How to use functional imaging information for radiotherapy planning

Anca-Ligia Grosu[a], Ursula Nestle[a], Wolfgang A. Weber[b]

[a]*Department of Radiation Oncology, University of Freiburg, Germany*
[b]*Department of Nuclear Medicine, University of Freiburg, Germany*

Introduction

The goal of this study is to discuss the role of functional/biological imaging (positron emission tomography – PET – and magnetic resonance imaging – MRI) in target volume delineation for radiation treatment planning.

Functional/biological imaging for gross tumour volume (GTV) delineation

FDG-PET in lung cancer

Fluorine-18 labelled glucose analogue fluoro-deoxy-glucose (FDG-PET) has an important significance in diagnosis, development of treatment strategy and evaluation of treatment response in lung cancer. To date, over 20 studies in more than 700 patients have shown that the use of FDG-PET image data may lead to an advantage for the patient. The main sources of this possible advantage are the better coverage of the primary tumour and the protection of healthy tissue. The high percentage of changes in target volumes by FDG-PET reported (20–100%) in the literature concerning various parameters of the planning process is mainly caused by two factors: the ability to distinguish the tumour from collapsed lung tissue (atelectasis), and the higher accuracy of FDG-PET in lymph node staging compared to CT [1]. However, because inflammation in the collapsed lung may also lead to FDG accumulation, PET does not help for GTV definition in these cases.

The gold standard method for the delineation of the GTV has not been set yet. The problem is the low resolution of PET images, which is caused by physical factors (size of the detector crystals, positron range in matter, non-collinearity of annihilation gamma-rays and detector scatter) and also by biological factors (movements of the target during acquisition due to relatively long acquisition times), which leads to a blurred margin of the accumulating structure [2].

MET-PET and FET-PET in brain gliomas

The higher sensitivity and specificity of amino acids (AA)-PET in the diagnosis of gliomas in comparison to CT and MRI was demonstrated in many clinical trials. Summarising the data of the literature, we found 45 trials between 1983 and 2007, including 1721 patients, which investigated the role of L-(methyl-11C) methionine (MET)-PET in diagnosis of gliomas. Eleven studies including 706 patients were based on PET/MRI/CT stereotactical biopsies. Between 2000 and 2007, 12 trials including 361 patients evaluated the role of O-(2-(18F)fluorethyl)-L-tyrosine (FET)-PET in the diagnosis of brain gliomas. In three studies evaluating 126 patients the results were based on PET/MRI/CT stereotactic biopsies. All these studies have shown that the sensitivity and specificity of MET-PET and FET-PET for malignant gliomas is significantly higher (85–95%) in comparison to MRI, which has a high sensitivity but a lower specificity (Grosu et al., manuscript in preparation). The similarity between MET- and FET-PET for tumour visualisation was demonstrated in two studies [3,4].

At many centres, AA-PET (MET-PET or FET-PET) is routinely performed in order to differentiate between viable tumour tissue from radiation necrosis and other treatment related changes of the MRI signal. The higher diagnostic accuracy of AA-PET is the rationale for using this technique in target volume delineation of gliomas, since AA-PET can also provide information regarding tumour extension. In a series of clinical studies we demonstrated marked differences between AA-PET or SPECT and MRI in GTV delineation for radiation treatment planning [5–7]. In 39 patients with high grade gliomas imaged postoperatively, tumour contrast enhancement and MET uptake corresponded in only 13% of the patients. On average, 13 ml (33%) of the tumour volume defined on MET-PET demonstrated no contrast enhancement on MRI [8]. Based on these data we performed a small prospective study in which AA-PET or AA-SPECT was used for planning of stereotactic radiotherapy. In this study,

patients with recurrent gliomas lived significantly longer when AA-PET or single photon emission tomography (AA-SPECT) were integrated in target volume delineation. Median survival of patients who underwent AA-PET or -SPECT based radiation treatment was 4.5 months longer than that of patients who underwent CT/MRI based radiation treatment [9]. This is the first study to indicate that radiation therapy guided by AA-PET can improve patient survival.

