Invited articles

Biological imaging in radiation treatment planning for brain tumours

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The paper presents new techniques of intracranial tumour visualisation – positron emission tomography (PET) and single photon computed emission tomography (SPECT). In the course of these examinations one may use radiolabelled amino acids, which are characterized by increased uptake within the tumour. These techniques are very useful for precise 3D radiotherapy planning, especially in patients with post-surgical residual tumours or in cases when the tumour is located in the direct vicinity of surrounding skeletal structures, as is the case with meningiomas of the cranial base.
Precise definition of the target is a necessary element of modern radiotherapy, the results of which may be significantly improved by the use of biological markers in the course of visualization techniques.

Wizualizacja guzów wewnątrzczaszkowych przy użyciu aminokwasów znakowanych izotopami a planowanie radioterapii

W pracy przedstawiono techniki wizualizacji guzów wewnątrzczaszkowych (glejaków i oponiaków) w oparciu o pozytronową tomografię emisyjną (PET) i tomografię emisyjną pojedynczego fotonu (SPECT). Podczas tych badań wykorzystuje się większe, w porównaniu ze zdrową tkanką, powinowactwo guza do niektórych aminokwasów. Znakując wybrane aminokwasy izotopowo można uzyskać bardzo dokładny obraz guza. Techniki te można wykorzystać podczas planowania radioterapii, szczególnie u chorych po operacji, umożliwiają bowiem precyzyjne zaplanowanie dawki w obrębie pozostawionych fragmentów guza. Inną zaletą opisanej metody jest możliwość dokładnego określenia granic guza w sytuacji, gdy znajduje się on w bezpośredniej bliskości struktur kostnych. Jest to zwłaszcza istotne w przypadku oponiaków zlokalizowanych na podstawie czaszki.
Precyzyjne określenie granic tkanki nowotworowej jest niezbędne w nowoczesnej radioterapii, a zastosowanie nieinwazyjnych technik wizualizacji z wykorzystaniem znaczników biologicznych może znacznie poprawić wyniki leczenia.

Key words: Positron emission tomography (PET), single photon computed emission tomography (SPECT), radiotherapy, intracranial tumours
Słowa kluczowe: pozytronowa tomografia emisyjna (PET), tomografia emisyjna pojedynczego fotonu (SPECT), radioterapia, guzy wewnątrzczaszkowe

Introduction

CT & MRI

3D conformal treatment planning in radiation oncology is based on computed tomography (CT) and magnetic resonance imaging (MRI). MRI shows the anatomical structures of soft tissue with a high accuracy. CT is important for the delineation of bony structures and for the accurate computation and visualisation of radiation dose. However, both CT and MRI image the tumour using differences in the density (that is, intensity of the signal) of the tissues, the property to enhance contrast or to accumulate water (oedema). All these signs are not specific only to tumour tissue. They can also be observed in changes due to other causes such as surgery, trauma and vascular disease. This sometimes makes the tumour diagnosis and delineation difficult and represents the most important limitation of these CT and MRI investigations.

PET & SPECT

Biological imaging visualises biological pathways. Positron emission tomography [PET] and single photon computed emission tomography (SPECT) are characterised by the visualisation of tumours using radioactive tracers with a higher affinity for tumour when compared to normal tissue. Basically, we have a biological paradigm where PET and SPECT can offer additional information about

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tumour extension and biology, when compared to CT or MRI.

PET & SPECT with amino acid tracers

Radiolabelled amino acids are intensively taken up by glioma cells whereas there is only a low uptake by normal cerebral tissues. The most important radiolabelled amino acids used in the diagnosis of gliomas are [11]Carbon-methionine (MET), [123]Iodine-alpha-methyl-tyrosine (IMT) and O-2(^{18}F)fluoroethyl-L-tyrosine (FET).

MET-PET

Gliomas

The mechanism and biological significance of increased ^{11}C-MET uptake in gliomas is not yet completely understood. Planas et al [1] have shown that although MET is incorporated into proteins, its uptake is probably not a measure of protein synthesis. The increased uptake seems to be mainly due to an activation of carrier A- and L-mediated transport at the blood brain barrier (BBB). The main advantages of this tracer in neuro-oncology are given in Table I.

