The role of PET in head and neck cancer

Abstract

PET and PET/CT are the procedures of choice for molecular imaging in the head and neck area. The current data of the literature show, that functional imaging with fluorine-18-deoxyglucose (^{18}F-FDG) provides the possibility to obtain information about the viability of malignant lesions. The use of hybrid systems, PET/CT, enables physicians to assess both, morphology and function, and achieve a high diagnostic accuracy exceeding 90%. PET with ^{18}F-FDG is the most sensitive method to detect tumor recurrence. However, false positive results must be considered due to unspecific changes following treatment, especially radiotherapy. The use of quantitative PET scans as well as the application of a second tracer, enhance the capability of PET to assess questionable masses more accurately. Follow up examinations with PET and ^{18}F-FDG provide data about early changes in the tumor metabolism due to chemotherapeutic treatment. Studies in patients undergoing surgery and radiotherapy demonstrated, that PET with ^{18}F-FDG can be used for the prediction of individual survival.

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Introduction

Tumors of the oral cavity and the oropharynx are number six in the list of the most common cancer types for men in Germany [1]. The standardized mortality rate increased continuously from 1950 to 1992, followed by a 26% decrease until 2005. Oropharynx cancer is age dependent with a maximum for 60-64 years. Besides the common squamous cell carcinoma, which accounts for about 95% of tumors in the head and neck area, a variety of other histologies exist, including sarcomas and even endocrine tumors.

Like in other tumors, accurate methods are needed for tumor staging to guide the patient to the appropriate therapy: surgery, chemotherapy, and/or radiotherapy. Besides endoscopic evaluation, including histological assessment of the primary tumor, morphological methods are used to assess the primary tumor according to size, location, and infiltration of the surrounding structures as well as for the detection of metastatic lesions in the lymph nodes and other tissues. Magnetic resonance imaging (MRI) and contrast enhanced axial computerized tomography (CT) are established procedures for the assessment of a head and neck tumor. However, morphology based methods always demand changes in the tissue structure, which do not necessarily exist in the initial phase of a malignant lesion. Lymph nodes may be infiltrated by the malignant tumor while they appear with normal size in CT. This is why functional methods can provide additional information for staging purposes.

Results

Tumor diagnostics

Ultrasound (US) and CT have improved the diagnosis and staging of head and neck tumors in the past. MRI and contrast enhanced CT are established procedures for the assessment of a head and neck tumor. Within the last ten years MRI has gained increasing interest due to the possibility to obtain non-invasively high contrast images of morphological structures. Leslie et al. evaluated CT and MRI for T-and N-staging of squamous cell carcinoma of the oral cavity and oropharynx in patients with primary or recurrent disease [2]. Interestingly, the accuracy for the staging of primary tumors was 77% for MRI and 67% for CT. The authors note that despite the fact that the T-stage results were comparable for MRI and CT, the delineation of a tumor was better with MRI. In contrast to the staging results, the detection of recurrent tumors was improved with an accuracy of 89% for MRI and 100% for CT [2]. The main problem with both imaging modalities was the N-staging, because the procedures failed to identify small metastases. Considering a node size exceeding 10 mm as malignant, MRI had a sensitivity of 75% and specificity of 63%, while CT had a sensitivity of 35% and

a specificity of 100% [2]. Others compared CT, MRI, US, and single photon emission tomography (SPET) for the detection of cervical lymph nodes in patients with squamous cell carcinoma [3]. The highest sensitivity was achieved for MRI (85.7%), followed by CT (77.7%), SPET (75.6%), and US (70.7%). However, the accuracy of all methods did not exceed 70% in this study. The authors conclude that despite high specificity rates, none of these imaging methods is reliable in evaluating occult regional metastases [3]. The data demonstrate that other methods are needed to improve the staging accuracy, especially for N-staging.

Functional methods are primarily based on nuclear medicine procedures. Basically, a radiopharmaceutical is used to generate functional images. A radiopharmaceutical is generally containing two major parts: the isotope, which is needed to obtain a signal outside the body and the pharmaceutical, which determines the functional information achieved by the examination. In the last fifteen years positron emission tomography (PET) has found increasing attention for oncological examinations. PET is based on the application of radiopharmaceuticals labeled with positron emitting isotopes, primarily fluorine-18 (^{18}F). These isotopes have the advantage to annihilate with a high energy radiation of 511 keV. Furthermore, the radiation is emitted with an angle of 180 degrees, providing the use of the so called coincidence technique. Thus, the spatial resolution of PET is higher by a factor of 3-5 as compared to conventional nuclear medicine procedures based on single photon emitting isotopes.

