

**Thesis for the degree of doctor of philosophy (Ph.D.)**

**Comparative evaluation of in vivo brain metabolic maps in  
neurosurgical patients**

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## **I. Introduction**

The most common neurological diseases requiring surgery are brain tumours and haemorrhagic strokes. Routinely performed CT and MRI investigations made possible to differentiate these anatomical disturbances in better spatial resolution.

Brain tumours are composing 1,5 % of the malignancies. They are responsible for 1 % of deaths and 2,1 % of tumour related deaths. Malignancies of the central nervous system are the second leading cause of death in the population under 35. Brain tumours are the most common solid type of cancer in childhood and early adolescence. The number of late adolescent brain tumours are increasing. These tumours are mainly malignant and to our knowledge they have no cure. The affordable postoperative radiation techniques and chemotherapeutical modalities have serious adverse effects thus treatment of these tumours is challenging. The overall survival of low-grade gliomas is 35-60%, the median survival of anaplastic astrocytoma is approximately 3 years. Despite the aggressive treatment the patient with glioblastoma multiforme usually dies within one year.

The astrocytomas and oligodendrogliomas are the main histological groups of the low-grade gliomas. Symptomatology develops slower than in the high-grade gliomas. Beside focal neurological deficit epileptic seizures occur more frequently. Without treatment raised intracranial pressure leads to death. Natural course may vary thus after diagnostic procedures many factors should be taken into account. Important to estimate the expected natural course based on localisation and histology. If the tumour is not space occupying and is not located in an eloquent area, or not causing medically refractory epilepsy than no invasive therapy is recommended, only tight patient control. If the tumour is located in surgically easily accessible area the resection could be the first choice.

The main treatment options for malignant brain tumours are surgical resection, irradiation and chemotherapy. Tumours containing oligodendroglial components have

relatively better outcome. Combination of existing treatment options and discovering new horizons are needed to improve survival. To achieve the best results the cooperation between diagnostic expert, neurosurgeon, radiotherapist and oncologist is mandatory.

In many of the cases the tumour borders are not clearly visualised even on MRI scans. Further problems are arising when the residual parts are not distinguishable from recurrent tumour in the operated brain. After tumour removal the number of epileptic seizures is decreasing. That fact raises the option those beyond tumour borders in subcortical structures functional alterations develop. Beside that the surgical procedure leads to changes in cerebral circulation. These are often analogous with the vasospasm observed after aneurismal subarachnoid haemorrhage. The diagnosis of vasospasm is most accurate with angiography but could be followed with transcranial Doppler ultrasound (TCD) with confidence. In many of the cases there are no concordances between the severity of vasospasm, the condition of the patient and the alterations visualised on CT.

The PET does not decrease the importance of CT and MRI but its functional approach gives another dimension to clinical work. Imaging metabolical alterations on histological level raises the possibility to diagnose specific pathologies when structural changes are not apparent. Beside that the difference of brain tumour metabolism from normal brain tissue gives the opportunity to visualise them from this point. The importance of positron emitting isotopes with short half-lives was discovered in early forties, but the image reconstruction became available only in the sixties. In the first period, PET investigations served mainly scientific purposes, but the number of diagnostic measurements also increased. In several diseases it was proved that the diagnostic sensitivity and specificity are comparable to other methods and in many cases overweight them.

Introduction of the PET in 1994 raised the opportunity among the patient of Neurosurgical Department of the University of Debrecen to extend the use the available

diagnostic methods that improved the quality of care. With the help of routinely available [ $^{18}\text{F}$ ] – 2 – fluoro- 2 – deoxyglucose (FDG) and [ $^{11}\text{C}$ ] – methyl – methionine (MET) we can answer to those questions that arising from metabolical points during neurosurgical patient care. Positron emission tomography makes possible to investigate the molecular events in vivo in three dimensions and in time. The aim of my studies was to investigate questions arising during neurosurgical patient attendance when the connections of structural and functional changes are in front.

## **II. Aims of the studies**

1. We investigated whether a connection exists between FDG and MET accumulation, biological grade, histology and survival in patients with brain tumours. We checked the diagnostic accuracy and value of double tracer studies and evaluated the importance of the PET in different clinical periods of neurosurgical patient care.
2. Subcortical FDG metabolism was analysed in patients with epilepsy as a clinical sign of a brain tumour. The tumour removal leads to decrease in number of epileptic fits and the recurrence is often diagnosed with the recurrence of fits. The hypothesis was that beyond tumour borders where the pathological lesion or a cortical surface in vicinity serves as a pacemaker, a modulator area could be identifiable by observing alterations in FDG uptake.
3. The aim of our study was to determine and characterize alterations of regional cerebral glucose uptake patterns that might be induced during the postoperative vasospasm after aneurysmal SAH. Based on the functional reserve of the central nervous system we supposed that abnormal metabolic response couldn't be excluded in patients without focal neurological

signs following aneurysmal surgery. We investigated the possible adverse effect of surgical procedure by observing changes in brain FDG uptake.