Table I. Main advantages of ^{11}C-MET

– It is very sensitive in delineating various brain tumors including, high and low grade gliomas, meningiomas, pituitary adenomas and metastases.
– The transport of across the BBB is mediated by a specific transport system (L and A type amino acid transporter). Thus a disruption of the BBB is not required for tumour MET uptake.
– MET uptake is low in the normal white and gray matter.

It is important to mention that low grade gliomas, especially oligodendrogliomas, show a high MET uptake in comparison to FDG-PET [2]. Nevertheless, several studies have demonstrated a correlation between MET uptake and histological tumour grading [3, 4]. Comparing CT, MR and MET-PET using stereotactic biopsies, Mosskin et al [5] and Ogawa et al [3] concluded that MET-PET has a greater capacity to outline correctly the true extent of brain gliomas, when compared to CT and MR. This observation has important consequences for therapy planning and monitoring of patients with brain gliomas.

The initial findings regarding the value of MET-PET and FDG-PET in the follow-up of irradiated patients with brain gliomas were reported by Würker et al [6]. They analyzed 10 patients with brain gliomas, investigated with FDG-PET and MET-PET, before and after brachytherapy with ^{125}I seeds. After one year, glucose metabolism was not significantly changed whereas MET uptake showed a significant dose-dependent decrease.

The integration of MET-PET data into treatment planning systems in radiotherapy has been described by Julow [7] for brachytherapy but without validation of the image fusion method. Nuutinen et al [8] have described the feasibility of MET-PET for radiation treatment planning of low grade astrocytomas but have used no image fusion tool.

We introduced MET-PET in the treatment planning for stereotactic radiotherapy [9] and our study demonstrated that the automatic image fusion based on mutual information measured provides a fast and robust way to reorientate MET-PET and CT data sets.

This first clinical experience reported by our group [9] showed that MET-PET can improve target volume definition for stereotactic fractionated radiotherapy of gliomas. We used the CT/MET-PET images to define the tumour volume for radiation treatment planning. In patients with malignant gliomas we delivered 60 Gy in 2 Gy fractions according to 3D traditional treatment planning and four fractions of 5 Gy using the stereotactic technique.

The boost volume was defined according to the MET-PET/CT/MRI fusion images. The gross tumour volume (GTV) for the stereotactic treatment planning corresponded to the PTV and represented the MET uptake. This approach is useful especially for operated patients. In these cases using CT or MRI, any residual tumor cannot be differentiated from post-operative BBB disturbances or from post-operative oedema.

Meningiomas

The high affinity of meningiomas for MET has been described in previous studies [10]. The objective of stereotactic fractionated radiotherapy is to achieve a high tumour control with a minimal risk of side effects. The exact definition of tumour extension is therefore an important step in stereotactic radiation treatment planning.

For meningiomas, the GTV is outlined by considering the contrast enhancement areas in CT and MRI. Previous studies demonstrated the impact of both types of investigations in tumour volume definition [11]. However, meningiomas infiltrate the regions of the sella, cavernous sinus, tentorium, falx cerebri and dura mater structures. In these regions, characterised by a high contrast enhancement comparable with the enhancement of the meningioma itself. Thus using MRI or CT alone it is impossible to define the tumour infiltration with a high degree of accuracy.

