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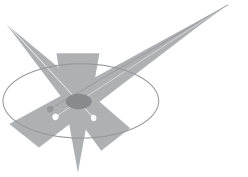

Original Paper

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The results of postoperative irradiation in malignant glioma patients

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Summary

Aim

The purpose of our study was to conduct a retrospective analysis of malignant glioma patients treated with postoperative radiotherapy in order to assess the clinical outcome and identify prognostic factors which may alter the prognosis.

Materials/Methods

We have retrospectively reviewed the medical records of 107 patients with histologically confirmed cerebral high grade gliomas (HGG) treated with postoperative radiotherapy from November 1997 to December 2002 at the Department of Radiotherapy of the Holycross Cancer Centre in Kielce. The total dose varied from 20 Gy in 5 fractions to 62 Gy in 31 fractions. The overall survival (OS) and the progression free survival (PFS) were calculated by using the actuarial method according to Kaplan and Meier. A multivariate analysis was made using the Cox regression model to identify independent prognostic factors. The following factors were studied for the prognostic significance for OS and PFS: histology, sex, age, the WHO performance status and the neurological deficit status, the size and localization of the tumour before surgery, the extent of the resection, the time from the operation to the start of the irradiation, the total dose of radiotherapy and the response to treatment three months from the end of radiotherapy.

Results

The overall survival (OS) was 0.38 and 0.13 at one and two years, respectively, and the progression free survival (PFS) was 0.13 and 0.06 at one and two years, respectively, for the whole group of the postoperatively irradiated patients. In the multivariate analysis: histopathology, age, performance and the neurological status before the onset of radiotherapy, the total dose of irradiation and the response to the treatment observed three months from the end of radiotherapy were found to be significant prognostic factors for the overall survival, while histopathology, age, performance and the neurological status at the beginning of the irradiation and the total dose of the radiotherapy were found to be significant prognostic factors for the progression free survival.

Conclusions

The prognosis for high-grade glioma patients remains poor. The combined treatment, operation and radiotherapy, resulted in the overall survival of 0.38 at one year and 0.13 at two years and the progression free survival of 0.13 at one year and 0.06 at two years in the study group. In the multivariate analysis: histopathology, age, performance and the neurological status before the onset of radiotherapy, the total dose of the irradiation and the response to treatment observed three months from the end of radiotherapy were found to be significant prognostic factors influencing the overall survival, while histopathology, age, performance and the neurological status at the beginning of the irradiation, the total dose of radiotherapy were found to be significant prognostic factors influencing the progression free survival. The assessment of the prognostic factors is very important, because it is a guide to the treatment selection by clinicians.

Key words malignant glioma • postoperative radiotherapy • retrospective analysis

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Background

For the past few decades, a growing number of new cases of malignant brain tumours has been observed [1]. Approximately 1.3% of all newly diagnosed cases of neoplasms in Poland in 1999 were malignant gliomas (about 1370 patients) [1]. Malignant gliomas, which include anaplastic astrocytoma and glioblastoma multiforme are the most common primary brain tumours in adults, accounting for more than 40% of the malignancies of the central nervous system and occurring at a rate of five cases per 100.000 population per year. [2–4]. The medical management of patients with malignant gliomas still remains controversial, because of the poor prognosis of this clinical entity and a very unsatisfactory outcome where only palliative results can be achieved, irrespective of the type of the treatment employed.

In many oncological centers worldwide the standard therapeutic approach for the past few decades was to combine the maximum neurosurgical resection of the tumour followed by postoperative radiotherapy. The clinical application of chemotherapy as the primary treatment remains controversial, although its role as a salvage therapy at the time of the progression after the first line treatment was found to be efficient in obtaining a short time improvement in malignant glioma patients [5–8]. The rationale for postoperative irradiation in malignant glioma patients has been to postpone the tumour regrowth after surgical excision and therefore increase the survival. The clinical data showed three to six-month improvement in the overall survival due to postoperative radiotherapy [2,9–11]. Despite the long application of postoperative radiotherapy in the management of patients suffering from malignant gliomas, many clinical problems connected with this sequential therapeutic option still remain unanswered.

Aim

The purpose of our study was to conduct a retrospective analysis of malignant glioma patients treated with postoperative radiotherapy in order to assess the clinical outcome and identify prognostic factors which may alter the prognosis.

