The basic principle of positron emission tomography (PET) is the use of positron-emitting isotope labeled pharmaceuticals, which bind to a specific receptor or are integrated into a metabolic pathway. Positron-emitting isotopes are characterized by a beta plus-decay, in which a positron is emitted. This positron collides with any of the many shell electrons in the neighboring atoms, with which it annihilates and produces two 511keV gamma rays. The two photons are detected in coincidence by the PET scanner. Since the annihilation reaction occurs within the body, photons travelling through of the body tissues, are attenuated. To obtain quantitative results, attenuation correction is necessary and performed by using data from a transmission scan. This scan must be acquired in addition to the emission scan and takes around 30-50% of the total imaging time. The shortest duration transmission scans are obtained using X-ray CT like in combined PET/CT scanners. On a dedicated PET/CT scanner, CT data is acquired within less than 30 seconds compared to the 12 to 15 minutes for a transmission scan on a PET alone machine. The great additional advantage of using CT data for this purpose is, that the CT images, which are “hardware” co-registered with PET images, can also be used for anatomic referencing for the PET lesions, thereby enhancing the diagnostic accuracy of integrated PET/CT imaging. The clinically most widely evaluated positron-emitting isotope labeled pharmaceutical is fluorine-18 fluoro-2-deoxy-D-glucose (FDG). This glucose analogue is transported into the cell by specific transporters and phosphorylated by hexokinase to F-18-FDG-6 phosphate, which is inert to further metabolic processing or transmembrane back-transport outside the cell, and is therefore accumulated within the cells. The physical half-life of FDG is around 110 minutes and makes this PET tracer also attractive for PET imaging at imaging centers without a cyclotron. FDG is used as metabolic marker in oncology, cardiology, neurology and inflammation imaging. All currently available data point in the direction that PET/CT is more sensitive and specific than either of its constituent imaging methods and probably also, when viewing images obtained from separate PET and CT systems side by side. Many groups have demonstrated PET to be more sensitive than CT (Fig 1) over the last 10 years [1]. In PET/CT probably the most relevant additional effect is that CT data frequently add specificity to the FDG-PET data [2]. However, FDG-PET data also help to specify findings on CT, such as lymph nodes with equivocal appearance.

PET/CT has developed into the fastest growing imaging modality worldwide according to the industry, with between 500 and 1000 new systems being installed in the year 2004, whereas all major manufacturers are offering somehow similar systems [3, 4].

Technical aspects of PET/CT

Artefacts

There are some potentially critical technical issues when using CT data for attenuation correction in PET/CT. The measured attenuation maps for PET/CT are the CT images obtained from polychromatic X-rays of around 100keV. These are transformed to μ-maps at the spatial resolution corresponding to the PET images and correspond to attenuation images at 511keV, the photon energy relevant in PET.

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. They all can result in alterations of SUV values of lesions or in the appearance of artifactual lesions. Iodine and barium contrast agents used in CT do not attenuate 511keV photons much as they do 100keV photons, thus errors are introduced. The problem is however only

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substantial, when concentrated contrast is used causing enhancement above around 200 Hounsfield units [5]. Hence, 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 [6, 7].

Artifacts generated by motion can occur in many sites. In PET-CT the major artefacts occur in the regions adjacent to the heart and the diaphragm. Specifically, PET data are acquired during free breathing. In humans, 60% of the respiratory cycle is in end-expiratory position. However, CT is normally acquired at maximum inspiration, which leads to an anatomic mismatch between the two data sets with the lungs more expanded in CT, and in turn to an apparent photon deficit of the soft tissues just inferior to the diaphragm. Any lesion falling in this region will thus also show erroneous SUV values [8, 9]. Ideally, the CT data are acquired during end expiration [8].

**Imaging protocols**

Patients have to fast for at least 4–6 hours. Initially, measurement of blood glucose level is necessary to exclude patients with high blood glucose levels due to non-fasting or diabetes. For bowel contrast, 1 liter of dilute oral contrast media is given approximately 90 minutes prior to imaging. 10mCi or 370MBq of FDG are given 60 minutes prior to scanning. Bladder voiding is necessary just prior to scanning to eliminate the renally excreted FDG. At scanning, patient positioning is supine and comfortable arm positioning is chosen depending on the major diagnostic question (arms down for ENT tumors, up for most other indications). First, a low dose (20–60mAs) CT scanning (adapted to patients’body habitus) without i. v. contrast enhancement from the head to the mid-thigh is performed, followed by PET scans.
emission scanning starting from the mid-thigh moving towards the head. This minimizes pelvic image mis-registration due to bladder filling occurring between the PET and CT scans.

