The impact of positron emission tomography in the radiotherapy treatment planning*

Minireview

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Received July 27, 2006

Positron emission tomography (PET) is a new diagnostic method recently widely used in oncology. It is applied to distinguish benign and malign tumors, to diagnose relaps or posttherapeutic changes. PET is also complementary method to the standard used methods such as CT or NMR. Now it is used even as the predict factor of the treatment response and it can choose patients with worse prognosis. PET can help define a target volume in the radiotherapeutic planning. Daily using of PET in the oncologic praxis can change treatment strategy and it can improve therapeutic results. In our review we would like to summarize new informations about using PET in the treatment planning.

Key words: positron emission tomography, radiotherapy, target volume

In recent years the progress of radiotherapy (RT) and the establishment of new techniques and methods improve the therapeutic results. The strategy of RT has changed. The primary goal is not only to increase overall survival (OS) or disease free survival (DFS) but also to decrease the toxicity of the therapy. The way how to reach it is to ensure the precisionally treatment planning. Main problem is to define exactly treatment volume. In many oncologic centers in the daily practice it was obtained the using of computer tomography (CT) or magnetic resonance (MR). Recently it has been considered the including even positron emissing tomography (PET) into the RT planning.

Better imaging means better treatment for patients. For patients with localized disease and no evidence of macroscopic disease elsewhere a more aggressive treatment may be considered. In patients with advanced disease a conservative plan may be used to remove the pain and preserve the function.

PET mainly by using 18-F-fluorodeoxyglucose has its place in the diagnosis of malignant diseases. It can distinguish benign and malignant tumours, it can earlier show dissemination then other diagnostic methods. In some type of cancer it can be an important predictive factor of the relapse. PET can be also used in the detection of residuum of the disease.

18-F-fluorodeoxyglucose uptake in tumors is proportional to the glycolitic metabolic rate of viable tumor cells, reflecting increased metabolic demand for glucose.

Recently the using of PET is investigated even in the RT planning. Due to toxicity of RT it is necessary to precisely draw the target volume. Experiences with PET using in RT planing were published several studies mainly of lung cancer, cervix cancer or malignant lymphomas which used PET in planning processes.

It was estimated that 30–60% of treatment plans could be changed when PET finding are incorporated into the plan. The most frequent changes are upstaging of disease or the finding of new distant metastasis [1, 2].

PET cannot replaced standard imaging modalities but it can supplement those modalities in detection of tumors and new information can change target volume.

For the drawing of gross tumor volume (GTV) it is necessary the using of the fusion of CT and PET imaging. CT gives anatomical structure, PET biological activity of the tumor [3].

Adding PET to the management of the radiation planning offers changes in the treatment strategy to being either less aggressive or possibility for treatment even additional tumor sites.

*This study was supported by the research grant IGA MZ CR NR/8322-3

Sensitivity, specificity and significance of PET for radiotherapy

The problem of sensitivity and specificity of PET is discussed in comparison to CT and MR imaging and impact of PET on target volume definition.

When a scan is to be used for RT planning patients must be scanned in a precise position that will be repeated in subsequent RT sessions. This position simulates the treatment position.

Lung carcinoma. The role of PET in patients with lung carcinoma is in the staging of the disease and tumor targeting. The accuracy of PET in the staging derives from its high sensitivity 95% and specificity 81% for detecting tumour in the lung tissue. Sensitivity and specificity for mediastinal nodal disease is 88% and 91%, resp. PET offers a very high negative predictive value for mediastinal involvement 91–97%. Using PET in the diagnosis of new patients enable to detect distant metastatic disease. These results upstage disease and can change treatment strategy [4, 5, 6].

Dose escalation or intensification may, in some cases, improve the prognosis, on the other side also the toxicity of the therapy has to have an important role in the treatment strategy. To reduce toxicity due to RT it is necessary to reduce the volume of dose-limiting organs. The diagnostic accuracy of mediastinal involvement is better on PET scan. Using PET in the RT planning can be the way how to reduce the toxicity. Study of Ruysscher et al.(12) used PET scan in the RT treatment of patients with non-small cell lung cancer (NSCLC). Results of this study support the use of selective mediastinal node irradiation based on PET scan.