Materials and Methods

We have retrospectively reviewed the medical records of 107 patients with histologically confirmed cerebral high grade gliomas (HGG) treated with postoperative radiotherapy from November 1997 to December 2002 at the Department of Radiotherapy of the Holycross Cancer Centre in Kielce. Four patients were excluded from the analysis. Three of them were lost from the follow up immediately after radiotherapy, and no medical record was available for the analysis. The remaining patient suffered from early progression during the second week of radiotherapy and the irradiation was stopped. He was then referred for the second operation. The population under study consisted of 55 males and 48 females. The mean age was 53.9 years (range 18–79 years with the standard deviation of 12.52). Initially, all patients were subjected to neurosurgical intervention and the extent of the tumour resection was determined from operation reports. Near total resection was made in 47 patients, the subtotal and the partial resection in 54, and 2 patients underwent biopsy only. In 52 cases the tumours were localized in more than one lobe. The pathology report revealed the glioblastoma multiforme in 73 patients (71%) and anaplastic astrocytoma in 30 patients (29%). The pre-radiotherapy WHO performance status was 0 and 1 in 64 patients, 2 in 26 patients and 3 in 13 patients. The assessment of the patient's neurological status was made according to the EORTC/MRC Neurological Deficits Score [12] and in 23 cases it was 1, in 21 was 2, in 32 patients it was 3 and in remaining 20 cases it was 4. The clinical characteristics of the patients is summarized in Table 1. Postoperative irradiation was initiated between 0.3 and 8.2 months after surgery (the mean value was 1.5 and the standard deviation of 1.30). The patients were treated with a Co-60 unit or a linear accelerator with 6 or 15 MeV photons in the supine

Table 1. Patients characteristics.

Characteristics	Category	Number (%) of patients	
Sex	Males	55	(53.4%)
	Females	48	(46.6%)
Age	≤50 yrs	36	(35%)
	>50 yrs	67	(65%)
	≤45 yrs	22	(23.7%)
	45–60 yrs	44	(47.3%)
	>60 yrs	37	(35.9%)
WHO PS before RTH	0–1	64	(62%)
	2	26	(25%)
	3	13	(13%)
Neurological deficit status before RTH	1	23	(22%)
	2	21	(20%)
	3	32	(31%)
	4	20	(20%)
	unknown	7	(7%)
Histology	GBM	73	(70.9%)
	AA	30	(29.1%)
Tumour location (lobe)	frontal	18	(17.5%)
	temporal	19	(18.5%)
	parietal	13	(12.6%)
	> than 1 lobe	52	(50.5%)
	cerebellum	1	(1%)
Size of tumour	≤5 cm	51	(49.5%)
	>5 cm	51	(49.5%)
	unknown	1	(1%)
Extent of operation	near total	47	(45.6%)
	subtotal and partial	54	(52.4%)
	biopsy	2	(1.9%)

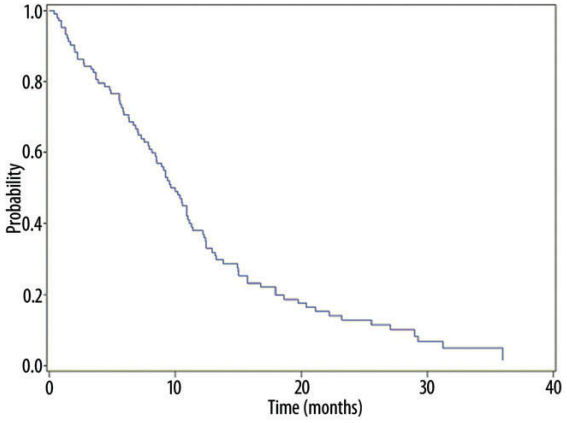

Figure 1. Overall survival probability curve.

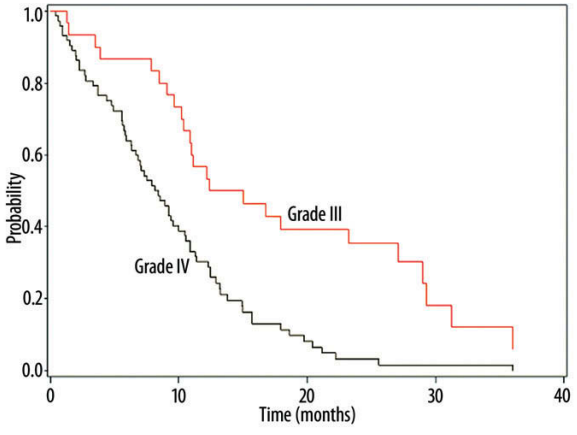

Figure 2. Overall survival probability by histopathology.

position. All patients were immobilised with thermoplastic masks. In all cases but three, 3-D treatment planning based on computed tomography (CT) scans was used. The planning target volume (PTV) encompassed the tumour bed with the oedema with an additional 2 cm margin around it. In 74 patients such a treatment was followed by a boost to the tumour bed with the surrounding oedema. In the standard techniques two opposed fields with the whole brain irradiation were used. The dose was calculated at an ICRU 50 reference point. The total dose varied from 20 Gy in 5 fractions to 62 Gy in 31 fractions. The most frequently used schedules of the irradiation were 60Gy in 30 fractions (62%) and 42 Gy in 15 fractions (18,5%).

