as extra-hepatic lesions. Therefore, it can be recommended that PET/CT in the evaluation of suspected recurrent disease should be performed as a contrast-enhanced PET/CT study since the patient otherwise has to return for an additional contrast-enhanced CT study (fig. 2).

3. Gastrointestinal stromal tumors

In two recent studies it was shown that patients without FDG uptake after the start of treatment had a better prognosis than patients with residual activity which is not demonstrated with ceCT (15, 28). Furthermore, lesions were better defined on PET/

Fig. 2 : Same patient as fig. 1 in the post-operative evaluation 6 months after surgery. Maximum intensity projection (MIP) (a) demonstrates uptake in several locations in the upper abdomen. Transaxial PET (b), contrast-enhanced CT (c) and fused PET/ceCT (d) at the level of the superior mesenteric artery (arrow head) demonstrates uptake in a mesenteric lymph node.

CT than when comparing PET and CT side-by-side. This is relevant information for clinical decision making.

PET/CT in lymphoma imaging

Hodgkin's lymphoma (HD) and Non-Hodgkin lymphomas (NHL) usually show avid FDG-uptake at initial staging (*fig. 3*) (29-31). In most PET studies, both diseases have been studied as one group. In comparison to morphological imaging with ceCT, metabolic imaging with FDG-PET showed a higher specificity in staging disease (30). A major indication for FDG-PET imaging is the evaluation of treatment response after completion of therapy, especially in those patients with residual masses, where it is unclear whether these masses represent tumor persistence (32, 33). In comparison to other nuclear medicine studies, FDG-PET shows a significant higher site and patient sensitivity than Ga-67 scintigraphy in staging as well as early therapy evaluation (34, 35).

To date, results regarding the use of FDG PET/CT in staging and restaging HD and NHL are limited (36, 37). Initial results suggest that PET/CT acquired with a non-contrast-enhanced CT scan is more sensitive and specific than ceCT for the evalua-

tion of lymph node and organ involvement in patients with HD and aggressive NHL (37). Especially in patients with FDG-avid bone lesions, FDG-PET is superior to CT alone or in combination with unilateral bone marrow biopsy in detecting bone marrow involvement, leading to upstaging in a relevant proportion of patients (38). Regarding therapy response evaluation, end-treatment PET/CT seems to be unnecessary if interims PET/CT shows complete metabolic response and the clinical course is uncomplicated. An imaging cost reduction of 27% in the study population could have been achieved by omitting end of treatment FDG-PET/CT in interim complete metabolic responders (39).

Regarding the use of intravenous-contrast-enhanced PET/CT, the available data suggests that intravenous contrast should be used when vascular compression/thrombosis has to be ruled out. Otherwise, for response assessment, ceCT is not needed.

PET/CT in head and neck (HN) tumors

Early results suggest that PET/CT is useful in HN tumors for loco-regional staging, identification of distant metastases and in therapy monitoring (40).

Fig. 3 : 26-year-old female patient with a newly diagnosed Hodgkin's disease. **a-d** Maximum intensity projection (MIP) (a) demonstrates uptake in lymphatic regions of the neck, axilla and mediastinum on both sides. Further diffuse uptake in the bone marrow is seen. Transaxial PET (b), non-contrast-enhanced CT (c) and fused PET/CT (d) demonstrates uptake in enlarged lymph nodes in the right axilla (arrow) as well as intrapulmonary soft tissue mass (arrow head), indicating stage IV disease by organ involvement. Bone marrow activation was due to anemia.

1. Loco-regional staging

The literature on the use of PET/CT regarding loco-regional staging in HN tumors is still sparse, but the easier differentiation of normal from abnormal FDG accumulations and the identification of tumor involved lymph nodes of normal size appear to be the major advantages. In a recent study of 68 patients with 168 abnormal foci of FDG uptake, it was found that PET/CT was relevant in determining the exact location in 74% of the lesions in patients with prior surgery, and in 58% in patients in untreated areas (40). The number of lesions whose pathological significance was equivocal on PET was 39, in PET/CT this number was decreased to 18. Impact on management occurred in 18% of patients.

2. Distant metastases

While such metastases are relatively infrequent in HN tumors, the information is relevant in view of the fact that the major therapeutic approach to HN tumors is surgery and radiation therapy. Obviously, finding a distant metastasis precludes a curative approach. In addition to detecting metastases, PET also is able to detect synchronous or metachronous tumors (41). Relevant tumors include lung and oesophageal carcinoma.

