RESULTS OF POSTOPERATIVE RADIOTHERAPY IN LOW-GRADE GLIOMAS

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SUMMARY

Purpose: To evaluate results of postoperative radiotherapy (PRT) for Low-Grade Gliomas (LGG).

Material/Methods: Between 1985 and 1995, 158 patients with LGG (WHO II) received PRT. A multivariate analysis for possible prognostic factors was performed. CT scans taken prior to surgery and at the time of recurrence were compared to define the recurrence pattern in relation to initial tumour site and the irradiated volume.

Results: Ten-year overall and progression free survival rates were 41% and 29%, respectively. A multivariate analysis revealed that good WHO performance status, seizures at presentation, duration of symptoms before treatment >12 months, age <45 years and gross total resection were associated with increased survival. All but three analysed recurrences occurred within the initial tumour sites. There was only one case of recurrence outside the previously irradiated volume.

Conclusions: Long-term treatment results were unfavourable for most LGG patients. Our data confirm the prognostic value of the above-mentioned factors.

Key words: Low-Grade Glioma, Postoperative Radiotherapy, Prognostic Factors, Pattern of failures.

INTRODUCTION

Despite relatively good clinical prognosis, Grade II WHO Low-Grade Gliomas (LGG) diffusely infiltrate surrounding brain structures and show in their natural history a tendency towards progression of malignancy by increasing anaplasia [1]. Management of such tumours, especially the use of immediate postoperative radiotherapy (PRT), is a subject of many controversies. Some authors show a positive impact of PRT on survival in retrospective studies [2,3,4,5,6,7]. Others report no difference in survival between patients (pts) irradiated immediately after surgery and those for whom radiotherapy was delayed until tumour progression [8,9,10, 11]. Recently conducted randomized studies have tried to define a real place of PRT in management of LGG. These first results showed that the increase of doses from 45 to 59.4 Gy and from 50.4 to 64.8 Gy did not improve the survival [12,13]. This finding has led many authors to the conclusion on the inefficacy of PRT in LGG. By contrast, others like Rudoler et al. [14] emphasize the strictly local site of failure in LGG as a need for PRT and consider the doses employed as inadequate, probably too low for LGG. Although the principle of limiting the irradiated volume to a tumour with 2 cm margins in LGG is not questionable, studies concerning the pattern of failure in LGG are relatively scarce and are mainly limited to small groups of patients [15,6,10,16, 14,17]. The high percentage of local failures in the range of doses of 45-65 Gy leads to a question whether or not dose escalation within the primary tumour site using new techniques such a brachytherapy, conformal radiotherapy or radiosurgery can improve the therapeutic ratio.

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We report treatment results, and prognostic factors in 158 pts with LGG treated with PRT at one institution over 10 years. Based on our experience we have also made an attempt to determine the pattern of recurrence with a view to finding a better definition of the appropriate volume to irradiate and possible future design for a dose escalation study.

MATERIALS

The records of 158 patients with WHO Grade II LGG treated with PRT at our institution between 1985 and 1995 were reviewed retrospectively. The characteristics of the patients and their treatment are summarised in Table 1. Radiotherapy started 2-20 weeks (median: 5 weeks) after surgery. For 7 pts it was a second surgery for LGG, they had been referred to strict observation after the first tumour resection. All patients were irradiated with curative intent. Total doses ranged from 44.0 to 66.0 Gy (median: 57.6 Gy). Doses per fraction were 1.8 – 2.0 Gy, three pts received 3.0 Gy per fraction during the first part (to 30.0 Gy) of their treatment due to initial poor performance status. High energy photons (Co60 or X 4 MV, 9 MV, 15 MV) were used in all pts. The tumour with 2-3 cm margins was irradiated in 126 (80%) pts, in 27 (17%) pts the whole brain was treated by a dose of 44.0-50.0 Gy with subsequent irradiation of the tumour with 2 cm margins by 56.0-60.0 Gy. Five (3%) pts had exclusively whole brain irradiation. A 2-D planning system *Mevaplan* was used in most patients, 3-D treatment planning system was not available. All patients were followed up clinically and had CT or MRI examinations every 3 months during the first 3 years, then every 6 months.

Tab. 1. Characteristics of 158 LGG patients treated with postoperative radiotherapy between 1985-1995.