### **III. Patients and methods**

#### *III.1. Neurooncological group*

##### III.1.1. Low- and high-grade gliomas

Fifty-two patients with supratentorial glioma underwent FDG-PET (F/M: 23/29, age: 7-67 years, mean  $39,7 \pm 15$  years, injected radioactivity  $139 \pm 69$   $\mu\text{Ci/kg}$ ). Thirty-three patients underwent MET-PET (F/M: 12/21, age 9-66 years, mean  $38,5 \pm 15$  years, injected radioactivity  $224,2 \pm 75$   $\mu\text{Ci/kg}$ ). The WHO Grade 2 tumours were classified as low-grade, WHO Grade 3. and 4. tumours as high-grade. T1 without and with contrast injection and T2 weighted MRI scans were performed before PET investigations.

##### III.1.2. Double tracer studies

Nineteen patients with brain tumour (F/M: 9/10, age: 8-65 years, mean  $32,9 \pm 16$  years, injected radioactivity  $145,5 \pm 19$   $\mu\text{Ci/kg}$  FDG, and  $289,4 \pm 114$   $\mu\text{Ci/kg}$  MET) were investigated with both tracers.

##### III.1.3. Clinical patients

In 102 patients (F/M: 42/60, age: 5-70 years, mean  $36,5 \pm 15,5$  years), with known or presumed intracranial tumours 157 PET investigations were performed. In 106 studies FDG and in 51 cases MET was used as the PET tracer. CT or/and MRI imaging accompanied the PET studies in each case. Sixty-two patients underwent only FDG-PET, twenty-one only MET-PET. Nineteen patients were scanned with both tracers (one patient was scanned with FDG pre- and postoperatively, one with preoperative with FDG and postoperative with MET).

The PET investigations were performed in standard circumstances (injected radioactivity  $116\pm 40$   $\mu\text{Ci/kg}$  FDG and  $290\pm 80$   $\mu\text{Ci/kg}$  MET). Results of pre- and/or postoperative studies are compared. The scans were analysed by two independent investigators.

### *III.2. Lesional epilepsy in patients with intracranial tumour*

Sixty-seven patients (F/M: 39/28, age: 14-70 years, mean  $40\pm 13,52$  years, injected radioactivity  $107,7\pm 41$   $\mu\text{Ci/kg}$  FDG) with supratentorial brain tumour or space occupying lesion associated epilepsy were investigated interictally in normoglycaemic conditions. The patients were collected prospectively and the results were processed retrospectively. All patients had epileptic seizures at least once during the course of their disease. The fits were complex partial and generalised, but the probable secondary generalisation were not proven by electroencephalographic methods.

Twenty-two patients had frontal, 8 had parietal and 37 had temporal lobe tumour or space occupying lesion. Thirty-six patients harboured pathology on left, 31 on right side. In case of one patient with bilateral symmetrical cavernous lesions, the right side was chosen as affected. Twenty-nine patients had operations prior to the time of the study, hence the recurrent tumours were scanned. Fourteen of them had been irradiated at least six months before the PET investigations. None of the patients had received chemotherapy and neither of them had hydrocephalus. T1 with and without contrast injection and T2 weighted MRI scans were performed before PET investigations.

### *III.3. Patients with aneurysmal subarachnoid haemorrhage*

Eight patients with aneurysmal subarachnoid haemorrhage (F/M: 5/3, age: 31-62 years, mean  $42,5 \pm 9,5$  years, injected radioactivity  $94,6\pm 50,9$   $\mu\text{Ci/kg}$  FDG) were investigated in postoperative period. All aneurysms were operated on applying the classic pteryonal

transylvian approach from the corresponding side and from the right side in case of the anterior communicating artery aneurysm. Occurrence and the time-course of vasospasm in both middle cerebral arteries and the proximal portion of the anterior cerebral arteries and within the distal intracranial portions of internal carotid arteries were monitored daily by EME-TC 2-64 B Ultrasonograph (EME, Überlingen, Germany) transcranially with a 2 MHz probe. Following the guidelines set by previous studies we set the threshold value for vasospasm in middle cerebral artery (MCA) at mean flow velocity (MFV) value of 120 cm/sec. MFVs between 120-200 cm/sec were considered an indication of mild-to-moderate vasospasm, while values over 200 cm/sec indicated severe vasospasm. The patients were treated with conventional 'triple H' therapy and received nimodipine. PET scans were obtained between 4-8<sup>th</sup> days postoperatively in normoglycemia. One patient with left MCA aneurysm and severe vasospasm was studied twice: first during the presence and then after the resolution of vasospasm. PET studies were followed up within 24 hours by a series of 4 mm slice thickness computed tomographic (CT) scans.

