CLINICAL VALUE OF PET/CT

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While CT provides mainly morphological data on a tumor in question, positron-emission-tomography (PET) can assess functional aspects of a lesion. However, both imaging modalities have their limitations, if they are acquired separately: Morphology alone has been found inferior to functional imaging when assessing lymph nodes for metastatic spread. Furthermore, characterization of parenchyma lesions may be difficult if based on morphological data alone. Functional imaging with PET can provide these functional data that are lacking in CT. However, in PET alone there is only limited anatomical information available. Accurate localization of a lesion within a certain organ, or even within a segment of an organ can be extremely difficult on PET alone.

Commercially available PET/CT scanners are based on two separate scanners, a CT and a PET, that are installed in series. A single examination table serves both imaging components of the PET/CT. The patient is positioned on the examination table followed by acquisition of the CT, then by acquisition of the PET. In between the two scans the patient remains in the same position on the examination table. This assures that morphological and functional data sets can be accurately fused after image acquisition. Patient motion in between the two scans or motion of internal organs may result in different positions of an organ or a lesion during CT and PET. This event may result in inaccurate co-registration of CT and PET. In the event of image mis-registration, manual adjustment may be performed software-based.

Differences between PET/CT systems apply to the number of detector rows with which the CT component is equipped. Currently up to 64 detector rows have been integrated in PET/CT. For the PET component different detector materials have been available. The three most common detector materials are Bismut-Germanate (BGO), Luthetium-Oxyorthosilicate (LSO), and Gadolinium-Oxyorthosilicate (GSO).

All available PET/CT-systems are equipped with a full-ring PET detector (360° coverage). The size of each detector crystal defines the spatial resolution of the tomograph, which may range from 2 to 5 mm.

Image evaluation of PET is performed both, qualitatively and quantitatively. The reader assesses the PET data for regions of focally increased tracer uptake (qualitative image analysis). A region of interest is drawn around a hot spot on PET offering quantitative analysis of the tracer activity in that area. Quantitative PET data are typically reported as standardized uptake values (SUV).

The SUV may be normalized for patient weight (as shown above) or patient body surface area. However, a potential benefit of the SUV as compared to qualitative image analysis alone has been discussed controversially. The SUV may be used to differentiate benign from malignant lesions, but the overlap of SUV values between these two entities often generates false diagnoses. Therefore, in most institutions the SUV is currently used as an add-on to qualitative image analysis while qualitative image analysis represents the back-bone for the correct diagnosis. The SUV does, however, provide an invaluable tool in patients undergoing PET imaging for follow-up of tumor therapy. With the pre-therapeutic SUV as a basis, a decrease in the SUV can indicate tumor response to a certain therapy.

For tumor staging accurate localization of a lesion must be considered of utmost importance. Several studies have been published on the accuracy of FDG-PET/CT for tumor staging of different tumors. Initiation of a stage-adapted therapy is known to improve patient survival for a variety of malignant tumors. Thus, FDG-PET/CT may impact the patient’s prognosis by altering patient management.

There are numerous studies available from the literature that covers the accuracy of FDG-PET for staging of lymphoma. Sensitivities for detection of viable disease range between 80% and 90% with specificities of 69%-99%. The tumor stage was altered at initial staging in 36% of patients compared to a conventional imaging algorithm including CT imaging. Considering the fact that treatment of lymphoma and the patients’ prognoses strongly depend on the tumor stage, this higher accuracy for lymphoma staging must be considered clinically relevant. Currently there is only one study comparing FDG-PET/CT with separately acquired CT and FDG-PET in the setting of primary lymphoma patients.

FDG-PET has been found of higher accuracy than CT when staging head and neck tumors with sensitivities of up to 90% for detection of lymph node metastases. There are, however, some limitations to PET in the head and neck region. Physiologically increased tracer uptake in salivary glands or in muscles of the head and neck may be difficult to interpret without anatomical correlation. In addition, activation of brown fat may be challenging. Thus, correlation with anatomy as provided by PET/CT will be helpful. A significant improvement was detected when assessing the TNM-stage of head and neck tumors with FDG-PET/CT as compared to CT alone and CT viewed side by side with PET. This difference was based mainly on more accurate assessment of the T-stage and the N-stage, rather than the M-stage.