AGE	Median /Mean Range	39 / 40 years 17-74 years
SEX	Female : Male	62 (39%) : 96 (61%)
PERFORMANCE STATUS	Grade 0 1 2 3 4	2 pts. (1%) 106 '' (67%) 33 '' (21%) 14 '' (9%) 3 '' (2%)
NEUROLOGIC STATUS BEFORE RADIOTHERAPY	Grade 1 2 3 4	61 pts. (39%) 34 '' (21,5%) 39 '' (24,5%) 24 '' (15%)
SEIZURES BEFORE TREATMENT	Present Absent	124 pts. (78%) 34 '' (22%)
DURATION OF SYMPTOMS BEFORE INITIAL SURGERY	Median / Mean Range	8 / 26 months 1-190 ''
TIMING OF RADIOTHERAPY	Delayed until progression Immediate after surgery	7 pts. (4%) 151 '' (96%)
HISTOLOGY	Astrocytoma - Fibrillary - Protoplasmic	116 pts. (73%) - 50 (43% astrocytomas) - 8 (7% '')

	- Gemistocytic	- 26 (22% '')
	- Non classified and mixed	- 32 (28% '')
	Oligodendroglioma	25 pts. (16%)
	Mixed glioma	17 '' (11%)
LOCATION	Frontal	47 pts. (30%)
	Temporal	34 '' (22%)
	Parietal	12 '' (8%)
	Occipital	2 '' (1%)
	2-3 lobes	56 '' (35%)
	Infratentorial	7 '' (4%)
SIZE OF TUMOUR BEFORE SURGERY	To 3 cm	24 pts. (15,0%)
	> 3 and ≤ 5cm	48 '' (30,5%)
	> 5 cm	65 '' (41.0%)
	No data	21 '' (13.5%)
SIZE OF TUMOUR BEFORE RADIOTHERAPY	No tumour detected	39 pts. (25%)
	To 3 cm	40 '' (25%)
	> 3cm and ≤ 5cm	14 '' (9%)
	> 5 cm	15 '' (9%)
	No data	50 '' (32%)
T STAGE	T1	49 pts. (31,0%)
	T2	17 '' (11,0%)
	T3	18 '' (41,5%)
	T4	24 '' (16,5%)
PRESENCE OF CALCIFICATIONS IN TUMOUR	Yes / No	20 / 114 pts. (12,5%)/ (73%)
	No data	24 '' (14,5%
TUMOUR ENHANCEMENT IN CT OR MRI SCANS	Yes	40 pts. (25,0%)
	No	70 '' (44,5%)
	No data	48 '' (30,5%)
EXTENT OF RESECTION	Total	39 pts. (25%)
	Subtotal	32 '' (20%)
	Partial/Biopsy	73/14 '' (46%) / (9%)

METHODS

The overall survival and survival without progression were estimated according to the Kaplan-Meier method. Both types of survival were calculated from the first day of PRT. Progression was defined as any relapse in case of complete remission after surgery followed by PRT, or any increase in the size of the residual tumour, or appearance of the mass effect or/and contrast enhancement in the earlier non-enhancing tumour. The influence on the overall survival of all known prognostic factors was estimated using a univariate analysis (UA) with a log-rank test. The following variables were included in the UA: age, sex, performance status, neurologic status before radiotherapy estimated retrospectively according to the EORTC/MRC scale (app. 1) [18], presence of seizures before treatment, mental changes, duration of symptoms before diagnosis, tumour location, histology, T stage according to the UICC classification (app. 2) [19], the size of tumour before surgery, the size

of tumour before radiotherapy, presence of calcifications in the tumour, contrast enhancement in initial CT or MRI scans, the extent of tumour resection, immediate versus delayed radiotherapy, the irradiated volume, total dose and the tumour response to radiotherapy. Factors influencing survival with the statistical significance of $p<0.2$ in the UA for which there were no missing data were included in the multivariate Cox-regression analysis (MA) for final estimation of prognostic signifycance. All data were analyzed using the STATISTICA PL (1999) statistical software. In pts with progression and with all radiological data available (initial and those from recurrence) the pattern of failure was analysed. CT scans taken prior to initial surgery and at the time of recurrence have been compared to define the recurrence pattern in relation to the initial tumour site and to the irradiated volume. According to the available radiological data the initial and recurrent tumours were drawn in the simulator films. Differences in scale between scans and the simulator films and differences in head position were taken into account. If there was any doubt as to the location of the recurrent or initial tumour a second opinion of a radiologist was sought.