Also van der Wel et al. incorporated PET into treatment planning of NSCLC patients. The size of primary tumor and the pathologic lymph node areas was assessed by CT only to avoid the problems of tumor size determination on PET. Elective nodal RT was omitted. When the lymph nodes were abnormal on PET but negative on CT, the whole pathologic anatomic region of mediastinum was taken as the GTV. Incorporation of PET scan data in the RT planning reduced the radiation exposure of the lung and esophagus significantly. Investigators calculated treatment plans for CT-PTV and CT/PET-PTV for all patients. Nodal GTV was smaller on PET, GTV for the primary tumor was the same. CT/PET planning decreased radiation fields in 11 from 21 cases; in 3 patients it increases the radiation fields. Even if there is an improvement of the including PET into treatment planning there are however also some problems: such as misses of the area, the movement of the chest, and problem with the fusion of the methods [7].

In the study of Hicks et al. 153 patients with NSCLC were investigated. PET changed the stage of 33% of patients and also changed the target volume in 25 % cases. PET helped distinguish the atelectasis and tumour infiltration [8].

Weber et al. reviewed 16 studies including 1355 patients with NSCLC. All patients underwent PET before treatment for preoperative staging. Sensitivity was 85% and specificity was 97%. In studies comparing CT and PET the sensitivity and specificity for CT alone was 66% and 71%. In 17% of patients PET correctly modified the tumour stage. In only 2% of patients the tumor stage was incorrectly diagnosed by PET [9].

In the meta-analysis of Gould et al. there were included 39 trials. They compared CT and PET in the mediastinal staging in patients with NSCLC. They concluded that PET is more accurate than CT for mediastinal staging, more sensitive (85% vs. 61%) but less specific when CT shows enlarged mediastinal lymph nodes (78% vs. 93%) [10].

Interobserver variability in GTV delineation by two different radiation oncologists was significantly reduced, when PET/CT was used in comparison to CT alone. Due to using PET the GTV are often changed (30–60% of cases). It can be decreased in the case of the presence of the atelectasis or it can be increased with the respect to distinguishing new nodal involvement. The therapeutic item can be also changed from curative to palliative in the case of the presence of metastasis. On the other hand, the enhanced FDG uptake in inflammatory disease might limit the use of PET in treatment planning [11, 12, 13, 14, 15].

Head and neck cancer. Treatmen approache in head and neck carcinoma is usually the combination therapy- surgery, radiation, chemotheraphy. For staging it can be used several modalities. Staging the neck involvement alone shows the following sensitivities and specificities: PET 70% and 82%, CT 66% and 74%, MR 64% and 69% and ultrasound 84% and 64%. But no modality has the capability of detecting micrometastatic disease [16].

In the study of 12 patients of head and neck cancer, all underwent presurgical PET scan. Physical and radiologic finding don't suggested nodal metastasis, but PET scan discovered two positive nodal metastasis. Pathological staging approved nodal metastasis in 5 of 12 patients. PET was in one case false positive. For the radiation oncologist it is necessary not only consider GTV by staging modalities but also estimate subclinical involvement (CTV) [17].

Paulino et al. in their study of head and neck cancer, found that about 25% of patients would be underdosed when only CT is used for RT planning. Accurate delineation is especially important with the use of intensity-modulated radiation therapy (IMRT) [18]. False negative PET results were observed in micrometastatic disease. False positive findings occurred in inflammatory lymph nodes and in some structures (tonsils, salivary glands) [19].

Esophageal carcinoma. Kato et al. compared the results of PET in patients who had squamous cell carcinoma of the esophagus and underwent radical esophagectomy. PET scans were found to be more accurate than CT scans in the identifying abnormal mediastinal lymph nodes with 77,8% sensitivity, 92,9% specificity and 84,4% accuracy compared with 61,1% sensitivity, 71,4 % specificity and 65,6% accuracy for CT scans. [20].

PET is a very useful approach in determining depth of invasion, T stage and the presence of peritumoral lymph node involvement [21, 22, 23].

Cervical cancer. Cervical carcinoma stage IIb and more, is usually treated by radiotherapy. The size of treatment fields depends on the nodal involvement. Patients without involvement of iliac lymph nodes can be cured by the field involving the whole pelvis. The involvement of external iliac lymph nodes shifts the proximal border to the high of L2/3. If there are present the pathologic para-aortic lymph nodes, it is necessary include to the treatment filed all para-aortic lymph nodes to the high of Th12/L1. CT and MR are lower sensitivity and specificity in the distinguishing of the involvement of lymph nodes. PET can show tumor invasion in cases of normal size of nodes. Positive PET scan on para-aortic nodes extend radiation therapy field [24].