One of the most common radiopharmaceuticals for PET is ^{18}F labeled deoxyglucose (FDG), which has found widespread use for oncological studies [4]. FDG is transported like glucose into the cells, also phosphorylated by hexokinases, but not further metabolized. The dephosphorylation rate is generally low in most of the malignant tumors for at least one hour. One of the initial studies performed by Minn et al. (1988), compared the ^{18}F-FDG data with flow cytometry in head and neck tumors [5]. The authors found no correlation with the histologic grade of the tumors, but a correlation was noted for the ^{18}F-FDG uptake ratio and the proliferating cells as measured by flow cytometry [5]. We compared the tumor perfusion using ^{15}O-water and ^{18}F-FDG uptake with flow cytometry data in 35 patients with head and neck tumors [6]. Interestingly, the tissue perfusion data did not correlate neither to the ^{18}F-FDG uptake nor to the flow cytometry results. The ^{18}F-FDG data revealed two subgroups with a significant correlation of the ^{18}F-FDG surface uptake values (SUVs) in each subgroup with the proliferative index [6]. It was assumed that the difference between the two uptake groups was related to a different expression of oncogenes. The data demonstrate, that functional methods like PET with ^{18}F-FDG are closely related to molecular biological processes and may therefore be helpful to assess a malignant lesion in more detail. Thus, the initial diagnosis and staging of a lesion may be improved and further information can be obtained, which is helpful for the individual therapy management.

Several studies have focused on the aspect of diagnostic accuracy of PET in head and neck tumors. Gambhir et al. (2001) performed a meta analysis of data about the use of PET in oncology [7]. Their evaluation of studies concerning head and neck tumors comprise 298 patients and 580 lesions assessed for tumor diagnostics and 591 patients with 2113 lesions evaluated for tumor staging [7]. PET and CT results were compared and an average sensitivity and specificity of 93%, 70% for PET and 66%, 56% for CT respectively were calculated from the literature data for primary tumor diagnostics. The data were comparable for tumor staging except for a higher specificity of PET and CT as compared to the diagnostic studies (PET: sensitivity 87%, specificity 89%; CT: sensitivity 62%, specificity 72%). The clinical situation however is usually associated with a certain prevalence of disease prior to any diagnostic procedure. Then diagnostic methods are applied and it is expected that the gain in information will enhance the probability or suggest the absence of disease. This is the classical application for the Bayesian statistics [8]. The data from Gambhir et al. (2001) can be analyzed using the Bayesian approach. Figure 1 demonstrates the association of prior probability of disease and the posterior probability for a true positive and a false negative result. Overall, PET provides a higher gain in information as compared to CT. Especially the rate of false negative results with PET is significantly lower as compared to CT. The differences between the probability curves reflect the gain in information obtained with a diagnostic procedure (Fig. 2). PET provides more information than CT for all prior probability levels. The advantage of combining a morphological method, CT, with a functional procedure, PET, is also assessed by using the literature data and the predicted gain in information is calculated. The results show, that especially in patients with a low prior probability of disease the combination of PET and CT will be helpful.

The recent development of hybrid systems, combining PET and CT, is a major step forward to achieve the most accurate correlation between morphology and function. Due to

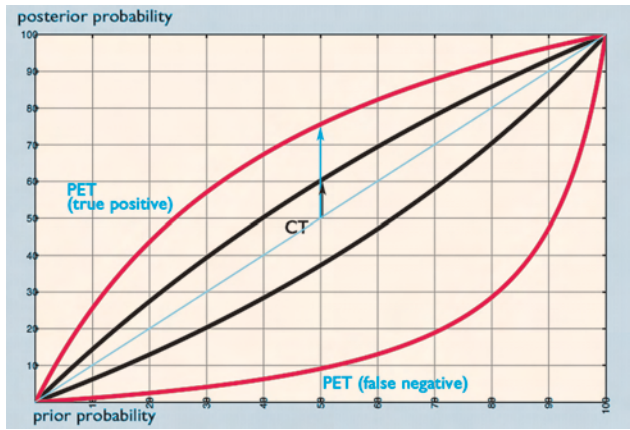

Figure 1. Bayesian analysis of the data from Gambhir et al. (2001) regarding tumor diagnostics. For a 50 % prior probability of disease a positive CT examination accounts for a gain in information of about 10%, while a positive PET scan provides an increase of the probability by 25%. In particular, the probability for false negative scans is low for PET, therefore providing an improved diagnostic accuracy.