RESULTS

Treatment outcome: With a median follow-up of 79 months for a living patient (range:52-167 months) 96 of 158 pts relapsed. The median time to progression was 50 months. Eighty-five pts died of progressive tumour and four from an intercurrent disease. Five pts (2 with, 3 without progression) were lost from the follow-up between 45 and 124 months. The 3-, 5-, and 10-year actuarial overall survival percentages were 68-, 55, and 41%, respectively (fig. 1). The 3-, 5-, and 10-year actuarial progression free survival percentages were 59-, 48-, and 29%, respectively (fig. 2). In 78 (49%) pts with residual tumour visualised on CT or MRI scans made after surgery and before radiotherapy precise estimation of response to radiotherapy was possible. There were 51 (65.5%) complete responses, 9 (11.5%) partial responses, 9 (11.5%) no changes, and 9 (11.5%) progressions. Of 60 pts with response to radiotherapy, 75% responded within the first 3 months after PRT, in 25% of cases responses were delayed from 6 to 26 months.

Prognostic factors: The univariate analysis (UA) showed that the overall survival was increased by the following factors: a better WHO performance status ($p<0.00001$) (fig. 3), complete tumour regression after radiotherapy following surgery ($p<0.00001$), seizures at presentation ($p=0.00005$) (fig. 4), age under 45 years ($p=0.0002$), size of tumour before radiotherapy ≤ 3 cm ($p=0.0006$), duration of symptoms before diagnosis ≥ 12 months ($p=0.0007$), better neurologic status according to EORTC/MRC scale ($p=0.003$), T1/T2 stage of the tumour according to the UICC classification ($p=0.003$), histology of oligodendroglioma or mixed glioma ($p=0.004$) (fig. 5), total or subtotal resection ($p=0.009$) (fig. 6), no contrast enhancement in initial CT or MRI scans ($p=0.02$), and the size of tumour before surgery ≤ 3 cm ($p=0.03$). Sex, mental changes, presence of calcifications, tumour location, immediate *versus* delayed radiotherapy, total radiation dose, irradiation volume (tumour with margins exclusively *versus* whole brain irradiation) did not influence the overall survival. There was no difference in survival between different subtypes of astrocytoma; in particular gemistocytic astrocytoma did not worsen the survival.

The multivariate analysis (MA) retained only seizures at presentation, performance status, duration of symptoms before diagnosis, age, extent of resection as prognostic factors for the overall survival. Patients with oligodendroglioma showed better survival at the limits of statistical significance (table 2). Unfortunately, the highly significant in UA response to treatment evaluated after radiotherapy and the presence of contrast enhancement could not be included in the MA due to missing data.

Toxicity of PRT: Acute side effects were evaluated in the whole group, whereas late effects were considered in 145 (92%) pts. Acute toxicity was minor, only in 8 (5%) pts prolongation of the treatment time beyond 5 days was required because