3. Detection of recurrence

Detection of recurrence of HN tumors with CT and MR is notoriously difficult because of the frequent alteration of the anatomy due to extensive surgery and persistent contrast enhancement of non-malignant tissue. PET has been found to have a high negative predictive value as it is excellent in excluding recurrence but only a moderate specificity (42, 43). This is due to persistent FDG accumulation in the HN regions exposed radiation therapy, which is due to sterile inflammation (44). PET/CT has the same problem, but the anatomic correlation helps to identify a biopsy site, if biopsy is deemed to be necessary for definitive exclusion of tumor recurrence.

It is somehow obvious that a contrast-enhanced study is needed at the time-point of staging, as well as restaging, since the complex anatomy only can be assessed by the use of contrast enhancement. The infiltration of adjacent structures, as well as the typical aspect of partly affected lymph nodes, is only visible on contrast-enhanced studies. However, also here, it is not clear whether a recently performed, separate contrast-enhanced CT study is sufficient or a combined contrast-enhanced PET/CT is necessary.

Other indications

1. Thyroid carcinoma

Patients with differentiated thyroid cancer commonly are diagnosed and treated with iodine-131 (¹³¹I), if thyroglobulin level is elevated. In a study by Shamma et al., 61 consecutive patients with elevated thyroglobulin levels or a clinical suspicion of recurrent disease underwent 18F-FDG PET/CT. They concluded that PET/CT imaging provided precise anatomic localization of recurrent or metastatic thyroid carcinoma, leading to improved diagnostic accuracy. In addition, the findings of this study sug-

gested that further assessment of ¹³¹I WBS-negative, thyroglobulin-positive patients by 18F-FDG PET/CT may aid in the clinical management of selected cases (45).

2. Primary liver tumors and pancreatic carcinoma

In a study by Petrowsky et al., 61 patients with proven malignancies of the biliary tract were evaluated by PET/CT. PET/CT detected all gallbladder cancers. PET/CT and ceCT provided a comparable accuracy for the primary intra- and extra-hepatic cholangiocarcinomas. All distant metastases were detected by PET/CT, but only 25% by ceCT. Regional lymph node metastases were detected by PET/CT and ceCT in only 12% vs. 24%. PET/CT findings resulted in a change of management in 17% of patients deemed resectable after standard work-up (46).

Differentiation of pancreatic masses into chronic pancreatitis or pancreatic carcinoma remains difficult with all imaging modalities. In a study by Heinrich et al., 59 patients with suspected pancreatic cancer were staged by abdominal CT, chest X-ray and CA 19-9 measurement and FDG-PET/CT, and findings were confirmed by histology (47). Cost benefit analysis was performed based on charged cost of PET/CT and pancreatic resection. The positive and negative predictive values for pancreatic cancer were 91% and 64%, respectively. False-positive results were due to inflammatory pseudotumor, pancreatic tuberculosis, chronic pancreatitis and focal high-grade dysplasia, which was suspicious for malignancy by brush cytology. PET/CT detected additional distant metastases in five and a synchronous rectal cancer in two patients. PET/CT findings changed the management in 16% of patients with pancreatic cancer deemed resectable after routine staging ($p=0.031$). In total, PET/CT reduced cost by \$74,925 (\$1,270 per patient). Despite its impact on the staging of pancreatic cancer, neither PET nor PET/CT can replace ceCT and endoscopic ultrasound.

Obviously, also for the above mentioned indications, contrast-enhanced CT studies are indispensable in the assessment of local and loco-regional disease extension.

3. Gynaecological tumors

To date, only few studies using PET/CT for restaging ovarian cancer are available (48, 49). In the study by Sironi et al., 31 women with ovarian carcinoma were treated with primary cytoreductive surgery (48). In all patients, histologic examination after surgical second-look was used to determine the diagnostic accuracy of PET/CT in the evaluation of disease status. The overall lesion-based sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT were 78%, 75%, 77%, 89% and 57%, respectively. In the detection of a tumor, a size threshold could be set at 5 mm, as this was the largest diameter of a lesion missed at PET/CT. The use of non-enhanced PET/CT improved the diagnostic accuracy compared to PET alone but was not as effective as fusion of contrast-enhanced CT images and FDG PET images demonstrated in other studies (50). Therefore, it is possible that IV-contrast enhanced PET/CT may become the technique of choice in staging of recurrent ovarian cancer (fig. 4).

