doi:10.4149/neo_2009_02_156

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

M. CHORVATH[1*], E. BOLJESIKOVA[1], L. PRUZINCOVA[2], V. PROCKA[3], B. RYCHLY[4], M. NOVOTNY, P. KALINA[6], V. BELAN[2], I. MAKAIOVA[3], J. STENO[5]

[1]Department of Radiation Oncology, St. Elisabeth Canc. Inst. 812 50 Bratislava e-mail: mchorvat@ousa.sk; [2]Department of Radiology Derer's University Hospital; [3]Department of Nuclear Medicine, Comenius University Bratislava; [4]Cytopathos, Centre of pathology Derer's University Hospital; [5]Department of Neurosurgery, Comenius University Bratislava, [6]Department of Neurology, Comenius University Bratislava[1]

Received June 12, 2008

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 ^{18}fluoro-deoxyglucose positron emission tomography (^{18}FDG/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 ^{18}FDG/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).

* Corresponding author

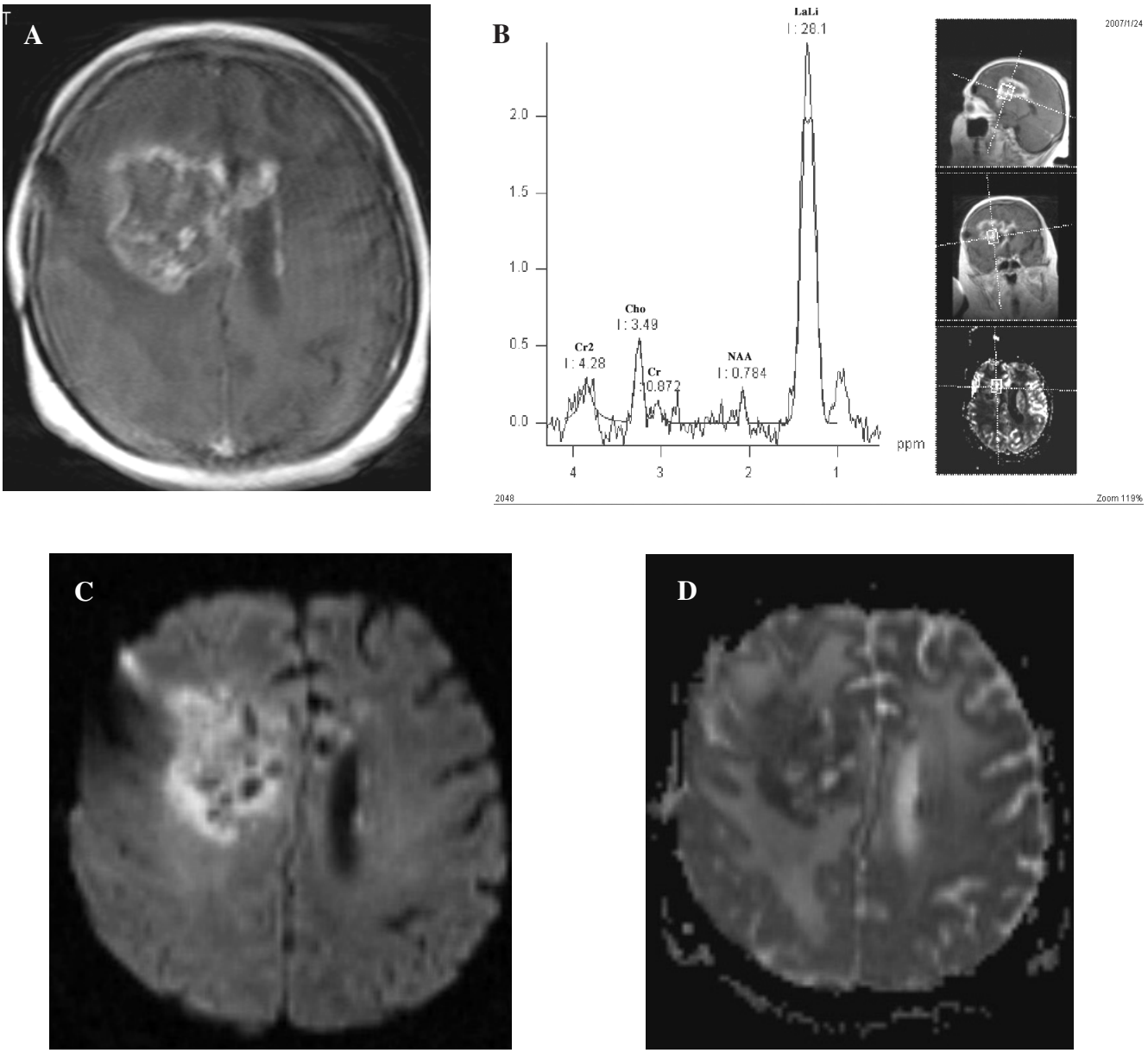

Figure 1A. Postcontrast T1 WI of the patient with histologicaly proven radionecrosis. Lesion has Swiss Cheese Like appearance.
B. MRS from the radionecrosis lesion: NAA, Cho and Cr levels are low, peak of the lipids is very high.
C. DWI (b = 1000). Lesion of the radionecrosis is mostly hyperintensive.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

^{18}FDG/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 ^{18}F-fluorine-2-fluoro-2-deoxy-D-glucose (produced in Nuclear Physics Institute, Řež 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.