The irradiation was combined with chemotherapy in five cases. Three patients were given temozolomide 75mg/m^2/d × 7d/week for 6 weeks during radiotherapy, followed by adjuvant therapy with this drug at a dose of 200mg/m^2/d × 5 days every 28 days for six cycles. Two patients were given adjuvant chemotherapy only and they received 4 and 6 cycles of temozolomide 200mg/m^2/d × 5 days every 28 days.

Acute and late radiation morbidity were scored according to the EORTC/RTOG scale. The response to the treatment

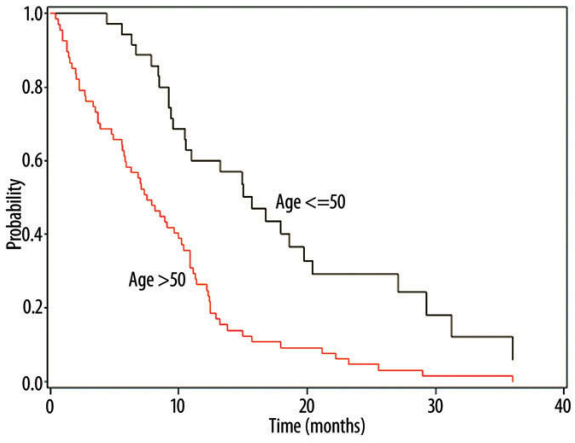

Figure 3. Overall survival probability by patients' age.

based on CT or magnetic resonance (MR) was assessed in 68 patients three months from the end of radiotherapy. In patients in whom relapse or progression was suspected, one of two diagnostic procedures had been carried out earlier. Twelve patients with rapid relapse manifested by clinical symptoms and with poor performance status did not have CT or MRI, and the progression was based on physical examination only. Thirty-one patients had complete response (CR), 20 partial response (PR) and 49 had progressive disease (PG). The response to treatment was not assessed in 3 patients because they were lost from the follow up. Salvage treatment was applied in 36 (35%) cases. Thirty-three patients were managed by surgical resection at the time of the relapse. Eight of them were also scheduled for chemotherapy after being re-operated. The remaining 3 patients received chemotherapy, as the only salvage treatment. The chemotherapy regimens consisted of 1 to 3 cycles of temozolomide 200mg/m^2 × 5 days every 28 days in 7 patients, and 1 to 8 cycles of lomustine 120mg/m^2 in one day every 42 days in 4 patients. Systemic treatment was carried on till the time of the progression. Fifty-seven patients were subjected to supportive care only at the time of their relapse.

The overall survival (OS) and the progression free survival (PFS) were defined as the time from the end of radiotherapy to death and to the development of progressive disease, respectively. Both values were calculated by using an actuarial method according to Kaplan and Meier. A multivariate analysis was made using the Cox regression model to identify independent prognostic factors. The following factors were studied for the prognostic significance for OS and PFS: histology, sex, age, the WHO performance status and the neurological deficit status, the size and localization of the tumour before surgery, the extent of the resection, the time from the operation to the start of irradiation, the total dose of radiotherapy and the response to treatment three months from the end of radiotherapy. The statistical analysis was made with SAS Proprietary Software Release 8.2 (TS2M0).

Results

At the time of the analysis, 93 patient died because of local recurrence or progression of the tumour. The overall sur-

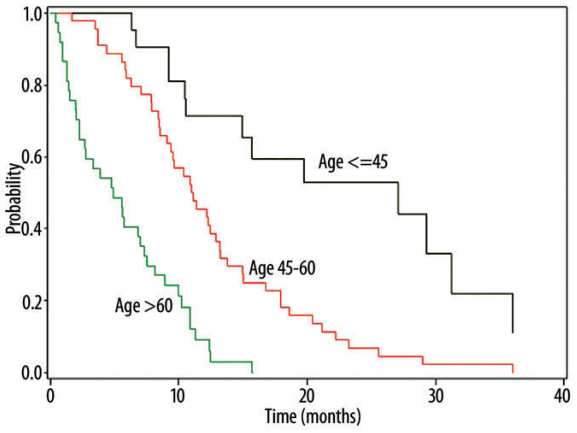

Figure 4. Overall survival probability by patients' age.