Detection of the primary tumor in cancer of unknown primary (CUP) has been an important indication of FDG-PET. The median survival for patients with CUP may increase from 12 to 23 if the primary tumor is detected and treated specifically. Detection rates between 24% and 53% have been reported for FDG-PET. These substantial differences in the detection rates result mainly from differences in the definition of the term “CUP”. If defined correctly a CUP is diagnosed if no tumor can be detected with morphological cross sectional imaging and blind nasopharyngeal biopsies have been negative. In this setting detection rates are low, even with FDG-PET and FDG-PET/CT.

Non-small cell lung cancer (NSCLC) has been one of the most important indications for FDG-PET imaging. Tumor staging in NSCLC patients strongly benefits from anatomical correlation of the PET data with CT. Several studies have demonstrated improved TNM-staging of NSCLC patients with FDG-PET/CT. This advantage relates to more accurate T-staging with improved differentiation of the tumor from an adjacent atelectasis, and, even more important, more accurate N-staging as compared with CT alone.

The solitary pulmonary nodule is another major indication for FDG-PET imaging. In this setting FDG-PET is used to differentiate between a benign and a malignant lesion. In a solitary pulmonary nodule potential FDG-uptake supports the diagnosis of a malignant lesion whereas an FDG-PET negative lesion may be followed-up. However, even in the case of FDG-negativity, close imaging follow-up remains necessary, as there are FDG-PET negative tumors. Lesion size is an important factor when it comes to using FDG-PET and PET/CT for assessment of pulmonary lesions. Small pulmonary lesions (<1cm) may appear PET-negative even though they take up FDG. This is caused by breathing-induced “smearing” of FDG-uptake.

Breast cancer patients may be staged with FDG-PET/CT. The primary focus of the examination will be the N-stage and the M-stage rather than local tumor assessment. Though specific FDG-PET protocols and PET/CT protocols have been developed to evaluate the primary breast tumor the high sensitivity of mammography and MR-mammography coupled with the high soft-tissue contrast of MR obviate the need to locally assess a breast lesion with PET/CT. Compared to PET more lesions could be definitely defined as malignant or benign with PET/CT. Compared with PET alone, PET/CT may reduce the number of false-positive findings by identifying areas of mild FDG-uptake in brown fat as benign.

Staging of colorectal cancer can be performed with FDG-PET/CT. So far FDG-PET and FDG-PET/CT have mainly been used for M-staging of patients with colorectal tumors. FDG-PET has been found of higher diagnostic accuracy than CT imaging when assessing the M-stage of patients with colorectal cancer. However, there are limitations of FDG-PET and FDG-PET/CT when it comes to detection of distant metastases. As described above, small pulmonary lesions may appear FDG-PET negative due to “smearing” of FDG-uptake. The same applies to small liver lesions. Since PET data are acquired during shallow breathing small lesions may appear FDG-PET negative, even though they take up the radioactive tracer. In fact, MRI has been found of higher diagnostic accuracy than FDG-PET/CT for liver metastases. By optimizing the CT component of the PET/CT small liver lesions may be detected on CT that are negative on PET. These lesions should be followed-up to exclude distant metastases. The value of FDG-PET in assessment of loco regional lymphatic spread has been discusses controversially. While some authors report an only limited value of FDG-PET and PET/CT in the setting of N-staging others report the opposite. The sensitivity does, however, not seem to be high enough to obviate the need for surgical lymph node resection in FDG-PET negative nodes following primary tumor resection. Implementation of a tumor-specific PET/CT protocol including whole-body PET/CT and PET/CT-colonography has the potential to improve both, assessment of the N-stage and the T-stage, offering an all-in-one imaging approach. However, there are only limited data available on this new imaging concept and further studies are necessary to define the actual accuracy of PET/CT-colonography.

