Post-therapeutical changes in the brain: novel trends in imaging and their influence on external beam radiotherapy

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Presented is the analysis of patients who underwent external beam radiotherapy (EBRT) to the brain in the period from 2003 to 2006 at the department of Radiation Oncology of the St. Elisabeth Cancer Institute.

The aim of our analysis was to identify risk factors of late delayed therapy induced injuries (LDTI) in the brain. The patients were regularly examined with magnetic resonance (MRI), including conventional and advanced techniques: perfusion imaging (pMRI), diffusion weighted imaging (DWI), MRI spectroscopy (MRS). The results from MRI were correlated with 18fluoro-deoxyglucose positron emission tomography (18FDG/PET) scans, as none of the listed method is sufficiently sensitive and specific by itself. Also clinical data records and treatment plans of these patients were analyzed.

In our cohort we found 6 patients with abnormal post-therapeutical changes, 4 of them with MR and 18FDG/PET scans characteristics for LDTI – radiation necrosis. In one patient biopsy was performed and radiation necrosis (RN) was confirmed.

Key words: radiation necrosis, MRI, PET, 3D conformal radiotherapy (3D-CRT).

The incidence of primary brain tumors was in Slovakia 347 new cases in the year 2003, men 177 6.8/100 000, women 170 6.8/100 000. The incidence of meningiomas was 62 cases, men 15 0.6/100 000, women 47 1.7/100 000.

Radical surgery followed by 3D conformal radiotherapy (3D-CRT) with or without chemotherapy remains a golden standard of treatment for high grade gliomas.

For subgroup of patients with low grade gliomas in presence of negative prognostic factors such as: age more than 40, progression of clinical symptoms such as pharmacologically uncontrolled seizures and initial tumor diameter more than 4-6 cm, contrast enhancing lesion, radiographic progression 3D-CRT or intensity modulated radiotherapy (IMRT) is a valid option.

Atypical and anaplastic meningiomas after biopsy or neurosurgery are also indications for EBRT.

Frequency of late complications after external beam therapy is a serious problem especially in subgroup of patients with good prognosis. The differentiation between LDTI and progression of tumor lesion or tumor recurrence play a crucial role in choosing the right treatment options for these patients.

Patients and methods

In the period from 2003 to 2006 altogether 110 patients with high grade gliomas were irradiated, 26 patients low grade gliomas and 24 patients with atypical and anaplastic meningiomas. In 6 patients MRI identified suspicious findings of LDTI in the brain. The characteristics of the patients were as presented in tables 1, 2, 3. 3D CRT with 6 MV X or Co 60 machine was used.

We applied different radiation techniques according to histology, extent of surgery, and performance status of patient. (Tab 4) These 6 patients with suspicious LDTI changes were regularly examined by MRI and PET at 3 months intervals. MRI’s were done using 1.5 T superconducting system.

LDTI was established based on radiological appearance on conventional MR and results of pMRI, DWI and MRS (Fig.1A-D).
POSTRADIOTHERAPY IN THE BRAIN

18FDG/PET scans were obtained with ECAT-EXACT HR+ scanner (Siemens) at 30 to 60 minutes and 4 to 5 hours after i.v. administration of 370 MBq of 18F-fluorine-2-fluoro-2-deoxy-D-glucose (produced in Nuclear Physics Institute, Rež by Prague, Czech Republic and BIONT Bratislava, Slovak Republic). “Two-dimensional” emission tomographic scanning mode was used, followed by filtered back projection (FBP) reconstruction technique. PET images were analysed visually and semi quantitatively using standard uptake value (SUV) method by two nuclear medicine physicians.

Treatment plans from these 6 patients were evaluated from the point of view of treatment technique, total dose (TD), dose per fraction, maximal dose. We analyzed the extent of surgery, concomitant chemotherapy and use of anticonvulsive drugs, diabetes and hypertension as potential risk factors.

Figure 1A. Postcontrast T1 WI of the patient with histologicaly proven radionecrosis. Lesion has Swiss Cheese Like appearance.
B. MRS from the radionecrosis lesion: NAA, Cho and Cr levels are low, peak of the lipids is very high.
C. DWI (b = 1000). Lesion of the radionecrosis is mostly hyperintensive.
D. ADC. Lesion of the radionecrosis is mostly hypointensive, illustrated cytotoxic edema.
Results

From 160 treated patients we identified 6 patients with LDTI. The pathological findings were as follows: oligodendroglioma Gr II, fibrillary astrocytoma Gr II, anaplastic meningioma Gr III, atypical meningioma Gr II, oligoastrocytoma Gr II, gemistocytic astrocytoma Gr II. Four of them after longitudinal follow up with pMRI, DWI, MRS, correlated with 18FDG/PET have LDTI of radiation necrosis, two patients have combined changes - radiation necrosis with progression of disease.