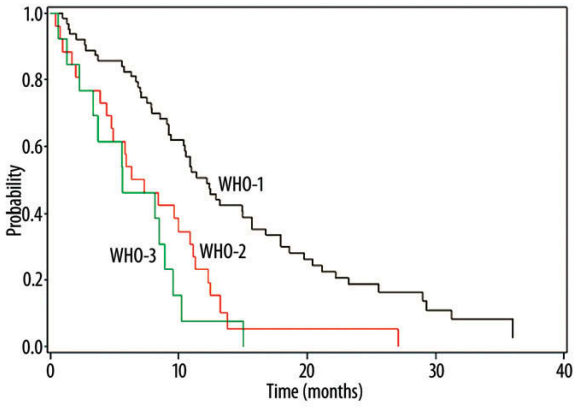

Figure 5. Overall survival probability by WHO PS.

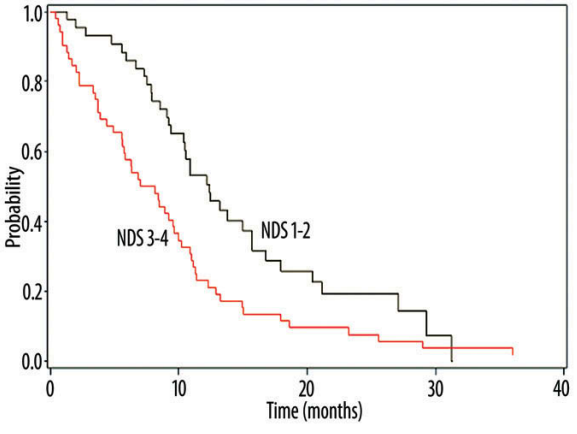

Figure 6. Overall survival probability by neurological status.

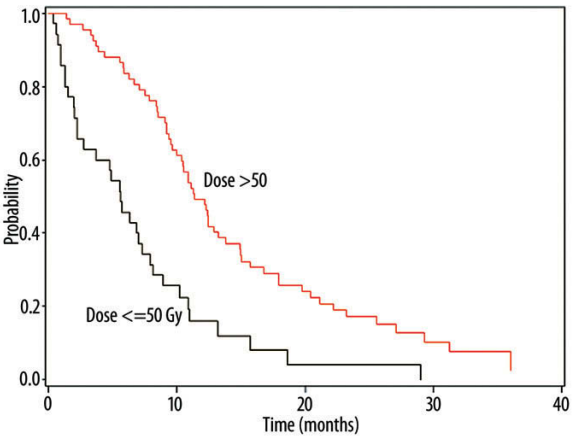

Figure 7. Overall survival probability by total irradiation dose.

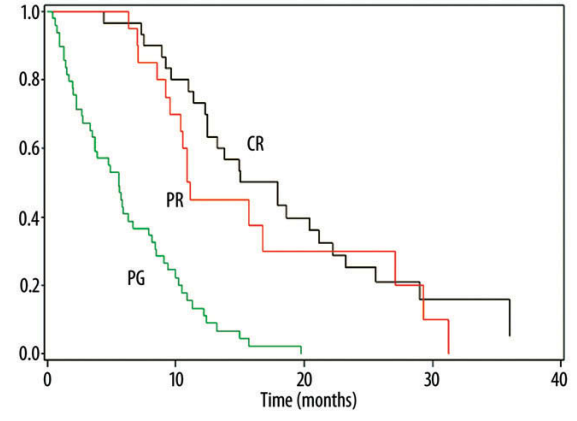

Figure 8. Overall survival probability by response to treatment.

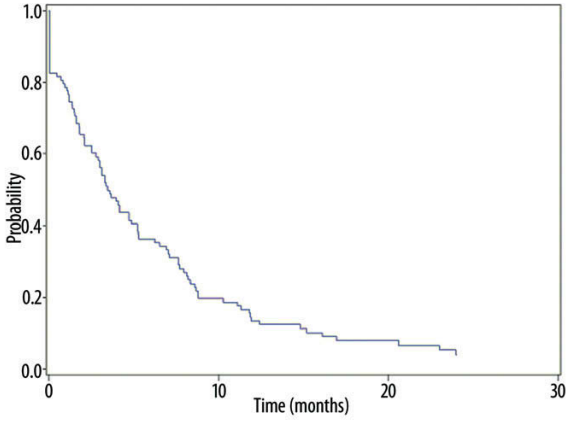

Figure 9. Progression free survival probability curve.