Assessment of tumor therapy has been challenging with morphological imaging procedures alone. Traditional morphological response criteria, such as the Response Criteria in Solid Tumors (RECIST) or criteria published by the World Health Organization (WHO) rely on a reduction in tumor size as the sign for therapy response. However, tumor size reduction often requires time to develop. Functional imaging modalities have been found of benefit over morphology alone when it comes to early therapy assessment. A decrease in FDG-uptake on PET typically precedes the decrease in tumor size, thus offering early characterization of a patient in responder vs. non-responder. Many studies have been published demonstrating a benefit of FDG-PET over CT or other morphological imaging procedures when it comes to therapy assessment. The question arises, if PET/CT may be able to outperform PET alone in the setting of therapy response evaluation. When characterizing a tumor in “responding” or “non-responding” one has to acknowledge, that all lesions have already been accurately localized on a staging examination performed before the start of the therapy. This obviates the need for just another anatomical localization in the setting of therapy assessment. The question to be answered seems rather: Does PET-tracer uptake decrease as a sign of tumor response, or does it not? This question can be perfectly answered with PET alone. Therefore, no advantage of PET/CT over PET alone can be expected when comparing the two imaging procedures for therapy assessment. As expected, nearly all studies on PET/CT in the setting of therapy response either found no difference between FDG-PET/CT and FDG-PET or did not even compare the two. There is only one study which was able to document an advantage of the additional anatomical information as compared to FDG-PET alone.

When discussing radiation therapy, fusion of anatomical data with function may improve the definition of the radiation target volume. Both, an increase and a decrease in the target volume have been described with FDG-PET and FDG-PET/CT as compared to CT alone. Differentiation of viable tumor from adjacent atelectasis is a major reason for a decrease in the target volume based on FDG-PET and PET/CT. More accurate assessment of loco regional lymph nodes with functional data has an effect on the target volume, both increasing or decreasing it. In the case of radiotherapy with a curative intent, the dose to non-tumor tissue has been the dose-limiting factor. In patients with NSCLC the use of FDG-PET/CT can effectively reduce the radiation exposure of non-tumor tissue allowing a radiation dose escalation. Further studies will have to assess if more accurate target volume definition translates into improved patient prognosis.

FDG-PET and FDG-PET/CT can be of benefit in interventional radiological procedures. Compared with CT alone PET and PET/CT have been found of higher accuracy when assessing the liver for residual disease after radiofrequency ablation (RFA) of liver metastases **However, a substantial number of false-negative cases caused by very small tumor residuals must be kept in mind. These small tumor residuals, not visible on CT or PET, lead to early tumor recurrence and require a close follow-up of patients**. Other authors report promising results when following-up patients with liver metastases undergoing therapy with application of 90Y microspheres.

If FDG-PET and FDG-PET/CT are used for therapy assessment, false-positive findings due to therapy-induced tissue regeneration and inflammatory reaction may occur. Regenerating tissue and inflammatory changes go along with an increase in glucose metabolism and this increased FDG-uptake may be difficult to differentiate from viable tumor.

This problem applies specifically to radiation therapy and interventional radiological procedures. The right time to perform FDG-PET following tumor therapy has been discussed controversially.

While early PET/CT following interventional radiological procedures (day 1 after the intervention) seems to be of benefit a four-week to eight-week interval is currently recommended between the end of radiation therapy and the PET/CT scan.

In many tumors recurrence can be detected earlier with functional imaging data as compared with morphology. In addition differentiation of residual and / or recurrent disease from non-viable tissue following therapy may be more easily accomplished with PET imaging. PET/CT offers the advantage of accurate anatomical localization of a recurrent tumor site which aids therapy planning if surgery, interventional therapy, or radiation therapy is an option. This increase in accuracy results from more accurate lesion localization and from better differentiation of a lesion from the urinary bladder. Anatomical correlation of focal tracer uptake improves differentiation of a hot spot into malignant or benign: While focally increased tracer uptake within a lymph node or the bone suggests metastatic disease, tracer uptake in the esophagus may be caused by therapy-induced esophagitis.

However, in tumors, which are treated with further systemic therapy rather than surgery, interventional procedures, or radiation therapy accurate characterization of the site of a lesion, may not be of clinical relevance.

SUGGESTED READING

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