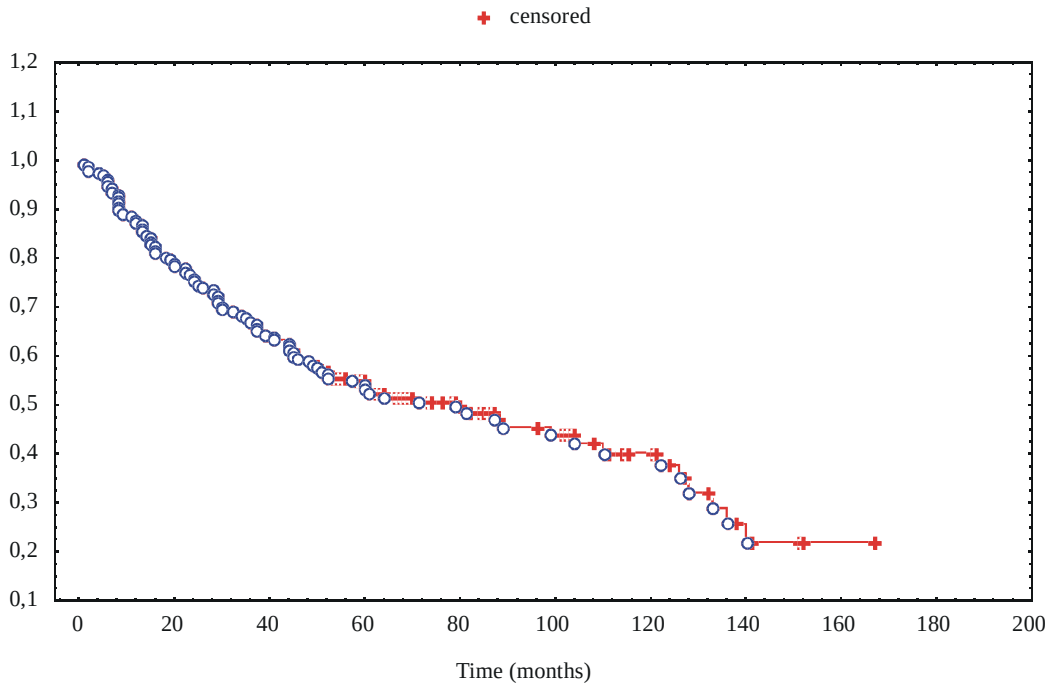

Fig. 1. Overall survival in 158 patients treated with PRT.

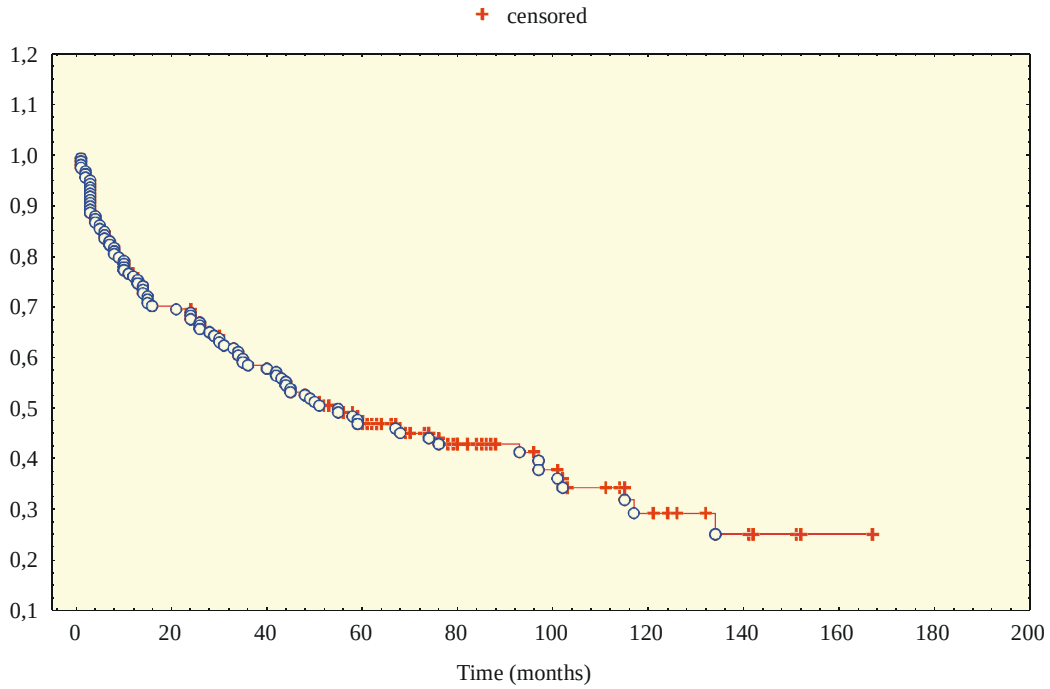

Fig. 2. Progression free survival in 158 patients treated with PRT.