#### *III.4. Controls*

##### III.4.1. Normal control (lesional epilepsy and subarachnoid haemorrhage)

For control purposes normal brain regional FDG maps were used that had been generated earlier in an independent study of healthy volunteers (n=7, F/M: 1/6, age: 19- 48 years, mean 33±9 years, received radio activity 59±27 µCi/kg FDG). The FDG-PET scans and SUV maps were performed and generated at the same method.

##### III.4.2. Lesional control

The second group comprised 12 patients with known cerebral lesion but without known history of seizures (F/M: 6/6, age: 31-60 years, mean 52±8 years, injected

radioactivity  $134 \pm 27$   $\mu\text{Ci}/\text{kg}$  FDG). Neither oedema nor hydrocephalus were present. The brains with left sided pathology were mirrored. The FDG-PET and SUV maps were performed and generated at the same method. This control group was used during the data analysis of patients with lesional epilepsy.

### *III.5. PET studies*

All studies (static cerebral PET scans) were performed using a GE 4096 Plus PET scanner (GE Medical Systems AB, Uppsala) after informed consent. The Institutional Ethical Committee of the Medical and Health Sciences Centre of the University of Debrecen approved the study protocol. The study protocol was identical for FDG and MET investigations for all patients. Complete neurological examination was performed on the day of PET-scanning. Each unsedated individual received the tracer in 30 seconds as an intravenous bolus injection in a dark, silent room, 30 minutes prior to scanning. After 30 minutes fifteen parallel axial scans (6.75 mm interslice distance within the 10.5 cm field of view) with spatial resolution of 6.5 mm full width at half-maximum were obtained from the canto-meatal line to vertex. To decrease errors caused by motion, the head of each individual was kept in the same position using a plastic mesh head holder in subgroup of patients with lesional epilepsy and aneurysmal subarachnoid haemorrhage. Corrections for tissue attenuation transmission measurements (25 min) were performed using a  $^{68}\text{Ge}$  source of 8 mCi activity before the emission scans. The PET images of the individual measurements were reconstructed applying a 4.2 mm Hannig filter (image matrix size: 128 x 128 x 15, image voxel size: 2 x 2 x 6.5 mm) after the completion of the necessary corrections for random coincidence, scattering, dead time and tissue-attenuation.

### *III. 6. Data processing*

#### III.6.1. Designation of regions of interest (ROI) in neurooncological group

Two picture analysis methods were used. First each tumour was described according to visual scale (1 – metabolic activity of the tumour is less than the contralateral white matter's 2 – metabolic activity of the tumour is between those of the white matter and cortex, 3 – metabolic activity of the tumour is higher than the cortical).

From reconstructed PET scans those slices were chosen where the highest uptake within the tumour could be distinguished. Than 10 connecting pixels (0,2x0,2 mm) were circumscribed and defined as hot spot (HS). Those pixels were collected into the 80% and 50% isocontour regions which activity concentration reached at least the 80% (HS80) and 50% (HS50) activity concentration in HS. That was not causing difficulties in groups 2. and 3. according to visual scale during MET investigations and in group 3.in FDG scans. If the size of the HS80 and HS50 was bigger then the tumour itself (group 1. in MET, groups 1. and 2. in FDG scans) the tumour borders were defined according to MRI and that region was named as HS50. The HS50 was mirrored and a ROI representing contralateral activity was defined (CA). In healthy centrum semiovale (ROI with 2 cm in diameter) the activity concentration of the white matter was measured, and mean cortical uptake was calculated (6 ROIs covered the whole cortical surface in contralateral hemisphere, MCU). In contralateral cerebellar hemisphere (ROI with 1 cm in diameter) activity concentration was also measured (CER). From data 12 activity ratios were calculated for all tumours (HS/CA, HS/WM, HS/MCU, HS/CER, HS80/CA, HS80/WM, HS80/MCU, HS80/CER, HS50/CA, HS50/WM, HS50/MCU, HS50/CER).

### III.6.2. Lesional epilepsy

The simplified standardized uptake value (SUV) was used to substitute true FDG utilization. SUVs were calculated voxel by voxel from axial slices according to regional distribution of FDG by dividing the concentration of the tracer in the particular voxel by the injected radioactivity/body weight. The individual SUV images were stereotaxically normalized onto a standardized computerized normal brain atlas using an automatic and interactive spatial standardization software (Register, McConnell Brain Imaging Center, Montreal Neurological Institute). To decrease FDG accumulation differences emerging from individual anatomical differences of the gyri, a Gaussian-weighted, isotropic spatial smoothing of 16 mm half-width were applied. Regions of interest (ROI) were plotted on the same manner on the same slices from both sides on frontomedial, frontolateral, frontobasal, temporolateral, temporomedial, temporolateral, parietal, occipitolateral and occipitomedial cortex. Thalamus, caudate nucleus, lentiform nucleus, hypothalamus, cerebellar hemisphere and pons were also included. The asymmetry indices were then calculated applying the following formula:  $(\text{affected} - \text{non-affected}) / (\text{affected} + \text{non-affected}) \times 0,5$ . The side of the tumour was chosen as affected. The brains with left sided pathology were mirrored. The asymmetry indices were calculated as follows:  $(\text{right} - \text{left}) / (\text{right} + \text{left}) \times 0,5$  in normal controls and as:  $(\text{affected} - \text{non-affected}) / (\text{affected} + \text{non-affected}) \times 0,5$  in lesional group.