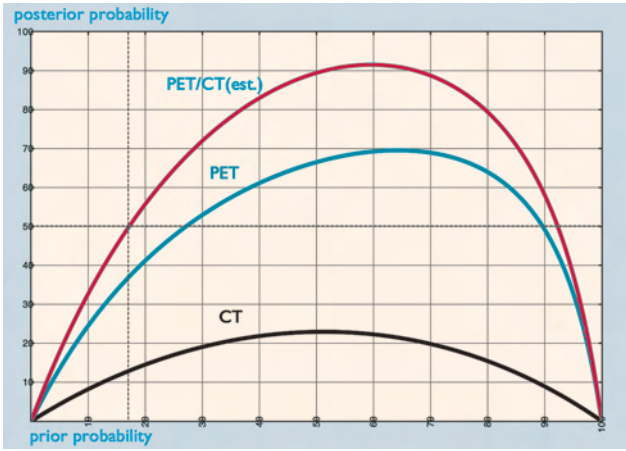

Figure 2. Gain in information by applying CT or PET. Furthermore, the expected gain for PET/CT is estimated from the data. The results demonstrate, that especially for prior probabilities of less than 20% the combination of PET and CT provides the most accurate results.

the sequential acquisition of CT and PET data the misalignment between CT and PET is kept to a minimum and the images can be reviewed side by side or as fusion images. Figure 3 demonstrates a patient with a head and neck tumor and lymph node metastases. The combined assessment of both, CT and PET, as well as the fusion images are helpful to delineate and locate the metastases (Fig. 3). Others compared PET/CT with PET and CT as individual modalities in patients with head and neck tumors [9]. Again, the lowest accuracy was noted for CT (74%), while PET (90%) and PET/CT (94%) were significantly more accurate. When Bayesian statistics are applied to the data, the highest gain in information is obtained with PET/CT. The intra-observer variation and the accuracy of the correct anatomical association of PET findings was evaluated by others [10]. As expected, PET/CT was the most accurate procedure to limit the intra-observer variation and achieve reproducible diagnostic results. The advantages of PET/CT are also reported by others [11]. These authors are among the first who have used PET/CT in patients and they emphasize that PET and CT are matching with a few millimeters difference. Therefore, the combined use of these imaging modalities improves the presurgical staging by providing both the anatomical location based on CT and the high lesion detectability of PET with ^{18}F-FDG.

The metabolically active tracer ^{18}F-FDG provides generally a high sensitivity for the detection of abnormalities. Therefore, generally false negative results are less likely than false positive results when ^{18}F-FDG is used for tumor diagnostics. However, little is reported about false positive results. Others assessed the clinical usefulness of ^{18}F-FDG-PET in recurrent nasopharyngeal carcinomas and compared the results to those of the MRI studies [12]. The overall sensitivity of PET, comprising the primary tumor site and the lymph node metastases, was 89.5%, while the specificity was only 55.6% [12]. One limitation of PET with ^{18}F-FDG was the number of false positive results obtained in these patients. However, the patients had received radiotherapy and also chemotherapy had