Additionally, if necessary, a i. v. contrast media CT study, taylor-made to the diagnostic problem can be acquired and fused with the PET images. This protocol does reflect the personal experience of the author, however depending on the manufacturer, different protocols may be used.

**Indications**

► **PET/CT in bronchial carcinoma**

In lung cancer, integrated PET/CT adds significant clinical information in comparison to PET alone, CT alone or image comparison of separate PET and CT [10-12] due to better lesion identification and localization and fewer overlooked lesions in tumors not consistently accumulating FDG. In carcinoid tumors, bronchiolo-alveolar lung carcinoma and malignant effusions, diagnosis can sometimes only be based on the CT findings.

Recently, 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 [10] (Fig 1). 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. 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 CT to define mediastinal vascular invasion.

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 [10]. FDG PET has been shown clinically useful in the evaluation of suspected lung cancer recurrence.

► **PET/CT in recurrent colorectal cancer**

Colorectal carcinoma is the most important cause of death due to cancer in the western world after bronchial carcinoma [13]. About 70% of patients have curable resectable tumor at initial diagnosis and are treated with curative intent. Approximately 50% of colon cancer patients will present with hepatic metastases, either at the time of initial diagnosis or as a result of recurrence [14]. The standard patient work-up for the detection of recurrence and metastases in colorectal cancer include regular clinical examinations, CT scans, colonoscopy and usually measurement of tumor markers such as CEA. 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 [15]. 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 [16]. Not only did PET/CT improve the localization of lesions, but also the certainty in interpreting lesions as normal or definitely abnormal.

In a study by Seltzner 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 [17]. Detection of intrahepatic tumor load, extrahepatic metastases, and local recurrence at the colorectal site were evaluated. 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 (specificity 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). Extrahepatic 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. g<5mm) were often not detected.

► **PET/CT in lymphoma imaging**

Hodgkin’s lymphoma (HD) accounts for less than 1% of all cases of cancer. Careful staging and treatment planning is required to determine the optimal treatment. NHL is less predictable than HD and has a greater predilection to disseminate to extranodal sites.

HD and NHL usually show avid FDG-uptake at initial staging [18]. 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 [18]. 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 [19].
To date, results regarding the use of FDG PET/CT in staging and restaging HD and NHL are limited [20]. Our own initial results suggest, that PET/CT acquired with a non-contrast-enhanced CT scan is more sensitive and specific than ceCT for the evaluation of lymph node and organ involvement in patients with HD and aggressive NHL [20]. With regards to exclusion of disease, PET/CT performed significantly better than ceCT (P < .05, McNemars test).

**PET/CT in head and neck (HN) tumors**

PET provides improved staging information when compared to CT and MR [21]. The limitations of CT and MR are mainly due to equivocal findings, such as normal or questionable size lymph nodes, which cannot be classified as normal or pathological. PET itself poses some image interpretation issues, as there is a number of situations where FDG accumulates in normal structures, which can be classified as such only with an anatomic reference. Early results suggest that PET/CT is useful in HN tumors for loco-regional staging, identification of distant metastases and in therapy monitoring [22].

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 [22]. 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.

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 specificity as it is excellent in excluding recurrence [23, 24] but only a moderate sensitivity. This is due to persistent FDG accumulation in the HN regions exposed radiation therapy, which is due to sterile inflammation [25]. 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.

**Other indications**

**Thyroid carcinoma**

Patients with differentiated thyroid cancer commonly are diagnosed and treated with iodine-131 (\(^{131}\)I), if thyroglobulin level is elevated. In case of differentiation of papillary or follicular cancer, tumor cells lose their ability to accumulate iodine and Hürthle cell carcinoma is not taking up iodine to start with. If thyroid cancer is iodine-negative, other imaging methods are needed for staging and restaging. It has been shown that FDG PET is a valuable imaging modality in patients with negative radiiodine scans. The advantage of PET/CT is perfect anatomical-functional coregistration. Exact localization of metastases and the differentiation of scar tissue from tumor issue is needed before surgery. Pitfalls such as contralateral posterior arynenoid muscle FDG accumulation in recurrent nerve palsy can be excluded with PET/CT, and Teflon induced granuloma formation is readily identified [26]. Integrated PET/CT imaging allows precise diagnosis and prevents unnecessary interventions.

**Gynecological tumors**

Epithelial carcinoma of the ovary is the fifth most frequent cause of cancer death in women, with half of all cases occurring in women over age 65 [27]. To date, only two studies using PET/CT for restaging ovarian cancer are available [28]. In the study by Sironi et al., 31 women with ovarian carcinoma were treated with primary cytoreductive surgery [28]. In all patients, histologic examination after surgical secondlook 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 [29]. Therefore, it can be expected that intra-venous contrast enhanced PET/CT can evolve into the technique of choice in staging of recurrent ovarian cancer.