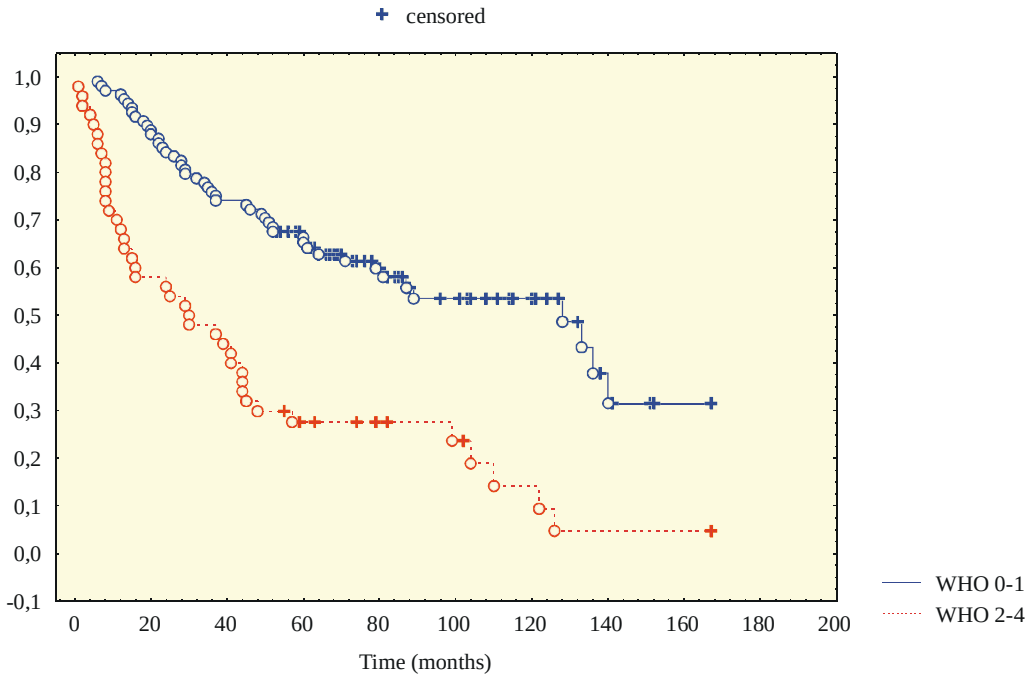

Fig. 3. Overall survival according to WHO performance status.

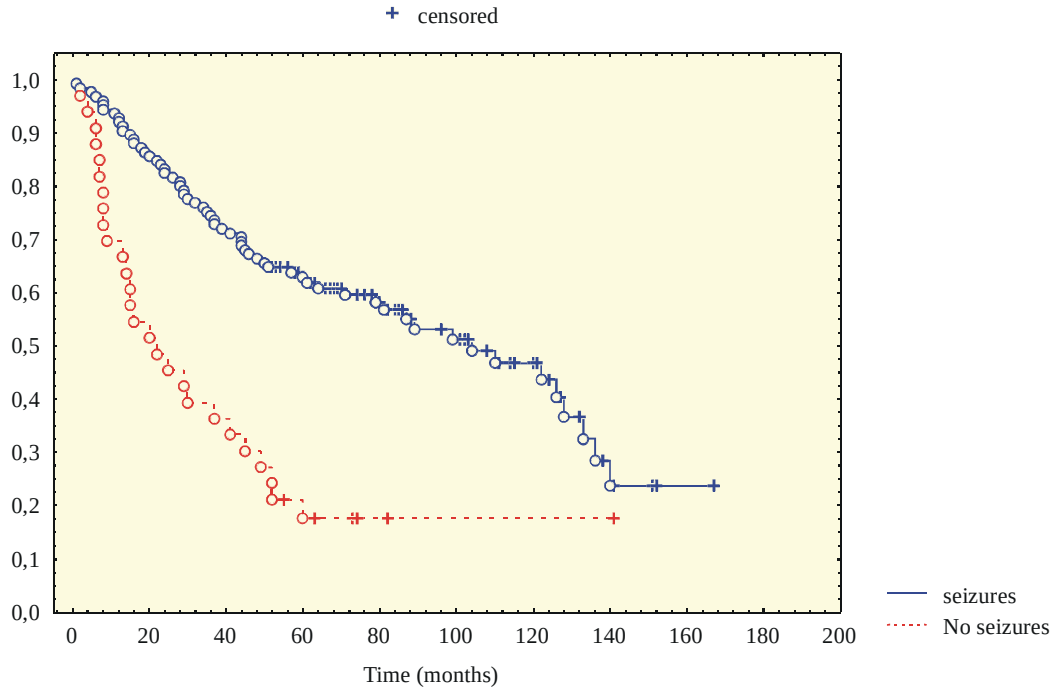

Fig. 4. Overall survival according to presence of seizures before diagnosis.