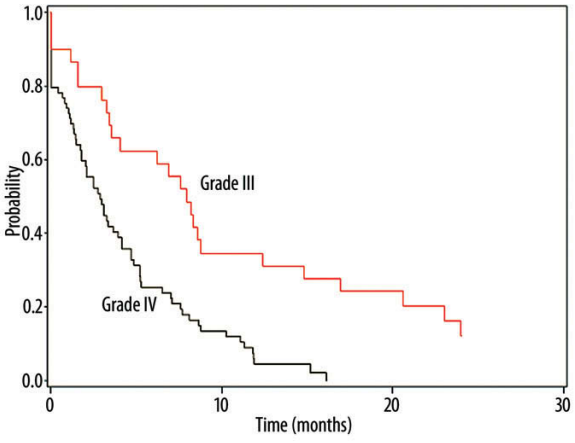

Figure 10. Progression free survival probability by histopathology.

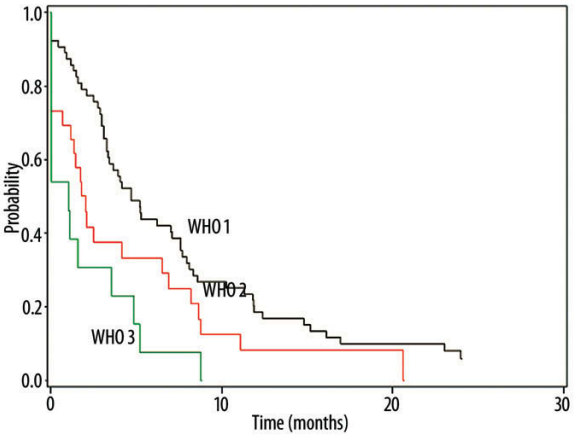

Figure 13. Progression free survival probability by WHO PS.

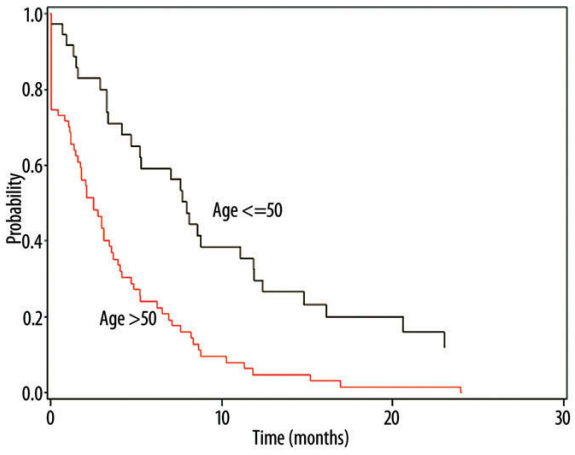

Figure 11. Progression free survival probability by patients' age.

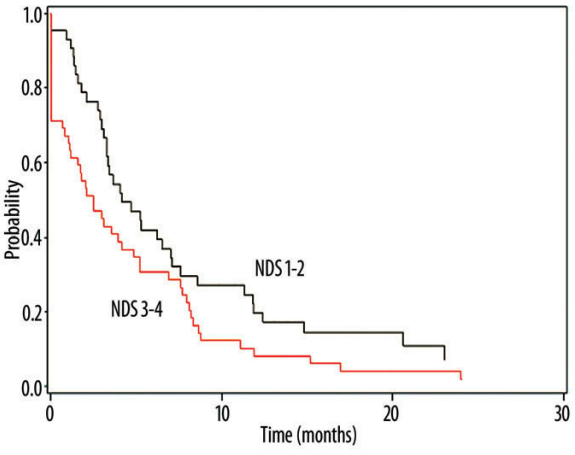

Figure 14. Progression free survival probability by neurological status.

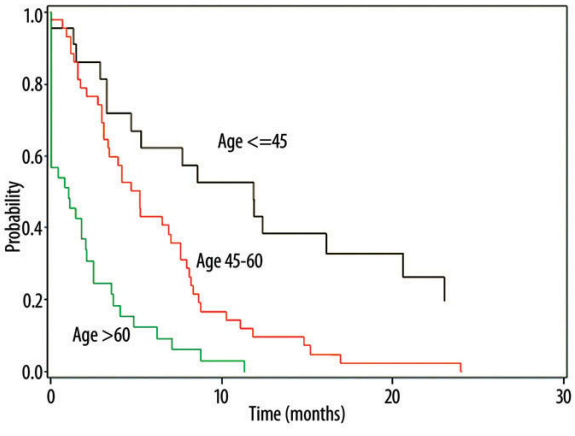

Figure 12. Progression free survival probability by patients' age.