### III.6.3. Aneurysmal subarachnoid haemorrhage

The simplified standardized uptake value (SUV) was used to substitute true FDG utilization. The individual SUV images were stereotaxically normalized onto a standardized computerized normal brain atlas using an automatic and interactive spatial standardization software (Register, McConnell Brain Imaging Centre, Montreal Neurological Institute). To

decrease FDG accumulation differences emerging from individual anatomical differences of the gyri, a Gaussian-weighted, isotropic spatial smoothing of 16 mm half-width was applied. The SUV images of cases #1, 5 and 6 has been mirrored to make the side notation of maps of all patients identical.

### *III.7. Statistical analysis*

#### III.7.1. Neurooncological group

For statistical purposes SPSS 11.0 for Windows software was used. In the analysis of HS/CA, HS/WM, HS/MCU, HS/CER, HS80/CA, HS80/WM, HS80/MCU, HS80/CER, HS50/CA, HS50/WM, HS50/MCU, HS50/CER ratios in low and in high grade tumours Mann-Whitney U test and Kolmogorov-Smirnov test were applied. The activity concentration in HS80 and HS50 ROIs in several cases exceeded the radioactivity concentration in HS thus the values were equalised to the HS. For correlation analysis Pearson's chi-square test and Spearman rank correlation were applied. Comparison of each histological group was done with the Kruskal-Wallis test. Survival was analysed by Kaplan-Meier plot and Cox regression.

#### III.7.2. Lesional epilepsy

Before statistical analysis each individual SUV map has been normalized to a global mean of five thus proportional scaling eliminated local SUV components attributed to the change in the global SUV. The statistics compared not the SUV values but the asymmetry indices between patients and controls. Two-tailed t-tests and nonparametric tests (Wilcoxon rank sum test) were applied in order to evaluate the differences between patient groups. The significance level was set at  $p < 0,05$  probability threshold. Metabolic shifts of each ROI in

individual patients, were considered as significantly hypometabolic if the measured value was lower than the mean control value minus 2SD.

### III.7.3. Aneurysmal subarachnoid haemorrhage

Statistics to evaluate comparisons of patient groups and controls were computed on a voxel by voxel basis using SPM 99b software. Before SPM analysis each individual SUV map has been normalized to a global mean of five. The statistics compared not the SUV values but the normalized differences between patients and controls. Two-tailed t-tests were applied in order to emphasize the distribution of SUV-differences between controls and patient groups. On the statistical parametric maps probability threshold  $p < 0.0001$  was chosen to highlight the differences.

## **IV. Results**

### *IV.1. Neurooncological group*

#### IV.1.1. FDG –PET studies

The low-grade and high-grade tumours are not distinguishable by HS, HS80 and HS50 activity concentration values according to Mann-Whitney U and Kolmogorov-Smirnov tests. The measured twelve ratios are significantly different between low-grade and high-grade tumours only in HS/CA (mean  $1,1 \pm 0,81$  versus  $1,3 \pm 0,53$ ,  $p < 0,014$ ). In the ratio of HS/WM between two groups the observed difference is close to significance (mean  $1,54 \pm 0,91$  versus  $1,92 \pm 1,21$ ,  $p < 0,072$ ). It is remarkable that except the HS50/CER ratio in high-grade tumours all of the calculated ratios are higher. The hypothesis that there is no significant difference is not supported by binominal test ( $B[12,0.5]$ ,  $k=11$ ,  $p < 0,0002$ ).

The FDG enhancement in three different groups of visual scale was distributed equally in low-grade tumours. High-grade tumours were only in the groups 2. and 3. in distribution of

60-40 %. We have found marked connection between low-grade tumours and the first group of the visual scale (Pearson Chi Square,  $p=0,009$ ).

Particular histological subgroups the HS (mean  $593,5\pm 366,3$ ) ( $p<0,061$ ), and HS50 (mean  $502,3\pm 297,48$ ) ( $p<0,064$ ) activity concentrations show increasing tendency in the order of accepted malignancy (Spearman test).

The survival curve of low-grade and high-grade tumours differs significantly according to Kaplan-Meier ( $p<0,0076$ ). There is no significance observed between survival curves of tumours in three groups of the visual scale ( $p<0,55$ ). According to Cox regression analysis the lower HS values show better survival.