Difficulties in tumour extension are also known for surrounding skeletal structures and these have special implications in orbital, base of skull or clivus meningioma infiltration. Using MET-PET, tumour borders can be defined with a higher precision and as a consequence, critical areas such as optic nerves, pituitary gland, cavernous sinus including the oculomotorius, the trochlearis, the abducens and the trigeminus nerves, the brain stem, and the hypothalamus can be spared from high radiation dose, Figure 1.
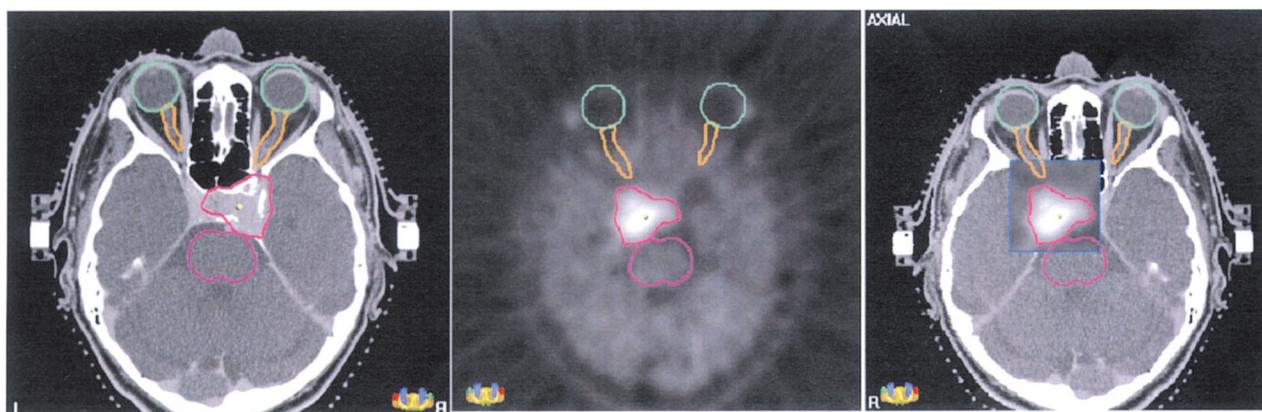
Figure 1. Meningioma WHO grade I. CT, MET-PET and CT/MET-PET image fusion [BrainLab system for stereotactic treatment planning]. The tumour is outlined using both investigations. MET-PET helps to define the tumour extension in the region of the sella with a higher accuracy. Critical organs such as optical nerves, cavernous sinus, cranial nerves can be spared

FET-PET

In preliminary studies it has been demonstrated that O-2(^{18}F)fluoroethyl-L-tyrosine [FET] shows a similar uptake in brain tumors as MET. The advantage of the amino acid analogue FET is that it can be radiolabelled with ^{18}Fluorine which has a more than five times longer physical half-life than ^{11}Carbon and can be distributed to PET centers without the necessity for an onsite cyclotron.

The aim of our investigation was to compare the uptake of FET with that of MET in patients with suspected primary or recurrent intracerebral tumours [12]. A total of 16 consecutive patients with intracerebral lesions [high and low grade gliomas and metastases] were studied on the same day by PET using MET and FET. Uptake of FET and MET was quantified by standardised uptake values. Tracer kinetics for normal brain and intracerebral lesions were compared. On the basis of the MET-PET studies, viable tumour tissue was found in 13/16 patients.

All tumors showed rapid uptake of FET and were visualised with high contrast. Mean uptakes of FET for normal gray matter, white matter and tumour tissue were respectively 1.1±0.2, 0.8±0.2, and 2.7±0.8 standardised uptake value [SUV]. In all three tissue types, uptake of MET was slightly higher (1.4±0.2; 0.9±0.1; 3.3±1.0 SUV; P<0.01). However, contrast between tumour and normal tissues was not significantly different between MET and FET.

Uptake of FET in non-neoplastic lesions [1.0±0.1 SUV] was significantly lower than in tumour tissue, P=0.007. For all lesions there was a close correlation, R=0.98, between MET and FET uptake.

In conclusion, in PET studies of human brain tumours, uptake and image contrast of FET appear to be very similar to that of MET. The specificity of FET for tumour tissue is promising but has to be addressed in a larger series of patients with non-neoplastic lesions.

IMT-SPECT

Gliomas

^{123}Iodine-alpha-methyl-tyrosine (IMT) is a synthetic amino acid whose uptake by gliomas has been shown to be closely correlated with uptake of ^{11}Carbon-methionine. In contrast to methionine, IMT can be imaged with the much more widely available SPECT. It has been demonstrated in several studies that IMT-SPECT enables the visualisation of gliomas with high contrast. Furthermore, IMT-SPECT has been found to be a specific test for differentiation of tumour recurrence and therapy induced changes [13-15].