Singh et al. incorporated PET into treatment planning of patients with cervical carcinoma IIIb stage. All patients underwent concomitant chemoradiotherapy. The overall survival estimate at 3 years was 61%. The cause specific survival rate on basis of the extent of lymph node metastasis diagnosed by PET was 73% at 3 years for those with no lymph node metastasis; 58% for those with only pelvic lymph node metastasis; 29% for those with pelvic and para-aortic lymph node metastasis; and 0% for those with pelvic, para-aortic and supraclavicular lymph node metastasis. They conclude that the level of regional lymph node metastasis detected by pretreatment PET is a significant predictor of overall and specific cause survival. They recommend that all patients with cervical carcinoma undergo lymph node staging by PET before treatment. Patients with no lymph metastasis and those with only pelvic lymph node metastasis should be treated with pelvic external beam radiotherapy (EBRT), brachytherapy (BRT) and concurrent chemotherapy (CHT). Patients with PET positive para-aortic lymph nodes should be treated also by EBRT to the para-aortic region. More aggressive therapy can be offer for these patients, such as escalation of the dose of RT, using IMRT or using more aggressive CHT. These patients are in higher risk of presence distant metastasis [25].

Grigsby et al. estimated 101 patients with cervix carcinoma. All patients underwent pretreatment CT and PET image scans. Then they were treated by chemotherapy, radiotherapy and brachytherapy. There was a statistically significant difference in the two years progression free survival (73% for CT and PET negative; 49% for CT negative and PET positive; 39% for CT and PET positive). Authors concluded that abnormal PET finding in lymph nodes is an important predictive factor of the progression of the disease [26, 27].

Rose et al. compared the PET finding with histopathologic report in patients with cervix carcinoma which underwent pretreatment PET scan followed by surgical treatment. Sensitivity of PET finding on lymph nodes was 75%, specificity 92%, positive predictive value 75% and negative predictive value 92% [28].

Lymphoma. CT is currently the principal imaging modality for diagnosing, staging and monitoring of malignant lymphoma. Lymph nodes of dimensions exceeding 1 cm in short-axis diameter on an axial CT are considered positive. CT does not identify lymphoma in normal size lymph nodes nor does it distinguish non-lymphoma nodal enlargement from involved nodal masses. Therefore involved nodes smaller than the threshold size may be excluded from treatment fields. Several trials confirmed that PET had higher sensitivity and specificity of detecting lymphoma compared to CT for both pre-therapy and post-therapy studies. Stumpe et al. showed PET and CT specificity of 96 and 41% for Hodgkin disease and 100 and 67% for non-Hodgkin lymphomas. [29].

Other study shows PET scan sensitivity, specificity and accuracy for staging Hodgkin disease 88%, 100% and 90%. For therapy monitoring and determining residual tumor its sensitivity, specificity and accuracy were 85%, 96% and 96%. For non-Hodgkin lymphomas FDG uptake varies on the type of lymphoma. Higher uptake is usually in clinically aggressive lymphomas. Mucosa associated lymphoid tumor lymphomas have on the contrary minimal FDG uptake. Overall sensitivity for non-Hodgkin lymphomas is variable and about 83%, specificity is 100% and accuracy 86% [30].

Brain Tumors. MRI is gold standard in the diagnosis of brain tumors. FDG-PET is not so much important in the diagnosis and the detection of brain tumor. The brain utilizes glucose very much unlike other tissues. Accumulation of FDG in normal brain tissue is very high. Therefore brain tumors cannot be distinguished exactly. This fact limits the using of FDG-PET in brain tumor imaging.

Other radiolabeled traces are used in the diagnosis of brain tumors. There are especially amino acids such as carbon 11 labeled methionine (MET), iodine –123 labeled a methyl-thyrosine (IMT) and fluorine 18 labeled O(2)fluorethyl-L-thyrosine (FET). These tracers are of high uptake in glioma cells and only low uptake in normal cerebral tissue [31–34].