#### IV.1.2. MET-PET studies

The low-grade and high-grade tumours do not differ significantly in HS, HS80 and HS50 MET activity concentrations according to the Mann-Whitney U and Kolmogorov-Smirnov tests. There is no significant difference between low-grade and high-grade tumours in twelve calculated ratios. It is remarkable that all of the particular ratios in high-grade tumours are higher. The hypothesis that there is no significant difference is not supported by binominal test ( $B[12,0.5]$ ,  $k=12$ ,  $p<0,00002$ ).

Distribution of low-grade tumours in three group of the visual scale was 35-15-50%. High-grade tumours were found only in groups 2. and 3., with the majority in 3. (15% versus 85%) (Pearson Chi Square,  $p=0,049$ ). The HS values in particular histological groups do not show significant increase in generally accepted malignant order of tumours (Spearman test). The survival curves of low-grade and high-grade tumours are significantly different according to Kaplan-Meier ( $p<0,0095$ ). The survival curves of tumours in three groups of visual scale are not found significantly different. The Cox regression analysis proved no significant difference between low and high HS values and survival indices.

#### IV.1.3. Double tracer studies

In patients who underwent PET studies with both of the tracers we found no difference in isotope uptake on visual scale in five patients. Only one patient belonged to the high-grade group. In fourteen patients the degree of the tracer accumulation was higher with methionine. From these patients only one was in high-grade group.

#### *IV.2. Lesional epilepsy in patients with intracranial tumour*

Significant alterations in corresponding ROI SUV have been observed in each group as classified according to lesion, i.e. in frontal tumours in frontal regions, in temporal tumours in temporal regions and so on. The calculated asymmetry indices significantly differed from the normal control values measured within the thalamus in frontal and temporal tumours as shown concordantly by the two-tailed t and Wilcoxon rank sum tests. The significant change in FDG uptake reflected the affected side more hypoglycolytic. Comparing in each group the asymmetry indices with the corresponding control ROI SUV values relative hypometabolism were noted in occipitomedial cortex on affected side in temporal tumours. The lentiform nucleus proved to be also significantly relatively hypometabolic on the affected side in patients with frontal tumours. In other parts of the brains no significant changes in SUV ROIs were observed in any of the patient groups when compared to controls.

The asymmetry indices were also compared to controls with non-epileptic brain lesions but only the territory of lentiform nucleus in temporal tumours showed significantly different (elevated) FDG uptake.

#### *IV.3. Patients with subarachnoid haemorrhage*

The postoperative TCD examinations revealed vasospasm in all cases from days 2-7. No significant elevation in mean blood velocity was measured in MCA after PET scans

except in patient # 6. In those six patients (cases #1-4,7,8) who were without focal neurological signs and their CT scans were also normal, the measured MFVs in the middle cerebral arteries on the operated side ranged between 120-200 cm/sec. On the other side no TCD sign of vasospasm was noted in most cases, in case # 4 maximal MFV reached 138 cm/sec. This was paralleled by increased FDG uptake compared to controls indicated by parametric maps in the lateral temporal and occipital cortex, as well as in the basal ganglia including the thalamus and the same change characterized also the white matter. The FDG uptake was more marked on the side of the operation and vasospasm with almost 70% larger volume. In those two patients in whom clinical signs have developed FDG-PET showed pathological decrease of glucose uptake in the frontal-temporal-basal cortex. This was most obvious and dominated within the frontal region on the side of the operation with the affected volume 40% larger.

## **V. Discussion**

### *V.1. Neurooncological group*

Neurooncological PET studies worldwide are mainly performed by FDG and MET. Based on elevated energy demand, the tumour cells accumulate the glucose analogue FDG more than the normal brain tissue. The higher rate of the protein synthesis and increased membrane transport of amino acids in tumour cells leads to elevated methionine uptake. That is why beside the diagnose and localisation of tumours the FDG-PET gives independent information from pathological methods about proliferation capacity of neoplastic cells. The latter does not need further explanation. The FDG uptake in gliomas is heterogeneous.

The increased glycolytic activity may come from the elevated hexokinase activity and from the overexpression of this enzyme which catalyses the first step of the final accumulation of FDG into cells. In brain tumours this is connected with increased activity but

the overexpression also cannot be ruled out. Early changes on cellular level, like changes in expression of glucose transporter genes can also play role in the observed increase of FDG uptake in high-grade gliomas. In high grade gliomas the alterations of chromosome 10 are frequent both in anaplastic and non-anaplastic parts of the tumour. In low-grade gliomas this observation is not common. The gene of the hexokinase enzyme is located here thus revealing changes on this chromosome may gives information about malignant transformation before histological proof. This phenomenon can reflect on the connection between the territories with higher uptake and malignant changes in low-grade gliomas.

The elevated MET uptake in cell cultures correlates well with the proliferation activity, the expression of Ki-67, the expression of proliferating cell nuclear antigen and the level of neovascularisation. It has been shown that the density of the cell cultures and the elevated MET uptake are connected. In chronic inflammatory lesions and in radiogenic damage the methionine uptake is not elevated. The acute inflammatory process and the acute ischemic stroke with reperfusion can exhibit elevated MET uptake.