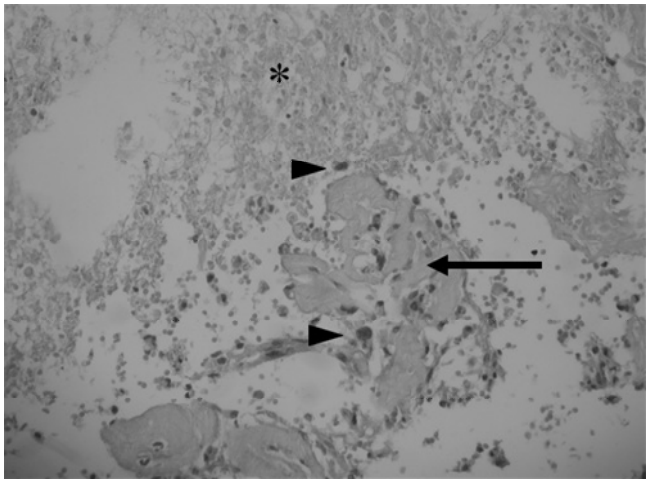

Figure 2. Radionecrosis:group of small vessels with fibrinoid necrosis (arrow), necrotic glial tissue (asterisk) and postirradiation atypical nuclei (arrowheads), HE, 400x.

Results

From 160 treated patients we identified 6 patients with LDTI. The pathological findings were as follows: oligodendroglioma Gr II, fibrilary 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 ^{18}FDG/PET have LDTI of radiation necrosis, two patients have combined changes - radiation necrosis with progression of disease.

In the case of one patient with fibrilary 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 coeficient (ADC) values in central non-enhancing part compared with tumor recurrence.

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

In patient with oligodendroglioma Gr II we observed absence of ^{18}FDG uptake at three months after completion of radiation therapy, but later on, after 12 months, increased ^{18}FDG 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 ^{18}FDG 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 ^{18}FDG 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

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

M – months
RN – radiation necrosis

Table 2. Late delayed therapy induced injuries in the brain

Pts. No.	Follow up/M/	RN	Interval from EBRT	Mixed changes	Interval from EBRT/M/
1	36	1	12		
2	36	1	11		
3	15	1	12		
4	30	1	17		
5	10			1	6
6	24			1	10

M – moths
EBRT – external beam radiotherapy
RN – radiation necrosis

Table 3. Concomitant therapy/ risk factors

Pts.No.	TMZ	DXM	Carbamazepin	Hypertension	Diabetes
1	0	0	1	0	0
2	0	0	0	0	0
3	0	0	0	1	1/Ins.
4	0	0	0	0	0
5	1	1	0	0	0
6	0	1	0	1	0

TMZ – temozolomide
DXM – dexamethason
Ins. – insulin

Table 4. Irradiation techniques

Pts.No.	Technique/Source	PTV	Site	No.of Fraction	TD/Gy	Norm izo	Dose	
		cm^3		Fr/Gy	Gy	%	Max	Mean
1	2WF 6MV X	312.8	temp.et pariet.dx.	30 x 2Gy	60	95	71.1	63.9
2	2OF 6MV X	313.2	temp.dx.	20 x 2Gy	40	95	46.0	40.3
	2OF 6MV X	1020	temp.dx.et.sin.	10 x 2Gy	20	95	22.7	21.5
3	2FW 6MV X	280	front.sin	30 x 2Gy	60	95	69.5	62.8
4	2WF 6MV X	280.4	occip.sin.	30 x 2Gy	60	95	71.0	63.8
5	3FT 6MV X	484.1	bifrontal.	30 x 2Gy	60	95	67.4	63.9
6	WBRT ^{60}Co	1250	front-temp-pariet.dx.	15 x 2Gy	30	93	33.2	32.3
	3FT 6MV X	639.9	hemisphere dx.	10 x 2Gy	20	95	22.4	20.3

WF – wedge fields
OF – opposite fields
3FT – 3 fields technique
WBRT – whole brain irradiation
PTV – planning treatment volume
Norm izo – normalization isodose
Dose Max – maximal dose
Dose Mean – mean dose