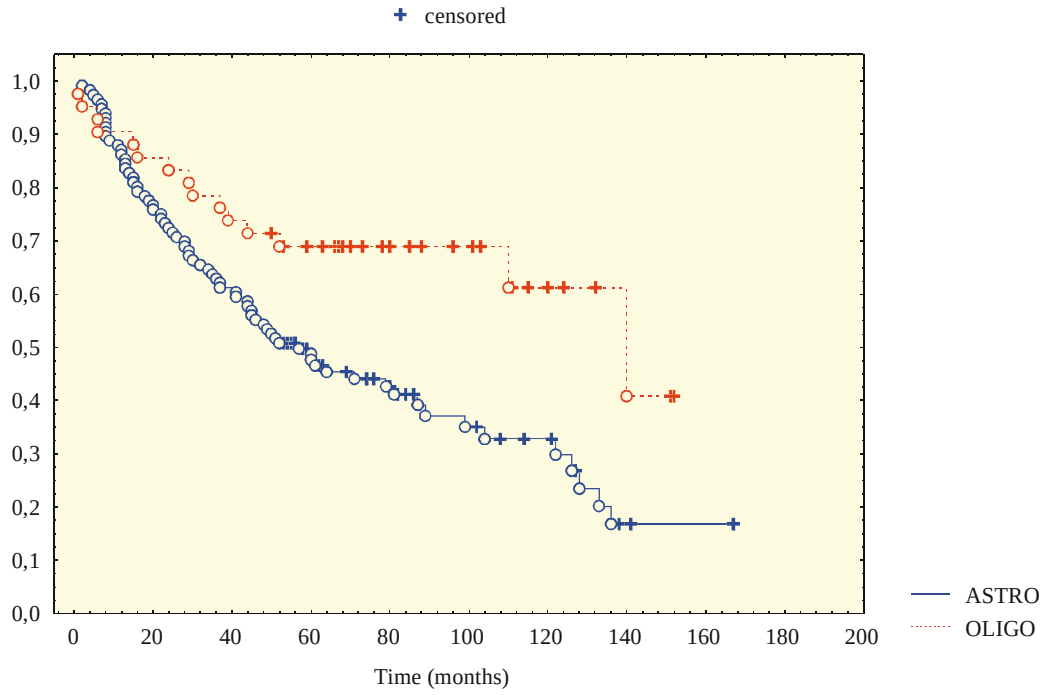

Fig. 5. Overall survival according to histology (ASTRO - astrocytoma, OLIGO - oligodendroglioma and mixed glioma).