Worldwide, *carcinoma of the uterine cervix* is the second most common cancer among women. One of the major factors in survival is the local extent of the disease (51). Even though the presence of lymph node metastases in the pelvic or para-aortic re-

gions does not change the stage, it does lead to changes in therapy, in particular of the radiation treatment plan. When using conventional radiological procedures like US and CT, the sensitivity for detection of para-aortic lymph node metastases was low in 1990 (20–40%) (52). In the study by Grigsby et al., tumor involvement of para-aortic lymph nodes using FDG-PET alone was better than standard CT (53). More importantly, PET findings were a better predictor of survival than those in CT. To date, in only few studies, PET/CT was used in the evaluation of gynecological malignancies, including mainly endometrial and cervical cancer. In a study by Sironi et al., PET/CT proved to be valuable for lymph node staging in patients with early-stage cervical cancer, with short-axis diameter greater than 0.5 cm being the size threshold for accurate depiction of metastatic nodes (54). In the study by Grisaru et al., 53 patients with different gynecological tumors were evaluated for staging or re-staging purpose using PET/CT and results compared to conventional imaging studies including CT and MRI (55). All ratios for sensitivity, specificity, positive and negative predictive values ranged over 93%, whereas sensitivity and specificity ratios for conventional imaging studies were 40% and 64%, respectively. A more elaborate work by the same authors demonstrated the usefulness of PET/CT in the localization of FDG uptake in the uterus and could differentiate physiological from pathological uptake in the uterus and ovaries (56). Most interestingly, increased uptake in the endometrium adjacent to a cervical tumor did not necessarily re-

flect endometrial tumor invasion. Additionally, increased ovarian uptake in postmenopausal women was associated with malignancy, whereas increased ovarian uptake may be functional in premenopausal patients.

4. Breast cancer

At present, the major clinical application of whole-body FDG PET is the assessment of systemic metastatic disease. The clinical value and the advantages of integrated PET/CT compared with PET alone are not yet clearly defined. Recent studies suggest an only marginal benefit in the use of PET/CT compared to PET alone imaging (57, 58). Integrated PET/CT may play an important role in planning radiation therapy, by providing an accurate estimate of the tumor extent (59).

5. Melanoma

Malignant melanoma can metastasise to any part in the body, including the brain, the gastrointestinal tract, and the myocardium. It is well known that malignant melanoma is one of the most avidly FDG-accumulating tumors. With exception of the brain, whole-body FDG PET is a very sensitive and effective imaging modality to stage patients with a high likelihood of metastases (Breslow ≥ 2 mm, known metastases). In patients in whom surgery is planned, whole-body PET/CT should be performed to exclude occult metastases (60).

Fig. 4 : (A-D) 53-year-old female patient with suspected ovarian cancer and retroperitoneal lymph nodes in ceCT. **a-d** Maximum intensity projection (MIP) (a) demonstrates uptake in lymphatic regions of the left inguinal region, right iliac region, level of the right kidney. Further two spots with focal uptake in the thorax is seen. Transaxial PET (b), non-contrast-enhanced CT (c) and fused PET/CT (d) at this level demonstrates an uptake in an internal mammary lymph node on the left side, also the second uptake corresponded to a lymph node (images not demonstrated).

Limitations of FDG-PET/CT imaging

The technical limitations of FDG-PET/CT imaging is related to the spatial resolution of PET imaging and to the uptake behaviour of different malignant tumors. A theoretical spatial resolution of 4 mm can be achieved by modern PET scanners. However, due to motion and the tumor related uptake ratio, a spatial resolution of 6–8 mm can be expected. Missing to low FDG-uptake is encountered with following tumors: mucin-rich adenocarcinomas of the oesophagus and stomach, renal cell carcinomas, gastrointestinal neuroendocrine tumors, well differentiated hepatocellular carcinomas and prostate cancer. As a general rule, squamous cell carcinomas do reliably show FDG-uptake and as above mentioned, adenocarcinomas with high mucin production may show only moderate to missing FDG-uptake. Further, it is not recommended to evaluate prostate cancer at initial staging by using FDG as tracer. For other indications like bladder cancer, FDG might be beneficial but has not been used in larger confirmatory studies. Most important, it has to be mentioned that detection metastases to the brain of even highly FDG-avid tumors like from lung cancer can not be reliably detected. Sensitivity ratios around 60% have been reported in the detection of such metastases (61).

Other radiopharmaceuticals for PET and PET/CT tumor imaging

Recently, various derivatives of choline, as well as C-11 acetate, have shown to accumulate in prostate cancer. While C-11 radiopharmaceuticals will probably not go into widespread use in the foreseeable future because of the difficulties in utilizing the short lived C-11 based substance (half-life of 20 minutes), F-18 choline and F-18 ethyl-choline are compounds, whose clinical utility is being currently explored in prostate carcinoma. The major questions to be answered in prostate cancer are the exclusion of lymph node involvement in primary staging and the identification of tumor in patients who show a biochemical recurrence with a rising PSA. Early results show some promise for staging, while the data suggest that choline PET is unable to distinguish prostate cancer from benign prostatic hypertrophy (62).

No alternative to PET imaging has been found yet which could match or surpass FDG and so in a clinical setting, FDG is likely to dominate PET and PET/CT imaging in the next decade.