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 ^{18}FDG/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 menigiomas EBRT leads to reduction of tumor growth. During EBRT acute reactions (headache, alopecia, nausea, vomitus) 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 demyelinization, 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, $1.18\pm0.13 \times 10^{-3}$ mm/s^2) than those of the non-recurrence group ($1.4\pm0.17 \times 10^{-3}$ mm/s^2 $p < 0.006$). [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 foci 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_{tCho}/I_{tCr} and I_{tCho}/I_{tNAA} were observed in neoplasis 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 from 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_2w images sensitivity was 87.5% and specificity 85.7%. On the basis on T_1w in addition with T_2w 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}FDG/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}FDG/PET. But later studies, in 1990's, showed that value of this technique in distinguishing between post-therapeutical 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}FDG/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}FDG/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}FDG/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. ^{11}C-methionine PET can provide additional information when used in combination with ^{18}FDG/PET in the evaluation of these patients. [23, 24] Because of short physical half-time of ^{11}C (20 min.) the role of novel amino acid tracers was discussed in different studies O-(2-^{18}F-fluoroetyl)-$_L$-tyrosine (^{18}F-FET), 3,4-dixydroxy-6-^{18}F-fluoro-$_L$-phenylanine (^{18}F-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 60.0Gy 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 pMRI, 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, O^6-methylguanine-DNA methyltransferase (MGMT) of tumor tissue could help in choosing an individualised treatment strategy for each patient.

Supported by VEGA 1/3430/06 grant

References

[1] Stupp R, HEGI ME, BENT MJ et al. Changing paradigms-an update on the multidisciplinary management of malignant glioma The Oncologist 2006; 11: 165–180. doi:10.1634/theoncologist.11-2-165 PMid:16476837

[2] GRIER JT, BATCHELOR T. Low-grade gliomas in adults The Oncologist 2006; 11: 681–693. doi:10.1634/theoncologist.11-6-681 PMid:16794247

[3] KARIM ABM, AFRA D, CORNU P et al. Randomized trial on efficacy of radiotherapy for cerebral low-grade gioma in the adult: EORTC of cancer study 22845 with the research council study BRO4: an interim analysis. Int. J. Radiation Oncology Biol Phys.2002; 52: 316–324. doi:10.1016/S0360-3016(01)02692-X

[4] Schiff D, BROWN PD, GIANNINI C. Outcome in adult low-grade glioma: The impact of prognostic factors and treatment Neurology 2007; 69: 1366–1373. doi:10.1212/01.wnl.0000277271.47601.a1 PMid:17893297

[5] RUBEN JD, DALLY M, BAILEY M et al. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy Int. J. Radiation Oncology Biol. Phys.2006; 65: 499–508. doi:10.1016/j.ijrobp.2005.12.002

[6] Tsien Ch, Gomez-Hassan D, CHENEVERT TL et al. Predicting outcome of patients with high grade glioma after radiotherapy using quantitative analysis of T1-weighted magnetic resonance imaging. Int. J. Radiation Oncology Biol Phys.2007; 67: pp 1476–1483. doi:10.1016/j.ijrobp.2006.11.020

[7] JOHANNESEN TB, LIEN HH, HOLE KH et al. Radiological and clinical assessment of long-term brain tumour survivors after radiotherapy. Radiotherapy and Oncology 2003; 69: 169–176. doi:10.1016/S0167-8140(03)00192-0 PMid:14643954

[8] Perry A, SCHMIDT RE. Cancer therapy-associated CNS neuropathology: an update and review of the literature Acta Neuropathol 2006; 111: 197–212. doi:10.1007/s00401-005-0023-y PMid:16463065

[9] KUMAR AJ, NORMAN EL, FULLER GN et al. Malignant Gliomas: MR Imaging Spectrum of Radiation Therapy- and Chemotherapy-induced Necrosis of the Brain after Treatment. Radiology 2000; 217: 377.

[10] Armstrong Cl, HUNTER JV, HACKEY D et al. MRI changes due to early-delayed conformal radiotherapy and postsurgical effects in patients with brain tumours. Int. J. Radiation Oncology Biol Phys.2005; 63: pp 56–63. doi:10.1016/j.ijrobp.2004.12.073

[11] Sugahara T, Korogi Y, Tomiguchi S et al. Posttherapeutic Intraaxial Brain Tumour: The Value of Perfusion-sensitive Contrast-enhanced MR Imaging for Differentiating Tumour Recurrence from Nonneoplastic Contrast-enhancing Tissue. AJNR Am. J. Neuroradiol., May 2000; 21: 901–909.

[12] HEIN PA, ESKEY CJ, DUNN JF et al. Diffusion-Weighted Imaging in the Follow-up of Treated High-Grade Gliomas: Tumour Recurrence versus Radiation Injury AJNR Am. J. Neuroradiol., Feb 2004; 25: 201–209.