Based on the same considerations PET gives the possibility to reveal tumoral remnants and recurrences. It also makes possible to disclose postoperative inflammatory processes that are common with brain-tumour barrier lesions that cannot be visualised by other methods. Results of excessive number of PET investigations show that high-grade tumours and their recurrences exhibit increased FDG and MET uptake that exceed the physiological level. In cases of low-grade tumours the FDG uptake is similar or less than the normal level. Radionecrosis does not accumulate either of the tracers. Inflammatory cells and cells in preneurotic state immediately after the irradiation can take up FDG more prominently.

In neurooncological PET studies we tried to find out data about biological behaviour of gliomas that can be used in clinical work and can be adapted to local circumstances. In FDG studies in visual scale groups 1. and 2., and in MET studies in visual scale group 1. the

HS80 and HS50 cannot be defined automatically because of the lack of the apparent difference from the other structures of the brain. The MRI/PET fusion made possible to delineate the tumour but it led to overestimation. The activity concentration in HS50 in many cases was more than that of HS. The borders of the tumours cannot be defined according to MRI also. The tumorous region delineated this way sometimes included e.g. cortical surface or basal ganglia that are enhancing FDG more prominently in normal conditions. That led to the elevation of mean activity concentration of HS50. In FDG studies this was observed in 11 cases (5 in group 1., 3-3 in groups 2. and 3.). This was found in two patients in MET studies (1-1 in group 1. and 3.). In FDG studies we have found significant difference between low-grade and high-grade tumours in HS/CA ratios ( $p < 0,014$ ). This is important in clinical practice, since we have data about biological grade before any treatment. There is a difference in HS/WM ratio also ( $p < 0,072$ ), but it does not reach the significance. Despite of that if the HS/CA ratio is over 1,8 and the HS/WM ratio is over 2,8 the diagnose of the high-grade tumour is suspected. If the tumour is on the visual scale in groups 2. or 3. the diagnosis is evident. If the ratios are low and the tumour is in group 1. on the visual scale than we can diagnose low-grade tumour (Pearson Chi Square,  $p = < 0,009$ ). There is a tendency of increasing FDG uptake in order of accepted malignancy ( $p < 0,061$ ), but our method has not proved to be sufficient to distinguish between particular histological groups. This might be caused by low number of individual tumours since there are data in the literature the FDG uptake of WHO grade 2. astrocytoma is less than of oligodendroglioma's of the same grade. Survival curves of low-grade and high-grade gliomas significantly different according to Kaplan-Meier but the survival curves related to the groups of the visual scale are not. The lower HS-FDG activity concentrations are connected with better survival (Cox regression analysis). Beside the visual scale observations the measurement of HS activity concentration is advised. The definition of this region is easy. Instead of using isocontour curves the

delineation of the tumour is suggested using CT/MRI/PET fusion. The contralateral territory of the tumour is sufficiently big thus bias from small ROIs can be avoided.

According to MET studies the individual ROIs, and the calculated ratios are not sufficient in distinguishing low-grade and high-grade groups or the individual histology. The tumours in visual scale group 1. are low-grade. Since we have found significant difference between low-grade and high-grade tumours using the visual scale only in group 3 (Pearson Chi Square,  $p=0,049$ ) we can state that under these circumstances the MET measurements are mainly for delineation of the tumour borders. Data from double tracer studies support this statement. The low number patients in individual histological groups might lead to results contrary to the literature.

False negative and false positive results could also influence our results. Necrotic glioblastoma does not enhance FDG. The definition of the HS on the tumour borders because of the cortical infiltration may also lead to improper measurement. In cases of low-grade gliomas subclinical epileptic activity generating excessive number of action potentials in or close to the tumour is exhibited in elevated FDG uptake.

There was no false positive MET measurement. Data can be found about in the literature in demyelinating diseases and in acute radiogenic necrosis. The false negative study is observable in benign, non-glial tumours or in glial scar.

If the diagnosis of the brain tumour is doubtful MET-PET is advocated as a first option because even low-grade tumours have increased level of protein synthesis and the amino acid transport is more pronounced across the brain-tumour barrier than in healthy brain tissue. Dubious MET study indicates FDG measurement. If the diagnose of the tumour based on CT or MRI is sure than double tracer PET is suggested in suspected low-grade gliomas. MET-PET helps to delineate the exact tumour borders and the level of FDG accumulation gives information about biological grade. In cases of heterogeneous FDG uptake the place of

biopsy can be determined. In postoperative cases or if the patient received irradiation the distinction between necrosis and recurrent tumour in high-grade gliomas the FDG, in low-grade tumours double tracer studies are advocated. The diagnosis of the recurrent low-grade tumour is possible only with MET-PET, but for the re-estimation of the biological behaviour FDG measurement is needed. If the follow up of the treatment is the aim the choice of the tracer depends on original grade of the tumour. During the interpretation of PET studies the clinical history and the results of CT and MRI scans should be accounted. The fusion of the latter with the PET images gives greater diagnostic accuracy.