In the case of one patient with fibrillary astrocytoma Gr II biopsy was done and radiation necrosis was confirmed.

Pathological ring enhancing lesion of radiation necrosis was found with the use of MR imaging features in four of six patients, in all cases in periventricular region and within corpus callosum; in one patient at the site of previous tumor, in four patients distant to the site of the primary tumor, in two cases with progression on the ipsilateral or contralateral side. In two cases there was regression in the follow-up studies, pMRI shows reduced blood volume in contrast to neoplastic lesions in all cases. In MRS we observed reduced choline/N-acetyl aspartate (Cho/NAA) ratio and increased N-acetyl aspartate/creatine (NAA/Cr) ratio in contrast to progression of tumor lesions. Lipid peaks were present in RN lesions. In DWI ring enhancing lesions of RN have a very low apparent diffusion coefficient (ADC) values in central non-enhancing part compared with tumor recurrence.

In longitudinal follow-up with 18FDG/PET in three months interval in two patients with atypical and anaplastic meningioma we found absence of 18FDG uptake in the correspondence with pMRI, DWI and MRS findings typical for RN.

In patient with oligodendroglioma Gr II we observed absence of 18FDG uptake at three months after completion of radiation therapy, but later on, after 12 months, increased 18FDG uptake emerged in the right temporal region above the original occurrence of tumor lesion. This uptake was not significantly greater than uptake in contralateral cortex. Three months later no uptake was present. In concordance with MRI findings, diagnosis of RN was established.

Similarly, in patient with fibrillary astrocytoma Gr II we observed decreased 18FDG uptake in the irradiated region nine months after radiotherapy. Six months later, there was increased uptake in the frontal lobe on the left side, but not higher than contralateral cortex activity. These findings remained constant until the death of this patients; RN was confirmed by biopsy. (Fig.2)

In two patients (one with oligoastrocytoma Gr III and one with gemistocytary astrocytoma Gr II), six months after completion of EBRT a low uptake of 18FDG not greater than uptake of cortex on contralateral side was observed. Both patients underwent incomplete surgical resection. In correspondence with pMRI, DWI and MRS a diagnosis of mixed postterapeutical changes with residual disease was established.

Treatment plans and clinical data records of these 6 patients were analyzed. For patients with pathological findings of low grade glioma we found the following negative prognostic factors: large treatment volume (technique of two opposite fields – one patient) , inhomogeneity within radiation field more than 10%, dose per fraction 2.0 Gy and total dose (TD) 60.0 Gy. (Tab 4)

In patients with anaplastic or atypical meningioma negative prognostic factors were inhomogeneity within radiation field more than 10% and total dose (TD) 60.0Gy.

Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Localisation</th>
<th>Extent of Surgery</th>
<th>Pathology</th>
<th>Follow up/M/</th>
<th>Exitus/Months/Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>Temporal dx.</td>
<td>gross TU removal</td>
<td>oligodendroglia Gr II</td>
<td>36</td>
<td>36/progression of RN</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>Temporal dx./B.G.</td>
<td>biopsy</td>
<td>fibrillary astrocytoma Gr II</td>
<td>36</td>
<td>15/progression of RN with embolisation</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>Frontal sin.</td>
<td>partial extirpation</td>
<td>anaplastic meningioma Gr III</td>
<td>15</td>
<td>10/progression of RN with embolisation</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Occipital sin.</td>
<td>gross TU removal</td>
<td>atypical meningioma Gr II</td>
<td>30</td>
<td>30/progression of RN</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>Bifrontal sin.</td>
<td>partial extirpation</td>
<td>oligoastrocytoma Gr II-III</td>
<td>10</td>
<td>10/progression of RN</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>Temporoparietal dx</td>
<td>biopsy</td>
<td>gemistocytic astrocytoma Gr II</td>
<td>24</td>
<td>24/progression of RN</td>
</tr>
</tbody>
</table>

M – months
RN – radiation necrosis
Of these six patients two patients died because of progression of RN, one patient with fibrillary astrocytoma Gr II, the other with anaplastic meningioma Gr III.

One patient with oligodendroglioma Gr II suffers from severe neurological deficits with Karnofsky Performance Status (KPS) 40, Eastern Cooperative Oncology Group Performance Status (ECOG) 3. MRI and 18FDG/PET findings of RN remain unchanged.

One patient with atypical menigioma Gr II is clinically and neurologically stabilized, with improved findings on MRI after corticosteroid therapy with KPS 80, ECOG 1.