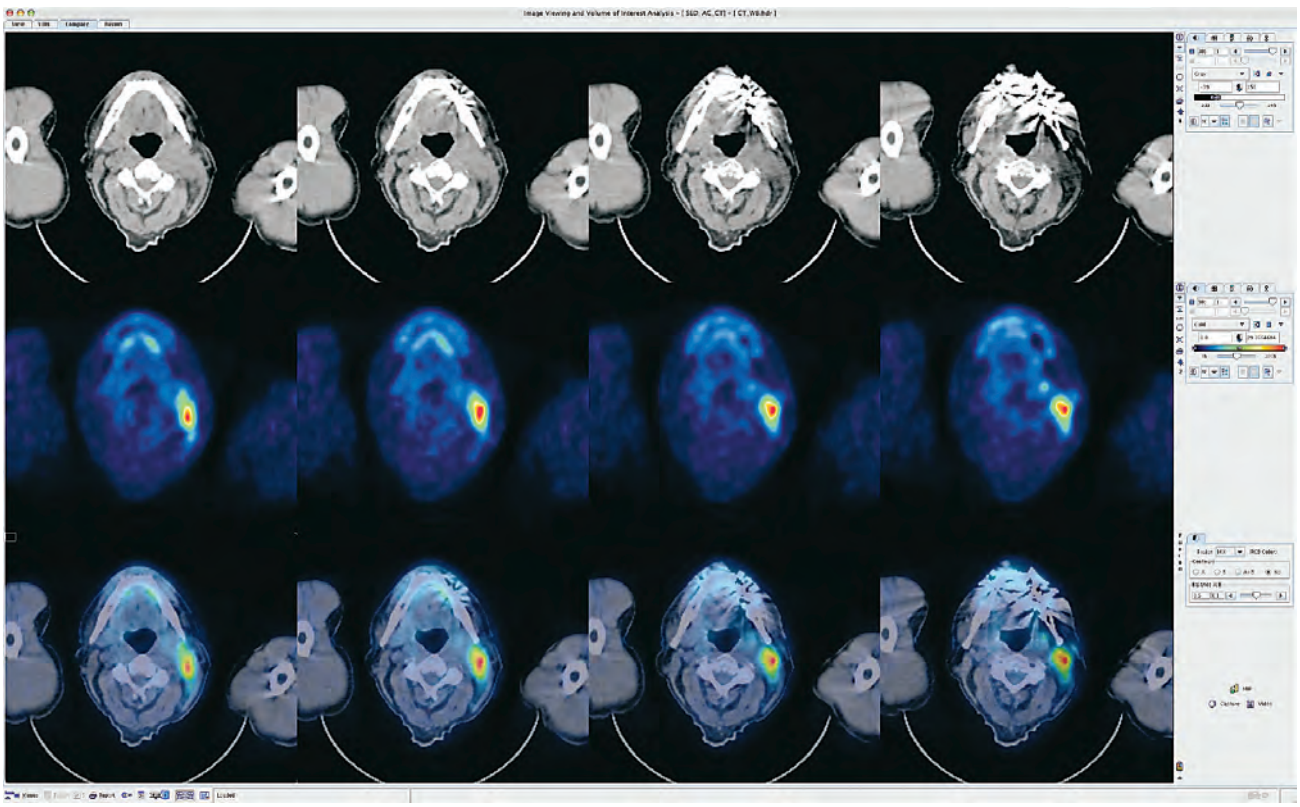

Figure 3. CT (upper row), PET ^{18}F-FDG (middle row), and fusion images (lower row) of a patient with a head and neck tumor and lymph node metastases on the left side of the neck. The combined assessment of anatomy and function improves the diagnostic accuracy.