Worldwide, cervical cancer is the second most common cancer among women. One of the major factors in survival is the local extent of the disease [30]. To date, in only two studies with small and heterogenous patient populations, PET/CT was used in the evaluation of gynecological malignancies including mainly endometrial and cervical cancer. In the study by Grisu et al., 33 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 [31]. 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 useful-
ness of PET/CT in the localization of FDG uptake in the uterus and could differentiate physiological from pathological uptake in the uterus and ovaries [32].

Breast cancer is often curable when diagnosed at an early stage. The sensitivity of PET in the detection of small lesions is limited, restricting its use in evaluation of primary breast cancer and axillary nodal spread. In addition, PET imaging is affected by tumor histology. FDG PET can miss slow growing cancer, such as tubular carcinoma, or non-invasive cancer, such as ductal or lobular carcinoma in situ. At present, the major clinical application of whole-body FDG PET is the assessment of systemic metastatic disease (Fig 2). It has to be cautioned, that some blastic osseous metastases can be false-negative, however no conclusive data is available. The clinical value and the advantages of integrated PET/CT compared with PET alone are not yet clearly defined. Integrated PET/CT may play an important role in planning radiation therapy by providing an accurate estimate of the tumor extent [33].

**PRIMARY SOLID LIVER TUMORS**

Imaging of primary solid liver tumors and their differentiation from other liver lesions is the domain of morphological imaging with ultrasonography, CT and MRI. Well differentiated hepatocellular carcinomas (HCC) and all benign solid liver tumors rarely show increased FDG uptake. On the other hand, in patients with known moderately to poorly differentiated HCC or cholangiocarcinoma (CC), PET imaging has shown to be useful, particularly in the detection of distant metastases and follow-up after treat-
Fig 3 – 56-year-old male patient with a known cholangio carcinoma of the liver-segment IV A/B. PET/CT performed for preoperative staging. Additionally, a contrast enhanced CT was acquired at the same time. (A) In the PET overview (MIP), FDG-uptake is seen in the liver as well as extrahepatic peritoneal and in the mediastinum. (B) In the fused axial images (top to bottom: PET, CT, fused image PET/CT), the primary tumor is seen in the liver-segment II and IVA. (C) Further, the uptake in the mediastinum is clearly located in a mediastinal lymph node (fused axial PET/CT). Histological work-up of this lymph node by transesophageal biopsy revealed a metastasis. The patient underwent palliative treatment.
Imaging of the pancreas with CT and MRI is the cornerstone in the diagnosis and staging of pancreatic disease due to the ability of these imaging modalities to exactly delineate it from vascular and adjacent structures. However, 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 [35]. 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 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.

MALIGNANT 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 (Fig 4). 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 ≤ 2mm, known metastases). Surgical resection is the treatment of choice for regional lymph node metastases or single distant metastasis. If multiple metastases are present, only palliative symptomatic therapy is indicated. In

Fig 4 – 64-year-old male patient with a history of a melanoma of the lumbar region. (A) In the PET overview (MIP), no pathological FDG-uptake is seen. (B) In the fused axial images (top to bottom: PET, CT, fused image PET/CT), multiple bilateral intrapulmonary lesions are seen which do not show any FDG-uptake.
patients in whom surgery is planned, whole-body PET should be performed to exclude occult metastases (Fig 4). At our institution combined PET/CT is important for planning minimally invasive surgery in the therapy planning of small lesions. Integrated PET/CT it is more patient friendly as patients need only one imaging appointment.

**OTHER INDICATIONS FOR TUMOR**

There are several less frequent tumors, where FDG-PET and PET/CT appear to be useful such as in esophageal cancer, testicular cancer, sarcomas and multiple myeloma. Possibly the major application where FDG PET appears of very limited value is prostate cancer. It is known, that FDG will accumulate in aggressive prostate cancers, but at that stage of the disease imaging is probably not very useful [36].

► **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 involving inflammation, where data suggest that FDG-PET is useful, are patients with fever of unknown origin, where infectious foci or sterile inflammatory processes such as in a vasculitis can be demonstrated [37]. Further, patients with widespread soft tissue infections or suspicion of chronic osteomyelitis, where the focus needs to be identified, and other imaging is not able to do so [38]. An other possible patients with osteosynthetic implants, where the suspicion of an infection has arisen [39].

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 peri-prosthetic artificial FDG accumulations, which makes it impossible to differentiate chronic sterile inflammation, infection and loosening from each other [40].

**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.

**Références**

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