#### *V.2. Lesional epilepsy in patients with intracranial tumour*

Subcortical FDG metabolism was analysed in patients with epilepsy as a clinical sign of a brain tumour. The hypothesis was that beyond tumour borders where the pathological lesion or a cortical surface in vicinity serves as a pacemaker, a modulator area is identifiable by observing alterations in FDG uptake.

Because several of the chosen regions of interest are small the use of normal MRI brain atlas is a crucial point to obtain reliable parameters. Standardisation thus allowed us to correct those changes that arise during scanning in slightly different positions. First automatic then manual correction was carried out in all cases to make each individual scan comparable and every identical ROI fit.

Comparison of both sides in each ROI alterations both toward hyper- or hypometabolic states resulted in differences from the normal controls at the site and in the lobe of the lesion. These changes correspond to the pathological lesion itself and no connection could be established with the consequent seizures. It has been considered as a proof of methodological accuracy.

The use of non-epileptic patients with known cerebral lesions as controls is confounding. The site of pathological process and the lesion itself increases the risk of unwanted selection bias. When we compared the data of different control groups no significant alteration has been noted. It might be the result of the overlapping of probability distribution of each group. Thus we think that the use of normal controls is adequate.

The role of thalamus has been mainly studied in primarily generalized epilepsies, however, there is also evidence for its participation in location related seizures. In generalised epilepsy the density of benzodiazepine binding receptors is decreased in thalamus and increased in cerebellar nuclei. In primarily generalised idiopathic epilepsies and in childhood epileptic encephalopathies, 90 % of patients had evidence of relative thalamic hypometabolism and a significant reduction in relative thalamic FDG uptake along with diffuse cortical dysfunction. The brains of patients with temporal lobe epilepsy have structural anomalies in areas outside the epileptic focus such as the thalamus. Functional imaging studies in patients with epilepsy have described alterations in the thalamus. In partial epilepsy different patterns of ipsilateral subcortical hypometabolism has been described with various pattern of cortical metabolic abnormalities. The thalamus is a nuclear complex that relays afferent and efferent projections with almost all cortical regions, mainly from and to the ipsilateral cortex but the also receives projections from other basal ganglia. The calculated asymmetry indices were significantly less than the control values at the region of thalamus in frontal and temporal tumours. The ipsilateral thalamic FDG uptake reflected a more hypometabolic state. The values could be underestimated because thalamic regions of interest represented all nuclei. However, decreasing the size of a ROI would have increased the probability for positioning errors.

The lentiform nucleus proved to be significantly relatively hypometabolic ipsilateral to frontal tumours. It supposedly indicates the disconnection of the synaptic circuits. The

lentiform nucleus has a large amygdalostriatal and frontal cortical projections with fibres to caudate and substantia nigra. An MRI study described atrophic caudate nucleus in patients with partial epilepsy while an another showed atrophy of the putamen after temporal lobectomy. The same disconnection can stand behind the observation that the ipsilateral occipitomedial cortex was found relatively hypometabolic in cases with temporal tumours. The pulvinar projects diffusely to parietal and occipital cortical areas. In a patient with parieto-occipital epilepsy a smaller caudate nucleus has been found .

The differences between image-based ratios of other cerebral parts were not significant even when the different ratios varied between ROIs. Thus it could be concluded that quantified values do reflect changes of pathobiological importance.

The observed decreased FDG uptake of lentiform nucleus and thalamus is most likely secondary to underlying pathology. These structures receive input from basically all other brain regions thus the cell loss or the diminished output from cortical surface subsequently results in decreased synaptic activity in subcortical nuclei. This reduction leads to a diminished FDG uptake. The thalamic outflow modulates the cortical and particularly the limbic excitability through a variety of circuits. Although seizures in tumorous patients do not originate from subcortical structures the influence of the latter on cortical sites of seizure initiation seems to be related to defective subcortical regulation of cortical excitability. The already disturbed synaptic net gets easily unbalanced by e.g. a tumour regrowth and in many cases even indicates this process.

### *V.3. Patients with subarachnoid haemorrhage*

Vasospasm and the subsequent delayed ischemic deterioration are well-known and frequent complications of aneurysmal SAH even in cases of technically successful surgical interventions. Its detection by TCD measurements dependably concurs with the values

obtained by the invasive method of angiography. It is important to point out that in our cases without focal neurological signs there was no relationship between the source of the bleeding, the severity of vasospasm measured in a given artery and the location of elevated FDG uptake. In other words it was often observed that the most marked elevation in the mean flow velocity did not allow a reliable prediction of subsequent ischaemia and/or its location.