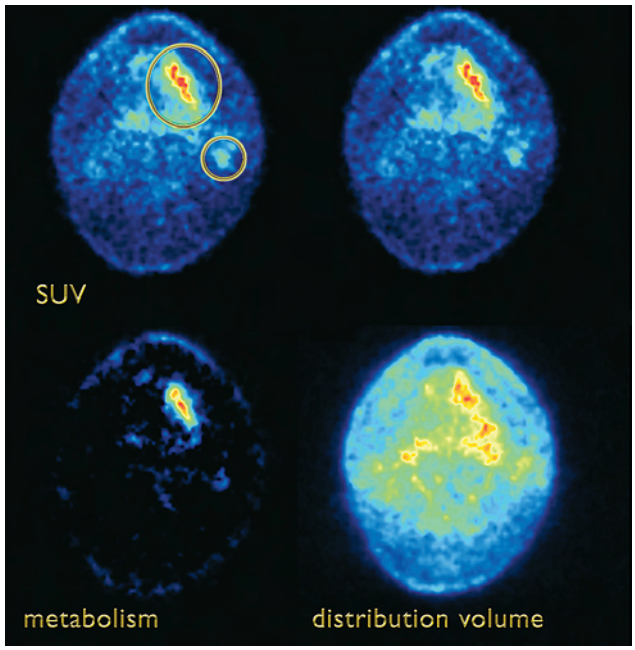

Figure 4. Upper: ^{18}F-FDG uptake image, displayed as a standardized uptake image (SUV). Enhanced ^{18}F-FDG accumulation in a tumor (ventral) and a lymph node on the left side of the neck.
Lower: Parametric images of the ^{18}F-FDG fraction, which is metabolized (left image), and the distribution volume of ^{18}F-FDG (right image). The data reveal a high ^{18}F-FDG metabolism in the primary tumor, but not in the lymph node. The ^{18}F-FDG uptake in the lymph node is primarily due to an enhanced distribution volume of ^{18}F-FDG and not due to an increased metabolism, which gives evidence for non-tumorous reasons for the ^{18}F-FDG uptake in this lesion. The histological evaluation confirmed the primary tumor as noted in PET and non-tumorous, inflammatory reactions in the lymph node identified in PET.

been given to most of the patients. Therefore, there is a higher likelihood of an enhanced, reactive metabolic activity in tissue, according to therapy.

The problem of ^{18}F-FDG uptake in both, malignant tumors as well as in inflammatory tissue, is a general problem in PET studies. False positive results are mainly based on the enhanced ^{18}F-FDG transport into leukocytes. To limit false positive results, generally two approaches are possible: the use of more sophisticated quantification methods to assess the ^{18}F-FDG kinetics or the application of a second radiopharmaceutical to achieve additional biological information about the lesions. Tracers specific for cell proliferation, hypoxia, amino acid transport, etc. provide additional information and can be considered as a second tracer.

The assessment of tracer kinetics demands dynamic PET studies. Usually dynamic data are obtained for 60 min beginning with the ^{18}F-FDG administration. The use of a volume-of-interest (VOI) based analysis provides the possibility to obtain time-dependent regional tracer concentrations. A two tissue compartment model can be applied to the data and detailed information about the ^{18}F-FDG kinetics can be obtained. Parametric imaging can help to identify those regions with an enhanced intracellular metabolism of ^{18}F-FDG and to differentiate these findings from areas with a primarily blood volume dependent ^{18}F-FDG accumulation. We use a fast method to differentiate between ^{18}F-FDG metabolizing regions and areas with a primarily decreasing ^{18}F-FDG concentration over time. This method had been found helpful for the classification of lesions. Figure 4 demonstrates a high ^{18}F-FDG accumulation in a primary tumor and a moderate ^{18}F-FDG uptake in a solitary lymph node. The parametric images clearly demonstrate, that the ^{18}F-FDG uptake in the primary tumor is related to the intracellular metabolism of ^{18}F-FDG, while the ^{18}F-FDG uptake in the lymph node is caused by an enhanced distribution volume for ^{18}F-FDG. Therefore, PET confirms a metabolically active primary tumor, but the tracer accumulation in the lymph node is most likely due to unspecific changes, e.g. inflammatory reactions. These findings were confirmed by histology. Using the most recent PET/CT systems today, it is possible to perform routinely a shortened dynamic acquisition for 30 min, followed by a whole body scan. Thus, parametric imaging can be combined with the advantages of whole body images.

Quantification is usually helpful, especially in follow up examinations of patients to assess a lesion more accurately. However, for the differentiation of a tumor from benign changes the use of other tracers may be preferable. If a cyclotron is available for the production of short lived isotopes, radiopharmaceuticals labeled with ^{11}C can be used to perform double tracer studies in patients due to the sequential application of ^{11}C and ^{18}F labeled tracers. Besides ^{18}F-FDG, we have investigated a synthetic amino acid, ^{11}C-aminoisobutyric acid (AIB), which is a marker for the A-type transport of amino acids into the tissue, in patients with sarcomas and other tumor types [13]. Interestingly, the A-type transport of amino acids was lower in inflammatory lesions, when we compared 36 tumors and 5 inflammatory lesions, examined with both ^{18}F-FDG and AIB (Fig. 5a-c). Therefore, AIB may be used in addition to ^{18}F-FDG if inflammatory changes are to be considered.

One of the promising tracers in oncology is 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT). This tracer is a substrate for the thymidine kinase and associated with the proliferation rate of tumors. However, initial results demonstrate, that ^{18}F-FLT is not helpful to differentiate between reactive and metastatic lymph node metastases [14]. One reason, as discussed by the authors, may be the B-lymphocyte proliferation in reactive lymph nodes. Another reason may be the dependency of ^{18}F-FLT kinetics on the extracellular adenosine triphosphatase (ATP) concentration, which has an impact on the structure and the performance of thymidine kinase.