MR-Spectroscopy in brain gliomas

Pirzkall [10] compared MR-Spectroscopy (MRS) and MRI in patients with high grade gliomas prior to surgery. T2-MRI is shown to estimate microscopic disease better than MRS. Metabolically active tumor detected by MRS is extended outside the region defined by T2-MRI in 88% of patients by as much as 28 mm. In a retrospective analysis of patients with recurrent brain gliomas treated with Gamma Knife radiosurgery based on T1-MRI, Graves [11] showed that the outcome of patients with tumour infiltration in MRS outside of the changes in conventional MRI was significantly worse than that of patients without additional information in MRS concerning tumour extension.

FDG-PET in head and neck tumours

In a first clinical trial with 41 patients, the group of Madani [12] performed a FDG-guided focal dose escalation using intensity-modulated radiation therapy (IMRT) for patients with head and neck cancer. While applying conservative doses to elective lymph node levels, doses to GTVs defined by CT and FDG-PET were escalated up to a NID_{2Gy} of 78.2 Gy. However, in preliminary evaluation of the pattern of recurrence, 4/9 locoregional recurrences were located outside the PET-defined GTV and 1/9 at the border of the PET-GTV, although the above mentioned contrast oriented method for FDG-based GTV contouring was used, which had been verified by correlation with pathologic specimens [13].

Choline-PET and MRI/MRS in prostate cancer

C11-acetate-PET and C11-choline-PET are two promising tracers in prostate cancer. However, their validity in local tumour demarcation, lymph node diagnosis, detection of recurrences and of distant metastases has to be clearly defined in future clinical trials.

Currently, there are no data available in the literature concerning the use of PET in radiation treatment planning of primary or recurrent prostate cancer. However, data exist from other biological imaging methods, namely MRS, about choline and citrate metabolites within the cytosol and extracellular space of the prostate. Recent trials analysing cancer location and extent within the prostate, extracapsular spread and cancer aggressiveness in pre-prostatectomy patients have indicated that the metabolic information provided by MRS combined with the anatomical information provided by MRI can significantly improve the assessment of cancer location and extent within the prostate, extracapsular spread and cancer aggressiveness [14]. The integration of H-MRS in brachytherapy treatment planning of patients with organ-confined but aggressive prostatic cancer could improve the tumour control probability, especially in small intraprostatic tumours [15].

Functional imaging for characterisation of tumour biology

Hypoxia

The tracers investigated for the evaluation of hypoxia are mainly nitroimidazole compounds, e.g. [^{18}F]Fluoromisonidazole [^{18}F]FMISO, which was the first nitroimidazole compound developed for PET, [^{123}I]Iodoazomycin arabinoside [^{123}I]IAZA and [^{18}F]-Azomycin arabinoside [^{18}F]FAZA [16]. With these tracers, the bioreductive molecule attracts a single electron leading to free radical metabolites that are further reduced and bound to cell constituents under hypoxic conditions. [^{60}Cu] labelled Methylthiosemicarbazone ([^{60}Cu]ATSM) has also being proposed for hypoxia imaging [17]. The integration of hypoxia-PET in radiation treatment planning is under investigation [16–18].

Proliferation

The proliferation of tumour cells is the basic mechanism for malignant growth. Therefore, attempts have been made to image this parameter, which is thought to be more specific for malignancy compared to e.g. glucose consumption. [^{18}F]-Fluorine labelled thymidine analogue 3′-deoxy-3′-[^{18}F]-fluorothymidine (FLT) is retained in the cell after phosphorylation by thymidin kinase 1, whose levels correlate with cell proliferation [19].

Angiogenesis

The $\alpha v\beta 3$ integrin is an important receptor for cell adhesion involved in tumour-induced *angiogenesis* and

metastasis. It mediates migration of activated endothelial cells through the base membrane during formation of new blood vessels. Particularly interesting is that this integrin is expressed only on the cell surface of tumour cells or activated endothelial cells, but not on normal endothelial cells of established vessels. Beer et al. [20] described the noninvasive imaging of αvβ3 integrin expression using F18-labelled RDG-containing glycopeptide and PET. In squamous cell carcinoma of the head and neck, for example, αvβ3 integrin seems to be expressed on the endothelial cells and not on the tumour cells. This suggests that RGD-PET could be used as a surrogate for the visualisation and evaluation of tumour angiogenesis.

Conflict of interest statement

None declared.

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