We compared the results of IMT-SPECT with MRI in tumour volume definition of brain gliomas and evaluated the influences of the information provided from IMT-SPECT for 3D conformal treatment planning [16]. In 30 patients with *non-resected*, histologically proven brain gliomas (13/30 glioblastoma, 12/30 astrocytoma grade III, 3/30 astrocytoma grade II, 1/30 oligodendroglioma grade III and 1/30 oligodendroglioma grade II).

IMT-SPECT and MRI were performed prior to treatment in the same week. A special software system allowed the co-registration of the IMT-SPECT and MRI data. The GTV defined on the IMT-SPECT/T2-MRI fusion images (GTV-IMT/T2) was compared with the GTV-T2 defined on the T2-MRI alone. On the IMT-SPECT/T1Gd-MRI overlays, the volume of the IMT tumour uptake (GTV-IMT) was compared with the volume of the Gadolinium (Gd) enhancement (GTV-T1Gd).

The initial PTV and the boost volume (BV) outlined on the IMT-SPECT/T2-MRI co-images were analysed and compared to the PTV and BV delineated using the T2-MRI alone. We found a higher IMT uptake of tumour areas compared to normal brain tissue, in all 30 patients we studied.

Mean GTV-IMT, mean GTV-T2 and mean GTV-T1Gd were respectively 43, 82 and 16 cm³. IMT tumour uptake outside of the contrast enhancement regions was

observed in all patients. Mean relative increase of tumour volume defined on the fusion images, GTV-IMT/T1Gd *versus* GTV-T1Gd alone was 78%. IMT tumour uptake areas outside of the GTV-T2 were registered in 7/30 patients. In these patients, the mean increase GTV-IMT/T2 was 33% higher than GTV-T2, defined according to the T2-MRI data alone.

The additional information provided by IMT–SPECT modified minimally the initial PTV (mean relative increase PTV-IMT/T2 *versus* PTV-T2 of 5%) but significantly modified the BV (mean relative increase BV-IMT/T2 *versus* BV-T2 of 37%).

We concluded that in a significant number of patients, the IMT-SPECT investigation improves the tumour detection and delineation in the planning process. This has important consequences in 3D conformal treatment planning, especially in the delineation of the BV, Figure 2.

Post-surgery gliomas

In 66 post-surgery patients with gliomas who were scheduled to undergo conformal radiotherapy, IMT-SPECT images were co-registered with T1- and T2-weighted MRI data sets [17]. On these *fusion* images, residual tumour volume was delineated using the combined information of IMT-SPECT and MRI, Table II.

The tumour volume defined on IMT-SPECT was compared with the volume of contrast enhancement in T1-weighted MRI studies and the volume defined by the hyperintensity in T2-weighted images. The regions with IMT uptake and/or MRI changes (Composite Vol

Table II. Relationship between IMT uptake on SPECT with Gd enhancement and T2-hyperintensity on MRI in 66 patients with post-surgery gliomas.
Number of patients with (+) or without (-) IMT uptake, Gd enhancement and T2-hyperintensity areas in SPECT and MRI from the total series of 66 cases: after Grosu et al [17]

Category	IMT uptake (+)	IMT uptake (-)
Gd enhancement (+)	25	34
Gd enhancement (-)	0	7
T2-hyperintensity (+)	25	41
T2-hyperintensity (-)	0	0

MRI/IMT), the regions with overlay of IMT uptake and MRI changes (Common Vol MRI/IMT), the area with IMT uptake without MRI changes (Increase Vol MRI/IMT) and the area with only MRI changes (Vol MRI minus IMT) were separately analyzed.

PTV and BV defined by using the MRI information alone was compared with PTV-IMT and BV-IMT defined by additionally using also the SPECT information. Focally increased IMT uptake was observed in 25/66 patients whereas contrast enhancement in MRI was outlined in 59/66 patients and hyperintensity area on T2-MRI was found in all 66 patients.

Mean Composite Vol T2/IMT was 73 cm^3. The Relative Increase Vol T2/IMT, mean Relative Common Vol T2/IMT and mean Relative Vol T2 minus IMT were respectively 4%, 6% and 90% of the Composite Vol T2/IMT.