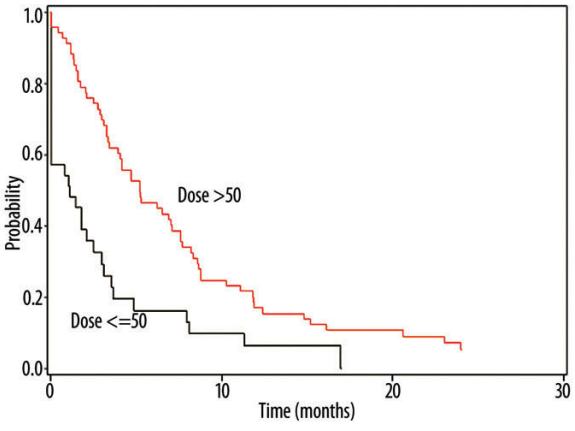

Figure 15. Progression free survival probability by total irradiation dose.

Table 2. Multivariate analysis of prognostic factors for overall survival.

		1-year OS rate	2-years OS rate	Mean (months)	P value
Histology	GBM	0.29±0.05	0.03±0.02	9.4	0.0001
	AA	0.57±0.09	0.35±0.09	18	
WHO PS	0–1	0.50±0.06	0.19±0.05	14.7	<0.0001
	2	0.23±0.08	0.05±0.05	8	
	3	0.08±0.07	0	6.4	
Neurological status	1–2	0.53±0.08	0.19±0.07	14.6	0.0068
	3–4	0.23±0.06	0.08±0.04	9.3	
Age	≤50 yrs	0.60±0.08	0.29±0.08	18	<0.0001
	>50 yrs	0.26±0.05	0.05±0.03	8.9	
	≤45 yrs	0.71±0.10	0.53±0.11	22.6	<0.0001
	45–60 yrs	0.45±0.07	0.07±0.04	12.5	
	>60 yrs	0.09±0.05	0	5.6	
Total dose of RT	≤50 Gy	0.16±0.06	0.04±0.04	7	<0.0001
	>50 Gy	0.49±0.06	0.17±0.05	14.5	
Response to treatment	CR	0.73±0.08	0.25±0.08	18.8	<0.0001
	PR	0.45±0.11	0.30±0.11	16.3	
	PG	0.13±0.05	0	6.2	

Table 3. Multivariate analysis of prognostic factors for progression free survival.

		1-year PFS rate	2-years PFS rate	Mean PFS (months)	P value
Histology	GBM	0.04±0.02	0	4.1	0.0001
	AA	0.35±0.09	0.12±0.08	10	
WHO PS	0-1	0.18±0.05	0.06±0.03	7.4	0.0012
	2	0.08±0.06	0	4,6	
	3	0	0	2	
Neurological status	1–2	0.20±0.06	0.07±0.04	7.5	0.0429
	3–4	0.08±0.04	0.02±0.02	4.7	
Age	≤50 yrs	0.29±0.08	0.12±0.06	9.7	<0.0001
	>50 yrs	0.05±0.03	0	3.9	
	≤45 yrs	0.43±0.11	0.20±0.09	11.9	<0.0001
	45–60 yrs	0.09±0.04	0	6.1	
	>60 yrs	0	0	2.1	

vival (OS) and the standard deviation for the whole group of the postoperatively irradiated patients was 0.38±0.05 and 0.13±0.03 at one and two years, respectively (Figure 1). The median survival for all patients was 12 months. In the multivariate analysis histopathology (Figure 2), age (Figures 3 and 4), performance (Figure 5) and the neurological status (Figure 6) before the onset of radiotherapy, the total dose of the irradiation (Figure 7) and the response to the treatment observed three months from the end of the radiotherapy (Figure 8) were found to be significant prognostic factors for the overall survival. The details of the multivariate analysis are presented in Table 2.

The progression free survival (PFS) and the standard deviation for the entire group of patients was 0.13±0.03 and 0.06±0.02 at one and two years, respectively (Figure 9).

The median PFS was 6 months for all the patients assessed.

Histopathology (Figure 10), patients' age (Figures 11 and 12), performance (Figure 13) and neurological status (Figure 14) at the beginning of the irradiation, total irradiation dose (Figure 15) were found to be significant prognostic factors in the multivariate analysis for PFS. The details of the analysis are presented in Table 3.