Rigorous evaluation of our PET observations, differences between the operated and non-operated sides and the controls suggest that even in cases of mild to moderate vasospasm, when focal neurological signs are not present elevated FDG uptake is detectable in a diffuse pattern. This implies an overall detrimental effect of SAH to the whole brain since in these cases the elevation in mean blood flow velocities were detected only on the side of the operation. These changes should be transient and reversible since the clinical outcome was favourable in all these cases. Our observations are corresponding to the results of microdialysis studies revealing connection with good outcome and early cerebral hyperglycolysis. The brain might tolerate the presumed brief and mild ischemia because defence mechanisms are activated which protect the brain from subsequent development of permanent ischemia. FDG-PET measures glycolysis but in the brain it might be correlated with glucose metabolism. The impending ischemia increases the glycolysis in cases without focal neurological signs. The regional blood flow possibly decreases with the increase of cerebral blood volume. We have no direct proof of that but the TCD findings. In the steady state in the brain according to the velocity constants in the three-compartment four-parameter model of Sokoloff and Phelps the intracellular phosphorylated FDG concentration is high and the blood plasma levels are low. This is attributable to high  $k_3$  (phosphorylation) and to a low  $k_2$  (rediffusion) constant. The evolved absolute values are influenced by blood flow and the plasma concentration beside  $k_1$  and  $k_3$  constants. The changes in glucose uptake could reflect the changes in perfusion. The normal autoregulation might be altered and parenchymal

vessels distal to the spastic segments show reduced capacity to dilate or already are maximally dilated. The latter might also result in an increased FDG uptake. It has been shown experimentally that the vascular compartment can make a contribution to the tissue activity curve. The elevated glycolytic activity could be regarded also as a result of increased energetic demand ( $k_3$ ) as a compensatory mechanism. The lumped constant in ischaemic brain tissue is increased as shown in animal models of stroke. This might also result in an increased uptake of FDG. The breakdown products of extravasated blood affect glycolysis by causing excitotoxicity with prolonged activation of glutamate receptors. With the reduction of CBF due to spastic narrowing of arteries the extended glycolytic activity of neural and glial cells is no longer detectable.

Special attention has been paid to the frontal-basal and temporal-basal regions that most likely must have been affected by the placement and position of retractors during surgery. Data from the literature attest to the evolution of only reversible and brief consequences of increased MFV that accompany the opening of the Sylvian fissure for selective resection of the amygdala and hippocampus. The observations describe only regional and temporal decrease in CBF and oxygen consumption in the cortical tissue that had been under retractor blades during surgery of patients with SAH caused by aneurysmal rupture. The decrease of FDG utilization within the cortex affected by the placement of frontal blade(s) might reflect on the operative procedure.

The heterogeneous distribution of elevated FDG uptake in patients with mild-to-moderate vasospasm might reflect an impending ischemic event that is thought to be the result of the activation of defence mechanisms. This supports the role of TCD monitoring in aneurysmal subarachnoid haemorrhage. The lack of elevated FDG uptake in severe vasospasm could be regarded as a sign of a definitive ischaemia. The decreased FDG uptake

in the frontobasal region might reflect on the possible adverse effect of improper use of retractors during surgery.

## VI. Conclusions

The aim of our study was to establish correlation between structural and functional changes observed in neurosurgical patients based on FDG and MET-PET studies. The new scientific results are summarized below:

1. The glioma patients by observing differences in HS/CA ratio of FDG uptake can be divided into low-grade and high-grade groups ( $p < 0,014$ ). Since the detectable differences in HS/WM ratio are only approaching significance ( $p < 0,072$ ), if the HS/CA ratio is over 1,8 and HS/WM ratio is over 2,8 the high-grade glioma is suspected. Combination with visual scale gives clinical accuracy. If the ratios are low or the tumour is in the group 1. according to the visual scale than low-grade tumour can be diagnosed (Pearson Chi Square,  $p = 0,009$ ). Interpreting the results of MET activity concentration measurements we recommend the use of visual scale in clinical practice rather than calculating ratios. Patients in group 1. are low-grade, patients in group 3. are considered as high-grade (Pearson Chi Square,  $p = 0,049$ ).

2. The FDG uptake is decreased in ipsilateral thalamus of patients with frontal and temporal tumours. In frontal tumours with epilepsy the FDG uptake of ipsilateral lentiform nucleus, in temporal tumours the FDG uptake of the occipitomedial cortex is decreased too. The observed changes are secondary, connected with deranged subcortical regulation of cortical excitability.

3. During the symptom free course of vasospasm followed aneurysmal subarachnoid bleeding, diffusely elevated FDG uptake is observed that can be interpreted as a defence mechanism of neural tissue against ischaemia. The lack of elevated tracer uptake in severe vasospasm could be regarded as an impending ischemic event. The frontobasal distribution of decreased uptake in these patients reflects the possible aggravating effect of the operative procedure.

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