Discussion

EBRT in combination with temozolomide represent golden standard in treatment of high grade primary CNS tumors. [1] In subgroup of patients with low grade gliomas, which include low grade oligodendroglioma, astrocytoma and oligoastrocytoma, the timing of EBRT is still controversial. The indication depends on prognostic factors such as: age of patients, tumor diameter, medical control of symptoms (epilepsy), extent of surgery, enhancing lesion on MRI [2, 3, 4]. In subtotally resected anaplastic and atypical meningiomas EBRT leads to reduction of tumor growth. During EBRT acute reactions (headache, alopecia, nausea, vomiting) occur, caused by increased intracranial pressure due to vasogenic oedema. These acute reactions are reversible and manageable by corticosteroids. Early delayed effects occur weeks to 2-3 months after irradiation. LDTI arise several months to years after irradiation. These are irreversible, progressive and sometimes fatal, caused by vascular endothelial damage, vascular ectasia and teleangiectasia, which result in increased capillary permeability with cytotoxic and vasogenic edema followed by demyelination, cognitive changes, radiation necrosis and finally perivascular coagulative necrosis affecting the white matter. Incidence of radiation necrosis varied from 2.8 % to 24% depending on total dose, dose per fraction, fractionation schedule and type of chemotherapy. [5]

To distinguish LDTI from tumor recurrence, as both are contrast enhancing lesions is one of the most serious problems in the long term follow-up of patients with brain tumors after treatment. Novel imaging MRI techniques such as pMRI, DWI and MRS could make the radiological findings more specific and distinguish between tumor progression and radiation necrosis. The specifications of cut point for differentiation between tumor progression and radiation necrosis was the topic of numerous studies. [6, 7, 8, 9, 10]
Sugahara et al. in the prospective study with 20 patients concluded that normalized relative cerebral blood volume (rCBV) higher than 2.6 and lower than 0.6 suggests tumor recurrence or non-neoplastic contrast enhancing tissue, respectively. [11]

Hein et al. in retrospective study of 18 patients analysed the value of DWI in the follow up of treated high-grade gliomas. They concluded that recurrence and non-recurrence should be differentiated by using mean ADC values and ADC ratios. ADC ratios in the recurrence group showed significantly lower values (mean ± SD, 1.43±0.11) than those of non-recurrence group (1.82±0.07, p < 0.001). Mean ADC of the recurrent tumours were significantly lower values (mean ± SD, 1.43±0.11) than those of non-recurrence group (1.4±0.17 × 10⁻³ mm²/s p < 0.006). [12]

Lev et al. concluded that rCBV values greater than 1.5 are indicative for high grade neoplasm. In a series of 30 patients with cerebral gliomas all 13 histologically proven high grade neoplasms had focci of normalized rCBV greater than 1.5. [13]

Asao et al. analysed 20 lesions; they found significant difference in the maximal ADC values between radiation necrosis and tumour recurrence. DWI was useful in differentiating recurrence versus radiation necrosis. [14]

Schlemmer et al. in a study including 56 patients performed proton MR spectroscopic evaluation of suspicious brain lesions after stereotactic radiotherapy. They concluded that increased signal intensity ratios \( I_{t\text{Cho}}/I_{t\text{Cr}} \) and \( I_{t\text{Cho}}/I_{t\text{NAA}} \) were observed in neoplasia compared with non-neoplastic lesions and contralateral normal brain. [15]

Kimura et al. analysed value of proton magnetic resonance spectroscopy in a retrospective study including 25 patients after stereotactic radiosurgery. The positive predictive value of Cho/Cr ratios of more than 2.48 for diagnosing metastatic brain tumour and of Cho/Cr ratios less than 2.48 for identifying radiation necrosis were 88.9% and 71.4% respectively. Choline/lipid (Cho/Lip) ratio in space occupying radiation necrosis was less 0.3. [16]

Wurm et al. found in their analysis six distinct cases (cerebral infarction, hypertensive encephalopathy - two patients; radiation necrosis, multiple sclerosis - two patients; mimicking supratentorial tumors after therapy in gliomas patients. Capability of advanced MR techniques such as pMRI, DWI, MRS and additional information from PET were discussed. [17]