FDG-PET/CT imaging for inflammation

The marked accumulation of FDG not only in many tumors but also in activated macrophages and granulocytes may make FDG-PET useful in imaging patients with inflammatory disease. There is not much substantial data on the use of PET/CT in this setting yet. However, localization of inflammatory foci into the appropriate soft tissue or bone structures and the additional information provided by CT will likely be very useful, and thus suggest an equally successful future of PET/CT in inflammation imaging as in tumor imaging. The disease entities invol-

Table of messages

- PET in conjunction with CT on a dedicated **PET/CT scanner is the modality of choice for the interpretation of following oncological disease:**
 - ENT-cancer: staging and restaging
 - Thyroid cancer: restaging of 131I WBS-negative, thyroglobulin-positive patients
 - Hodgkin's and Non-Hodgkin Lymphoma: staging and restaging
 - Non-small cell lung cancer: staging and restaging
 - Breast cancer: staging of high risk patients, restaging
 - Esophageal and gastric cancer: staging and restaging
 - Pancreatic cancer: staging and restaging
 - Colorectal cancer: staging and restaging
 - Gastrointestinal stroma tumors (GIST): staging and restaging
 - Gynecological malignancies including ovarian and cervical cancer: staging and restaging
 - Melanoma: staging of high risk patients, restaging
- PET/CT can be performed in conjunction with a dedicated **contrast-enhanced CT in the same session**
- **F-18 fluorodeoxyglucose is the most important tracer** for PET/CT in oncology
- **Knowledge of anatomy is crucial** in image interpretation
- **Therapy response assessment** is an evolving field in FDG-PET/CT imaging
- New tracers like **F-18 choline** are developed for prostate cancer
- **Limitations:**
 - Spatial resolution of PET imaging is limited to 6–8 mm
 - Acute inflammation does show FDG-uptake and can be misinterpreted as tumor and vice versa
 - Following tumors are in general not FDG-avid and should not be evaluated by FDG-PET/CT imaging:
 - well differentiated hepatocellular carcinoma
 - renal cell carcinoma
 - prostate cancer
 - well differentiated thyroid cancer
 - neuroendocrine gastro-intestinal tumors
 - Following tumors may show limited FDG-uptake: mucin-rich adenocarcinomas of the esophagus and stomach
 - Detection metastases to the brain can not be reliably detected

ving inflammation, where data suggest that FDG-PET is useful, are listed below.

1. patients with fever of unknown origin, where infectious foci or sterile inflammatory processes such as in a vasculitis can be demonstrated (63)
2. patients with widespread soft tissue infections, where the search of the focus is relevant
3. patients with a suspicion of chronic osteomyelitis, where the focus needs to be identified, and other imaging is not able to do so (64, 65).
4. patients with osteosynthetic implants, where the suspicion of an infection has arisen (66).

In the last indication, it should however be noted that differentiating loosening from infection in hip prostheses is a poor indication for PET. Hip prostheses will frequently exhibit physiologic granulation tissue formation in the prosthetic head region and show periprosthetic artificial FDG accumulations, which makes it impossible to differentiate chronic sterile inflammation, infection and loosening from each other (67).

Conclusions

PET/CT is currently rapidly growing world-wide. This is due to the fact that PET and CT complement each others' strengths.

All currently available data in tumor imaging with PET/CT point in the direction that — when available — PET/CT will be used as a primary staging tool in many tumor patients. Interesting developments are occurring regarding new radiopharmaceuticals, in imaging technology and there are other applications of PET/CT such as in infection, which appear to be clinically relevant.

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Disease history

73-year-old male patient with a non-small cell lung cancer of the left upper lobe, proven histologically at bronchoscopy. FDG-PET/CT was performed for staging purpose (*fig. 1*).

Questions

1. What stage of disease is likely?
2. Can brain metastases be excluded by FDG-PET/CT in general?
3. Should you recommend to perform a mediastinoscopy?

Fig. 1 : Maximum intensity projection (MIP) image (a), transaxial PET image (b), non-contrast-enhanced CT image (c) and fused PET/CT image (d) at the level of the primary tumor and, transaxial PET image (e), non-contrast-enhanced CT image (f) and fused PET/CT image (g) at the level of the supraclavicular region.

Answers

1. Stage IIIB since bilateral scalenus lymph nodes (N3) are involved.
2. No, sensitivity of FDG-PET/CT in the detection of brain metastases is limited to 60%; in symptomatic patients, a MRI of the brain should be performed.

3. No, even though mediastinal lymph nodes are probably involved in this case, mediastinoscopy can be omitted since the most crucial lesion is localized in the scalenus lymph nodes. Ultrasound guided biopsy of the scalenus lymph node should be obtained to confirm N3 disease.