Acute toxicity of the treatment was low. There were 45 (43.7%) cases of G0, 55 (53.4%) cases of G1 and 3 (2.9%) cases of G2 brain toxicity. Skin toxicity appeared as G1 in 76 (67.9%) cases and as G2 in 25 (24.3%) cases. The remaining 2 patients had no skin toxicity. All patients had partial or very rare total alopecia Severe late toxicity caused by radiotherapy was not observed but it had to be stressed that due to the very high rate of early relapse accompanied by mortality in every case reliable assessment of side effects was rarely possible.

Discussion

The median overall survival (OS) and the progression free survival (PFS) for the group analyzed remained poor, and were similar to the data presented in other reports. The median overall survival ranged from 5 to 14 months, and the median progression free survival ranged from 5 to 7.5 months [9,10,13–19]. High grade gliomas represent a heterogeneous group of diseases, therefore it is very important to identify the factors that can influence the clinical outcome in order to decide on the most appropriate treatment strategy. The prognostic factors could be divided in three groups: patients, tumour and treatment variables. In our study, patients' age, the neurological and performance status before the onset of radiotherapy were assessed to be statistically significant for both OS and PFS. The importance of these patients' variables was very well documented elsewhere and age [3,16,17,20–24], performance [3,9,11,14–17,22,25] and the neurological status [9,20,26] are commonly accepted prognostic factors. Fifty years was the simplest and the most frequently used age cutoff [3,10,20], whereas some authors accepted a more complex division: 60 years as age cutoff [16] or division of patients into three groups with cutoffs of 45 and 60 years [11], 40 and 60 years [17]. We carried out age analysis using the two above mentioned approaches and found statistical significance for both age divisions, favouring younger patients over elderly ones. This supports the thesis that the patient's age at the diagnosis is one of the strongest factors connected with prognosis. While the performance status is commonly assessed with the WHO scale, the neurological status is evaluated with different scales worldwide [11,13,27] the one most often used being the EORTC/MRC Neurological Deficits Score [12,25]. Patients in our study with poor performance and neurological status had statistically significant shorter OS and PFS. Both factors seemed to have a bigger impact on the clinical outcome in younger patients than in elderly ones [28]. Some authors considered the duration of the neurological symptoms before the diagnosis as a patient's variable useful in predicting the future course of the disease [3,9,11,26]. We did not analyze this for its significance in OS and PFS, because the medical data available for our study did not provide us with sufficient information about the clinical symptoms before operation.

Among tumour variables the primary grade and tumour histology appear to have the greatest effect on the clinical outcome [16,20–24]. Glioblastoma histology predicts poor prognosis compared with anaplastic astrocytoma. An oligodendroglial component is associated with a better clinical outcome in patients with grade 3 astrocytoma [29]. In our study, patients with diagnosed anaplastic astrocytoma lived twice as long as the patients with glioblastoma multiforme (the mean value of 18 months vs 9.4 months, respectively). Other variables such as tumour size and location have not been shown to be significant prognostic factors either in our study or in other analyses presented in the literature [14,17,25]. There is limited data on the prognostic value of the proliferation and genetic markers. Some studies showed a significant correlation between the chromosomal abnormalities and the survival and the chemosensitivity in patients with anaplastic oligodendroglioma [30]. In anaplastic astrocytoma loss or mutation of pTEN tumour suppressor gene is associated with poor survival [31].

Contrary to some authors who claim that the near total resection compared with biopsy only appears to be the most consistent prognostic factor associated with improved survival among the treatment variables [3,32], we did not find it to be the case in our analysis. The lack of correlation between OS and PFS rates and the extent of resection as explained by subjective judgment of the type of operation by different neurosurgeons were due to the infiltrating growth of high grade gliomas, the borders of this malignancy being difficult to be unequivocally assessed. It is commonly accepted that the delay in the initiation of postoperative irradiation beyond 6 weeks after surgery worsens the prognosis. Although such a belief is very strong among clinicians there is, however, few available data to support it [16]. In our study the interval between the surgery and the radiation was not a statistically significant factor influencing both OS and PFS. It is commonly accepted that the optimum conventional external beam radiotherapy is a 6-week course of treatment to a total dose of 60 Gy in 30 daily fractions [2,3,5,15,33]. The shorter palliative hypofractionated 1 to 3-week regimens gave modestly but significantly poorer outcome in malignant glioma patients [9,10,16]. In our study the patients irradiated with a total dose of over 50Gy lived twice as long as the patients who received a dose equal to or less than 50Gy (the mean survival of 14.5 months vs 7 months, respectively with $p<0,0001$) this relatively big gain in the survival compared with randomized studies was probably caused by the selection of patients with poor prognostic factors for hypofractionated treatment.