Another new tracer is ^{18}F-galacto-RGD, the pentapeptide cyclo(-Arg-Gly-Asp-D-Phe-Val-), which binds preferentially to the αvß3 receptor [15]. Integrins are an important group of genes, related to tumor growth, invasiveness and likelihood of metastases. Initial studies suggest the use of this tracer in patients with head and neck tumors, however further studies must be performed to assess the value of this tracer for the diagnostics or therapy management.

Other tracers like ^{18}F labeled tyrosine or the SSTR2 (so-

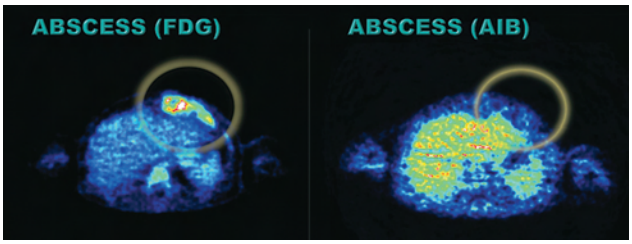

Figure 5a. Double tracer examination with ^{18}F-FDG (left) and ^{11}C-AIB (right) of a patient with an abscess. A high ^{18}F-FDG uptake is noted in the abscess, while no enhanced A-type amino acid transport is present.

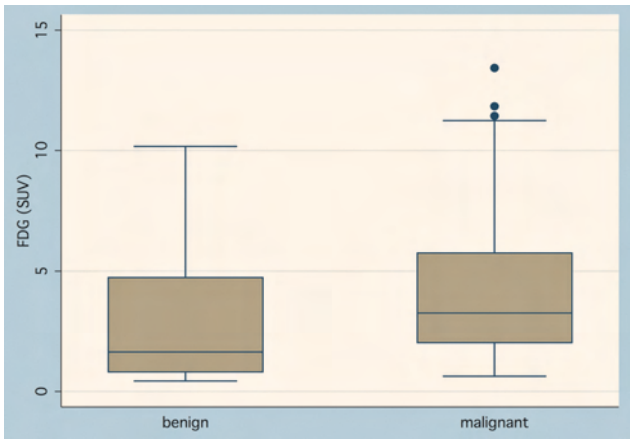

Figure 5b. Results obtained in 36 tumors and 5 inflammatory lesions. Significant overlap of the ^{18}F-FDG SUV for both groups.

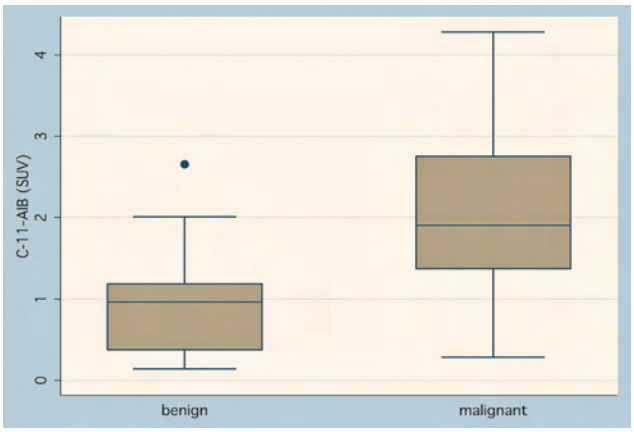

Figure 5c. The overlap of tumors and benign, inflammatory lesions is significantly lower as compared to FDG. C-11-AIB can be helpful to differentiate between tumor and inflammation due to the low uptake in benign lesions.

matostatin receptor 2) binding ^{68}Ga-DOTATOC ([1,4,7,10-tetraazacy-clododecane-N,N′N″,N′-tetraacetic-acid-D-Phe1-Tyr3]-octreotide) have found limited use. A high accuracy of dynamic ^{18}F-tyrosine examinations for the detection of recurrent laryngeal tumors, has been reported [16].

Therapy management

One major aim of new diagnostic methods besides improvements of tumor diagnostics is the individualization and optimization of therapy management. PET with ^{18}F-FDG is actually an established procedure for the follow up of oncological patients since several years [4]. In head and neck tumors one important topic is the improved detection of a recurrent tumor. Based on the data from Gambhir et al. (2001), who included 426 patients in the meta analysis, the sensitivity of ^{18}F-FDG-PET on a patient based analysis, is 93% and the specificity, 83% (CT has a 54% sensitivity and a 74% specificity) for the detection of recurrent head and neck tumors [7]. These data are comparable to those obtained for tumor diagnostics.