In prospective study by Lichy et al. on 35 patients with gliomas after radiotherapy the value of MRS was examined in the follow-up. MRI follow-up was performed 6 weeks after completion of RT and in 3-6 months intervals thereafter. In progressive tumors Cho/Cr was increased in 87.5% vs. 29.6% in non-progressive tumors p < 0.05. Cho/NAA was also significantly increased in comparison with non-progressive tumor lesions (93.8% vs. 14.3%, p < 0.01). Sensitivity was 81% and specificity 71.4%. On the basis on \( T_1 \text{w} \) images sensitivity was 87.5% and specificity 85.7%. On the basis on \( T_2 \text{w} \) in addition with \( T_1 \text{w} \) images, sensitivity was 93.7% and specificity 85.7%. Taking all techniques together sensitivity was 100% and specificity 85.7%. [18]

Zeng et al. shows that MRS data (Cho/NAA and Cho/Cr ratios) could distinguish in 85.5% of cases between recurrent glioma and radiation injury. With addition of ADC ratio 96.4% of subjects were correctly classified. [19]

In the 1980’s, \( ^{18} \text{FDG}/\text{PET} \) seemed to be very promising imaging tool for differentiation between recurrent brain tumour and radiation injury. [20]

This encouragement rose from the high metabolic sensitivity of \( ^{18} \text{FDG}/\text{PET} \). But later studies, in 1990’s, showed that value of this technique in distinguishing between post-therapeutic changes and brain tumor recurrences could be limited, because of lower specificity. [20, 21, 22] Recent studies have reported the sensitivity and specificity of \( ^{18} \text{FDG}/\text{PET} \) in differentiation of radiation injury from tumor recurrences between 81% to 100% and 40% to 100% respectively, greatly depending on primary tumor pathologic grade. Causes of false-positive results include recent radiation therapy, non-malignant inflammatory processes and subclinical seizure activity. False-negativity occurs mostly due to small tumor volume, but there is also significant issue of true-negative results in cases of low histologic grade. [20]

Relative limitation is also a high glucose utilisation in normal gray matter (this problem can be effectively reduced by delayed, two-phase scanning).

Rising issue in \( ^{18} \text{FDG}/\text{PET} \) is occurrence of hypermetabolic focal activity in the post-radiation areas, most probably due to activation of repair mechanisms. [20]

These findings were observed also in our study group - in 2 patients with radiological signs typical for RN. According to visual and standard uptake value (SUV) evaluation, the focal uptake was at the level of contralateral cortex activity (in both patients even in delayed scanning). This issue requires further investigation. In these cases, the interval between corresponding MRI and \( ^{18} \text{FDG}/\text{PET} \) examinations should be as short as possible.

Because of limitations of FDG PET (high glucose metabolism in normal brain, some brain tumors are hypometabolic) the usefulness of another tracers were evaluated. \( ^{1} \text{C}-\text{methionine} \) PET can provide additional information when used in combination with \( ^{18} \text{FDG}/\text{PET} \) in the evaluation of these patients. [23, 24] Because of short physical half-time of \( ^{1} \text{C} \) (20 min.) the role of novel amino acid tracers was discussed in different studies O-(2-\( ^{18} \text{F} \)-fluoroethyl)-\( L \)-tyrosine (\( ^{18} \text{F}-\text{FET} \)), 3,4-dihydroxy-6-\( ^{18} \text{F} \)-fluoro-\( L \)-phenylanine (\( ^{18} \text{F}-\text{FDOPA} \)). [25, 26, 27]

In conclusion, EBRT in combination with chemotherapy (Temozolomide) is the treatment of choice for patients with high grade glioma after surgery. Recommended total dose is 60Gy with 1.8 or 2.0 Gy per fraction. Treatment volume is based on post-operative MR scans. For patients in poor general status with low KPS hypofractionated schedules or chemotherapy only is probably a more appropriate treatment option.
For patients with low grade glioma the treatment algorithm was changed recently. The optimal treatment for each patient (surgery, radiation, observation, chemotherapy) should be individualised according to negative prognostic factors (age > 40, maximum tumor diameter 4-6cm, astrocytoma histology, tumor crossing through the midline, contrast enhancing lesion, presence of neurological deficits before surgery) Total dose for EBRT should not exceed 46-50.4 Gy with 1.8 Gy dose per fraction to the tumor bed with safety margin of 1-2 cm.

Large volume techniques or techniques with maximum dose more than 10% of prescribed dose are not recommended. IMRT could be helpful by minimizing the radiation dose to the healthy surrounding tissues without compromising the tumor dose. [28]

Newer imaging techniques pMRT, DWI and MRS in correlation with PET are helpful in differentiation between LDTI and recurrence of disease or tumor progression. Optimal timing of follow-up examination with MRI and PET needs further evaluation. In the future the analysis of the genotype - presence or absence of 1p19q, O6-methylguanine-DNA methyltransferase (MGMT) of tumor tissue could help in choosing an individualised treatment strategy for each patient.

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References


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