Mean Composite Vol T1/IMT was 14 cm^3 and the mean Relative Increase Vol T1/IMT, mean Relative
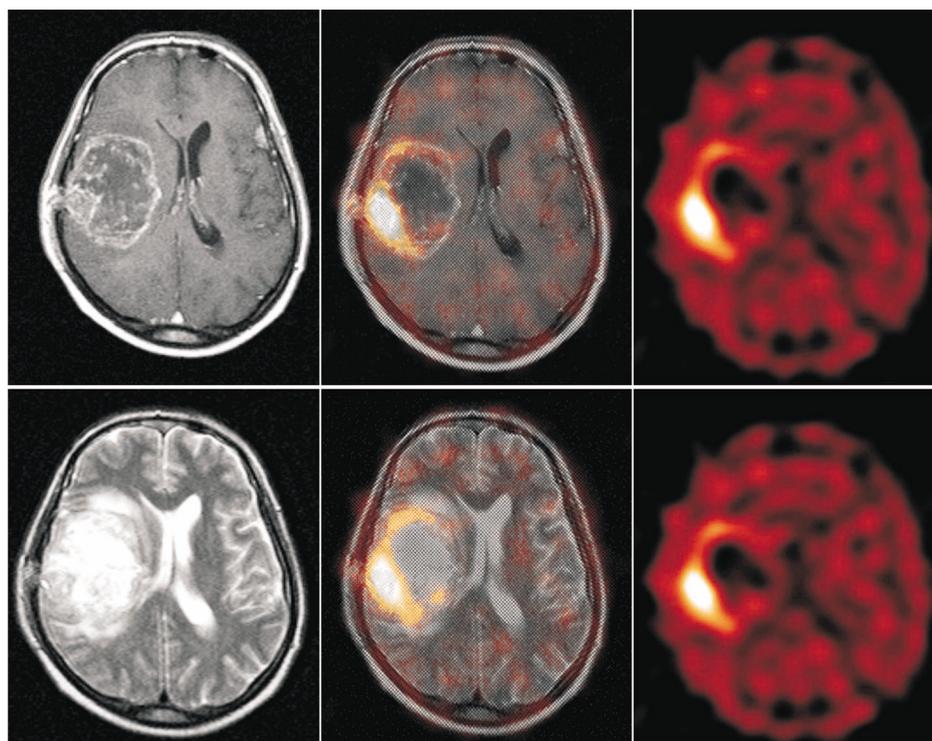
Figure 2. Glioblastoma T1-MRI with Gadolinium, fusion image T1-MRI/IMT-SPECT and IMT-SPECT [*upper*] and T2-MRI, fusion image T2-MRI/IMT-SPECT and IMT-SPECT [*lower*]. In this case the Gd-enhancement region on T1-MRI corresponds to the IMT uptake area on SPECT

Common Vol T1/IMT and mean Relative Vol T1 minus IMT were respectively 21%, 4% and 64% of mean Composite Vol T1/IMT.

In 19/66 patients focal IMT uptake was also located outside the MRI changes. In this subgroup mean Vol-IMT, mean Vol T1 and mean Vol T2 were respectively 19 cm³, 10 cm³ and 70 cm³. Mean Relative Increase T2/IMT was 14% and T1/IMT 61%. In this subgroup the additional information of SPECT leads to an increase of BV (mean Relative Increase BV-IMT) of 20%.

We concluded that, in post-surgery patients with brain gliomas the size and location of residual IMT uptake differs considerably from abnormalities in post-operative MRI. Because of the known high specificity of IMT uptake for tumour tissue, the findings in IMT-SPECT may significantly modify the PTV for radiation treatment planning. This helps to focus the high radiation dose on the tumour volume and to spare normal brain tissue.

FDG-PET

One of the most widely used functional investigations in the diagnosis of brain gliomas is ^{18}F-fluorodeoxiglucose (FDG)-PET. The rationale for the application of the glucose analogue FDG in the study of brain gliomas, is the known increased glucose metabolism in malignant tumour tissue. Almost 80 years ago, Otto Warburg [18] postulated that the rate of anaerobic glycolysis is positively correlated with the degree of tumour cell malignancy. Consequently is a high glucose utilisation rate and an increased utilisation of the glucose-6-phosphate intermediate will be observed.