Several studies compared CT, MRI and MET-PET with stereotactic biopsies. They suggested that MET-PET has a higher accurancy in defining the extent of gliomas than either CT or MRI. Herholz et al. showed sensitivity and specificity of MET-PET in differentiating between non-tumoral tissue and low-grade gliomas of 76% and 87% [31]. Voges et al investigated 46 patients with brain tumors. All patients underwent MET-PET. In 67% of cases the spatial extent of increased tracer uptake was larger than that of the contrast enhancement on CT and MRI images. Than patients underwent therapy using brachytherapy with ^{125}I seeds. One year after therapy new MET-PET were performed. The results showed a significant decline of MET uptake. Voges concluded that MET-PET may improve the definition of tumor volume and provide informations regarding therapeutic effects [32]. Grosu analysed 39 patients with gliomas. They used MET-PET and MRI-T1-Gd. In 79% of cases the region of MET uptake was larger than thant of Gadolinium enhancement and in 74% of Gadolinium enhancement area extended

beyond the MET enhancement. Analysis of MET-PET verus MRI-T2 showed that MET uptake did not correspond exactly to hyperintensity areas of T2 in any patients [33,34]. Nuutinen et al. used MET-PET in the radiation treatment planning in patients with low-grade gliomas. MET-PET was helpful in outlining of GTV in 27% of cases [35]. Schwaiger compared this MET-PET procedure and standard MRI with image fusion for evaluation of gross tumor volume definition for radiation therapy planning of high-grade gliomas in 39 patients. MET uptake was located beyond gadolinium (Gd) enhancement on MRI in 74% of the cases and was identified outside the hyperintensity areas on T2-weighted MRI in 50% of patients. In 69% and 100% of the 39 patients, the Gd-enhancement area and the edema extended beyond the MET uptake, respectively. Considering that Gd enhancement and edema located beyond the MET uptake were the result of prior surgery, these regions should be excluded from the gross tumor volume and, thus, not included in the radiation dose areas. An important consequence of the integration of MET-PET in the tumor volume delineation is the saving of the normal brain. These data suggest that MET-PET could be useful for excluding normal brain tissue from the high radiation dose, because it is a better tool for precisely delineating the target volume in the planning of radiation therapy [36].

MET-PET has been integrated into a dose-escalation protocol for patients with residual tumor after surgery of high-grade gliomas, and MET-PET/computed tomographic (CT)/MRI fusion images are used in the treatment planning for repeat irradiation of recurrent tumors.

The short physical half-life of MET (about 20 min.) limits its clinical usefulness to centres with cyclotrons. FET has longer physical half-life- about 110 min. Grossu and Weber showed that FET-PET and MET-PET were equal in their ability to diagnose glioma [33,34].

Magnetic resonance spectoscopy (MRS) can be considered a new method of diagnosis brain tumors. This imaging technology shows serial monitoring of biochemical changes in various intracranial pathological entities, including tumors, stroke, infections, epilepsy, and neurodegenerative diseases. In MR spectroscopy, each metabolite has its own signature, is measured as parts per million, and reflects specific cellular and biochemical processes. The most commonly examined metabolites include the following: N-acethylaspatate (NAA) and choline (Cho), a cell membrane marker that is readily elevated in tumors and inflammatory processes, reflecting rapid cell turnover. The levels of NAA are decreased in tumors because of desplace of normal ceberal tissue by tumoral cells. The rapid growth results in elevated Cho. Using PET and MRS in future can obtain more new information about tumoral growth and can exactly difinate extention of tumoral infiltration.

Although only preliminary data are aviable the amino acid PET are superior to use of either MRI or CT in the visualization of vital tumor extension in gliomas. More studies have to be investigated to include PET in the diagnostic and treatment management of brain tumors.

Conclusion

Positron emissing tomography (PET) can be also used after therapy to detect tumor residuum and obtain informations about treatment results. PET scan following radiotherapy should be delayed at least for six weeks, preferably three or four months so that inflammation within the radiation fields can dissipate. In case of lung carcinoma it is better to wait 4 or 6 months due to postradiation pneumonitis [37, 38].

Recently the PET is often used in after treatment follow up in malignant disease. It is shown that PET can play a role in the distinguish residuum and posttherapeutic changes in colorectal carcinoma. Meta-analysis show the sensitivity and specificity of PET for recurrent colorectal carcinoma is 97% and 76%.

PET cannot replace standard diagnostic methods but can accomplish them and can find new information about the disease. Patients undergoing CT and PET image scans have to be in the same position during both processing. Combined PET/CT scan has been helpful in the eliminating false positive interpretations of the PET scans. Controlled clinical trials are also needed to obtain more information and practice. In future could be expected the applying of new PET tracers such as carbon 11 labeled choline or fluorine 18 labeled choline in the diagnosis and targeting of prostate cancer, and the using carbon 11 labeled methionine in brain tumors. The using of hypoxia tracers should offer new informations about disease and maybe it can improve therapeutic results. Areas with high uptake of hypoxia tracers can obtain higher RT dose by using IMRT.

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