PET ^{18}F-FDG studies are usually performed for therapy monitoring to assess changes in tumor metabolism following therapy. The evaluation of 169 patients demonstrated a sensitivity of 84% and specificity of 95% for the assessment of therapy related changes in the tumor [7]. Again, PET was superior to CT (60% sensitivity, 39% specificity), because usually functional changes precede changes in tumor volume. Gambhir et al. (2001) noted a correlation of tracer kinetics and growth rates and report about a 33% change in therapy management due to PET results [7].

The prognostic value of PET with ^{18}F-FDG was investigated in a few studies. Based on the results obtained by others [5, 6], it can be expected that the quantitative evaluation of the ^{18}F-FDG uptake may be helpful to assess the proliferative aspect of tumors. Others evaluated the association of ^{18}F-FDG uptake, as measured by the SUV, and therapy outcome [17]. The authors performed ^{18}F-FDG studies in 73 patients prior to therapy (surgery and radiotherapy). An SUV of 10 was used for Kaplan-Meier analysis and revealed a highly significant difference in survival [17]. Therefore, the quantitative data of the initial ^{18}F-FDG uptake prior to therapy are predictive for therapy outcome. We investigated the correlation of changes in ^{18}F-FDG uptake and tumor growth rates in patients with head and neck tumors, receiving a cisplatinum based chemotherapy [18]. Dynamic PET studies were performed prior and after one chemotherapeutic cycle and the changes in tracer uptake were compared to the changes in tumor volume, as calculated from CT images. The growth rates and the changes in ^{18}F-FDG uptake (SUV) were correlated for both tumors (r=0.98) and lymph node metastases (r=0.94). Interestingly, the growth rates were different for the same changes in the ^{18}F-FDG uptake. Overall, tumors were more sensitive to therapy than lymph node metastases [18].

Future aspects

The recent developments in quantitative PET imaging direct to a better understanding of tracer kinetics by associating PET data with molecular biological data [19]. ^{18}F-FDG transport and phosphorylation is not only correlated to glucose transporters and hexokinases, but modulated by many other processes like angiogenesis, apoptosis, and proliferation. Thus, results obtained from dynamic PET data can be used to predict changes in gene expression patterns. However, in head and neck tumors more data are needed, correlating gene

expression with PET tracer kinetics in order to achieve a higher accuracy of both tumor staging and therapy management.

Besides ^{18}F-FDG, receptor targeting agents are getting more and more attention. Currently, ^{68}Ga-DOTATOC has found use in endocrine tumors [20]. The SSTR2 binding tracer can also be used to assess receptor positive tumors in the head and neck area, especially endocrine tumors or paragangliomas. Other receptor active tracers are under development. A few studies were performed with ^{68}Ga-bombesin, mainly in gastrointestinal stroma tumors (GIST) [21]. This tracer binds to three receptors, the gastrin releasing protein receptor, the bombesin-3 receptor, and the neuromedin-B. Besides GIST, some studies have been performed in prostate cancer (bombesin-3 receptor) and astrocytomas (neuromedin-B receptor). The value of the above studies in head and neck tumors has not been shown. Further tracers are in development at our center and will focus in future on aspects like angiogenesis, e.g. the VEGF (vascular endothelial growth factor) receptors. Due to the increasing availability of gene expression data, other differentially expressed receptors (tumor/reference tissue) will be identified and docking-ligand experiments will help to design new radiopharmaceuticals.

Five-year view

Current state-of-the-art systems, based on PET/CT hybrid systems, provide the best approach to assess a tumor in the head and neck area most accurately with an overall accuracy exceeding 90%. PET/MRI is visible at the horizon, but some years of development are needed to get systems for routine use. Further developments are also needed to provide other tracers besides ^{18}F-FDG to gain additional information for the differentiation of tumor and inflammation. Today and within the next years, receptor binding pharmaceuticals will find more frequent use to assess specific properties of a lesion. This will be especially helpful for patients treated with new chemotherapeutic drugs targeting dedicated receptors in the tumor.

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