FDG is transported across the BBB by the same carrier molecules as glucose, so that disturbance of the BBB is not necessary for FDG accumulation. Hexokinase transforms the FDG in FDG-6P and this then accumulates in tissue [19].

Clinical studies have demonstrated that the FDG uptake in tumour tissue is correlated with histological grading and has prognostic implications. Goldman et al [20] analysed 160 biopsies taken from 20 patients with low and high grade gliomas and compared the results with the FDG uptake in PET. They demonstrated that the FDG uptake in gliomas is anatomically heterogeneous and is regionally related to the presence of anaplasia.

An important finding for clinical practice is that FDG-PET investigations can be successfully used in the diagnosis of necrosis after radiotherapy or local administrated chemotherapy, and also in the differentiation of necrotic tissue from recurrence.

Gross et al [21] assessed the value of FDG-PET for 3D treatment planning in 18 patients with malignant brain gliomas. Using PET/MR fusion images, the tumour volume in PET was compared with tumour volume in MRI. This study showed that the difference in contrast between viable tumour and normal brain tissue in FDG-PET is small. The FDG uptake in gray matter is high,

and this makes the demarcation of the tumour borders from normal brain tissue difficult.

Nevertheless, tumour areas with lower cellular differentiation showed higher FDG uptake. An interesting finding in this study was that tumour areas with higher FDG-uptake were closely correlated with the Gd-enhancement areas in MR. Although FDG-PET offers in comparison to MR, no additional data concerning tumour extension, it could be used to define areas with higher anaplasia. This raises questions regarding the possible significance of this investigation in the definition of a *target in target*, which could be potentially useful in dose escalation studies.

Other biological investigation methods

Sophisticated techniques such as MR spectroscopy showed tumour signs extending outside the MRI derived PTV. In a recent study Pirzkall et al [22] compared MR spectroscopy and MRI in patients with high grade gliomas prior to surgery. These authors demonstrated that, although T2-MRI estimated the region at risk of microscopic disease as being as much as 50% greater than by MR spectroscopy, metabolically active tumour still extended outside the T2 region in 88% of patients by as much as 28 mm.

T1-MRI showed a lesser volume and different location of active disease compared to MR spectroscopy. Furthermore, in a retrospective analysis of patients with recurrent brain gliomas treated with Gamma Knife radiosurgery based on MRI-T1, Graves et al [23] showed that the outcome of patients with tumour infiltration in MR spectroscopy located outside of the changes in conventional MRI was significantly worse than in patients without additional information in MR spectroscopy concerning tumour extension.

[201]Thallium is taken up by the sodium/potassium symporter of viable cells. SPECT imaging with [201]Th has been used for several years for the differential diagnosis of radiation necrosis and tumour recurrence [24]. However, ^{201}Tl does not cross the BBB. Therefore, it is not possible to delineate tumour cell infiltration that has not caused a disturbance of the BBB.

Finally, brain tumours have been imaged in preliminary studies by [99m]Technetium-sestamibi which is a lipophilic cation whose cellular uptake is dependent on tissue perfusion and the mitochondrial membrane potential [24]. However, similarly to ^{201}Tl, ^{99m}Tc-sestamibi does not cross the BBB and is therefore limited in its use for delineation of tumour cell infiltration.

Conclusions

Stereotactic radiotherapy, radiosurgery and intensity modulated radiotherapy (IMRT) are characterised by the application of the radiation with high precision of an exactly defined target and by a very rapid fall-off of dose to spare normal tissue. The first requirement for the

success of this therapy is the correct definition of tumor extension.

Non-invasive imaging techniques are a central component of treatment planning in radiation oncology. The information gained from different imaging modalities is usually of a complementary nature, Table III.

Table III. Useful information from different imaging modalities

Modality	Information
MR	Describes the anatomical structures of soft tissue with a high accuracy.
CT	Important for the delineation of bone structures and for the accurate computation of radiation dose.
PET & SPECT	Offer additional information about tumor extension and biology.

Thus, the definition of tumour extension is characterised by a proper integration of different imaging modality information. Combining morphological (CT, MRI) with biological imaging data (PET, SPECT, MR-Spectroscopy) significantly improves the possibilities for the physician to interpret 3D brain data.

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