The survival gain of the radical compared with the palliative course of radiotherapy in patients with life expectancy of less than 6 months is relatively small, usually few weeks only. Therefore there is an opinion among radiation oncologists that it is not appropriate to offer a 6-week course of intensive treatment to such patients [2,9,13,14,25,26,33]. In our institution the patients whose life expectancy, based on prognostic factors, was considered to be less than six months, were scheduled to a hypofractionated course of radiotherapy, preferably to 42 Gy in 15 fractions. The assessment of life expectancy is very important, because it is a guide to treatment selection for clinicians. None of the presented clinical factors can separately predict survival and schedule for radical or palliative treatment. Several institutions have developed scoring systems to define the

prognosis for high grade glioma patients: Medical Research Council (MRC) in the UK, Radiation Therapy Oncology Group (RTOG), and Gupta and Sarin [9]. All these systems can be adapted to daily routine management of malignant glioma patients but at our centre we used a RPA-RTOG scale.

The response to treatment observed three months from the end of radiotherapy, based on radiological examination, was found to be a significant prognostic factor for the overall survival in the study patients. Some authors also considered the importance of this factor in predicting life expectancy [21,34,35], and the clinical application of this assessment could be found in the selection of patients with good response for salvage treatment at the time of the relapse. Currently, no standard of care exists for patients with recurrent high-grade gliomas. The majority of the study patients, at the time of their relapse, were under supportive care only. Salvage treatment could be applied to the minority of patients with a rather poor outcome, irrespective of the type of the treatment employed including re-operation [20,36], chemotherapy [24,37–39] or both [24]. Re-operation and chemotherapy are most frequently used at the time of the relapse, while re-treatment with radiotherapy (stereotactic radiosurgery or brachytherapy) is rarely applied because of the cumulative toxicity and the extended growth of the recurrent tumour.

Several attempts have been made to improve poor results of the therapy of malignant glioma patients using hyperfractionation [2], accelerated hyperfractionation [20], continuous accelerated fractionation [17], hypofractionation [2,15], particle therapy including neutrons, protons, helium ions etc. [2,33], hyperbaric oxygenation prior the courses of radiotherapy [40], hyperthermia [41], nicotinamide and carbogen [42], and immunotherapy [43].
Unfortunately none of them proved to be effective in extending PFS and OS compared with standard management. In a very selected group of patients dose escalation with stereotactic radiotherapy or brachytherapy [3,33,44] improved the survival. The use of chemotherapy as the postoperative treatment combined with radiotherapy remains controversial [6,8,9,45–48]. The improvement of the outcome presented in clinical trials [49,50] and the meta-analyses [7,8] was very limited in the whole group of malignant glioma patients. Anaplastic oligodendroglioma histology proved to be the most chemo-sensitive type compared to other tumours. Stupp et al. have recently reported a promising overall survival rate for glioblastoma patients in phase II trial of radiotherapy and concomitant temozolomide [51]. The place of chemotherapy in the management of malignant glioma patients will be elucidated in near future, because the results of the European Organization for the Research and Treatment of Cancer phase III clinical trial of radiation with or without temozolomide in patients with newly diagnosed high-grade gliomas and the Radiation Therapy Oncology Group study of radiation with or without PCV chemotherapy in newly diagnosed anaplastic oligodendroglioma should be reported this year [6]. The improvement of the outcome of the above poor prognosis requires that emphasis should be put on discovering novel therapies. It is therefore justifiable that clinicians should enroll malignant glioma patients for clinical trials.

CONCLUSIONS

1. The prognosis for high-grade glioma patients remains poor. The combined treatment, operation and radiotherapy, have resulted in the overall survival of 38% at one year and 13% at two years, and the progression free survival of 13.5% at one year and 6% at two years in the study group.

2. In the multivariate analysis: histopathology, age, performance and the neurological status before the onset of radiotherapy, the total dose of the irradiation and response to treatment observed three months from the end of radiotherapy were found to be significant prognostic factors influencing the overall survival while histopathology, age, performance and the neurological status at the beginning of the irradiation, the total dose of radiotherapy were found to be significant prognostic factors influencing the progression free survival.

3. The assessment of the prognostic factors is very important, because it is a guide to the treatment selection for clinicians.

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