[13] Lev MH, Ozsunar Y, Henson JW et al. Glial Tumour Grading and Outcome Prediction Using Dynamic Spin Echo MR Susceptibility Mapping Compared with Conventional Contrast-Enhanced MR: Confounding Effect on Elevated rCBV of Oligodendrogiomas Am. J. Neuroradiol., Feb 2004; 25: 214–221.

[14] Asao Ch, Korogi Y, Kitajima M et al. Diffusion-weighted imaging of radiation-induced brain injury for differentiation from tumour recurrence. AJNR Am. J. Neuroradiol., Jun 2005; 26: 1455–1460.

[15] SCHLEMMER HP, BACHERT P, HERFAHRT KK et al. Proton MR Spectroscopic Evaluation of Suspicious Brain Lesions After Stereotactic Radiotherapy AJNR Am. J. Neuroradiol., Aug 2001; 22: 1316–1324.

[16] Kimura T, Sako K, Tohyama Y et al. Diagnosis and treatment of progressive space-occupying radiation necrosis following stereotactic radiosurgery for brain metastasis: value of proton magnetic resonance spectroscopy. Acta Neurochirurgica, 2003 Jul; Vol. 145 (7), pp. 557–64. doi:10.1007/s00701-003-0051-0 PMid:12910398

[17] Wurm G, Parsaei B, Silye R et al. Distinct supratentorial lesions mimicking cerebral gliomas. Acta Neurochirurgica 2004 Jan; Vol. 146 (1), pp. 19–26; doi:10.1007/s00701-003-0151-x PMid:14740261

[18] LICHY MP, PLATHOW CH, SCHULZ-ERTNER D et al. Follow up gliomas after radiotherapy: 1H MR spectroscopic imaging for increasing diagnostic accuracy. Neuroradiology 2005; 47: 826–834. doi:10.1007/s00234-005-1434-0 PMid:16142479

[19] ZENG QS, LI CF, LIU H et al. Distinction between recurrent glioma and radiation injury using magnetic resonance spectroscopy in combination with diffusion-weighted ima-

ging. Int. J. Radiation Oncology Biol Phys.2007; 68: pp 151–158. doi:10.1016/j.ijrobp.2006.12.001

[20] LANGLEBEN DD, SEGALL GM. PET in differentiation of recurrent brain tumour from radiation injury. J Nucl Med 2000; 41: 1861–1867.

[21] Kahn D, FOLLETT KA, BUSHNELL DL et al. Diagnosis of recurrent brain tumour: value of 201T1 SPECT vs. 18F-fluorodeoxyglucose PET. AJR Am J Roentgenol 1994; 163: 1459–1465.

[22] OLIVERO WC, DULEBOHN SC, LISTER JR. The use of PET in evaluating patients with primary brain tumours: is it useful? J Neurol Neurosurg Psychiatry 1995; 58: 250–252. doi:10.1136/jnnp.58.2.250

[23] CHUNG JK, KIM YK, KIN S, LEE YJ, PAEK S et al. Usefulness of 11C-methionine PET in the evaluation of brain lesions that are hypo-orisometabolic on 18F-FDG PET. Eur. J Nucl. Med 2002; 29: 176–182. doi:10.1007/s00259-001-0690-4 PMid:11926379

[24] Van Laere K, Ceyssens S, Van Calenbergh F et al. Direct comparison of 18F-FDG and 11C-methionine PET in suspected recurrence of glioma: sensitivity, inter-observer variability and prognostic value. Eur J Nucl Med Mol Imaging 2005; 32: 39–51. doi:10.1007/s00259-004-1564-3 PMid:15309329

[25] Chen W. Clinical applications of PET in brain tumours. J Nucl Med 2007; 48: 1468–1481. doi:10.2967/jnumed.106.037689 PMid:17704239

[26] SCHIEPERS Ch, CHEN W, DAHLBOM M, CLOUGHESY T, HOH CK, HUANG SCh. 18F-fluorothymidine kinetics of malignant brain tumours. Eur J Nucl Med Mol Imaging 2007; 34: 1003–1011.

[27] Spaeth N, Wyss MT, Weber B, Schiedegger S, LUTZ A et all. Uptake of 18F-Fluorocholine, 18F-Fluoroethyl-L-Tyrosine, and 18F-FDG in acute cerebral radiation injury in the rat: implications for separation of radiation necrosis from tumour recurrence. J Nucl Med 2004; 45: 1931–1938.

[28] Hermanto U, FRIJA EK, LII MJ et al. Intensity-modulated radiotherapy(IMRT) and conventional three-dimensional conformal radiotheraphy for high grade gliomas: does IMRT increase the integral dose to normal brain? Int. J. Radiation Oncology Biol Phys.2007; 67: 1135–1144. doi:10.1016/j.ijrobp.2006.10.032