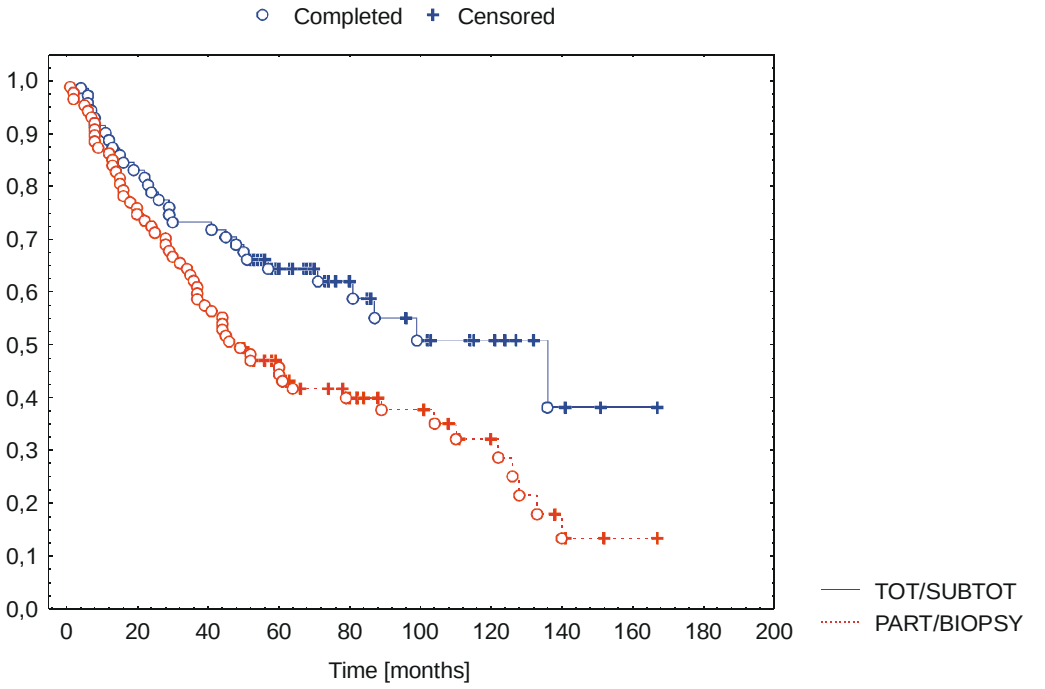

Fig. 6. Overall survival according to extent of resection (TOT/SUBTOT - total and subtotal resections, PART/BIOPSY - partial resections and biopsies).

Tab. 2. Prognostic factors influencing overall survival in multivariate analysis.

VARIABLE	RELATIVE RISK OF DEATH	95% CONFIDENCE INTERVAL	P-VALUE
Seizures before treatment			
Yes			
No	1,00	1,61-4,19	0,00001
	2,60		
Performance status			
0-1	0,41	0,26-0,64	0,0001
2-4	1,00		
Duration of symptoms			
before diagnosis			
≤ 1 year	2,39	1,49-3,89	0,0003
> 1 year	1,00		
Age			
< 45 years	1,00	1,19-1,90	0,0007
≥ 45 years	1,50		
Extent of resection			
Total or subtotal	1,00	1,04-2,61	0,03
Partial or biopsy	1,64		
Histology			
Astrocytoma	1,79	1,01-3,19	0,05
Oligodendroglioma	1,00		
or mixed glioma			
Neurologic status before			
radiotherapy			
Without deficits (1)	0,73	0,17-1,29	0,28
With deficits (2-4)	1,00		
Stage T			
T3-T4	1,14	0,60-1,64	0,61
T1-T2	1,00		

Appendix No 1.
EORTC/MRC Neurologic Deficits Score [18].

1. absence of any neurologic deficit detectable
2. minor neurologic deficits; without any impairment of normal activity
3. neurologic deficits leading to some impairment of normal activity (paresis, minor mental changes)
4. serious neurologic deficits leading to disability to care for himself: paralysis, aphasia, serious mental (emotional and/or cognitive) changes.
5. any communication with patient impossible

Appendix No 2.
UICC TNM tumour staging classification for supratentorial brain gliomas [19]
T1 – Greatest diameter ≤ 5 cm, located unilaterally
T2 - Greatest diameter >5 cm, but not encroaching on the ventricles or crossing the midline
T3 – Any size, definitely encroaching on the ventricular system, but not crossing the midline
T4 – Crossing the midline or the tentorium

of CNS (6 pts) or skin toxicity. Ninety-nine (63%) pts had no radiological or clinical signs of late toxicity. Forty-six (37%) pts had minor late toxicity: 18 pts had only radiological abnormalities (hypodensity in the white matter, cortical atrophy, calci-

fications), 20 pts showed only clinical symptoms (impairment in mental and/or affective functioning), and 8 pts had both radiological and clinical symptoms. There was no case of major toxicity such as radionecrosis.

Failure patterns: Histology of recurrence was determined in 24 of 96 progressions. There were 8 cases with initial histology, 10 with WHO Grade III gliomas, and 6 with WHO Grade IV gliomas (*glioblastoma)*. Thus, malignant transformation was confirmed in 67% of cases. Of 72 recurrences with unknown histology there were 57 (79%) radiological images suggesting malignant transformation (*butterfly glioma* or evident contrast enhancement in earlier nonenhancing tumour).

Localisation of recurrence in relation to the initial tumour site and the irradiation volume was possible in 73 of 96 cases. In these 73 pts, all radiological data from the initial tumour presentation and from recurrence and simulator films showing irradiation fields were available. As described above, original and recurrent tumours were drawn in the simulator films. Recurrences were located in 97.5% of cases at the initial site and all but one within the irradiation volume. More precisely, four types of recurrences were found: (1) sixty-six recurrences at the initial tumour site and apparently within the irradiation volume, (2) two recurrences outside the initial tumour, but within irradiation volume, (3) four recurrences at the initial tumour site with dissemination outside the irradiation volume, and (4) one recurrence outside the irradiation volume. This latter case is not clear, because the second tumour occurred in the controlateral hemisphere 6 years after the initial treatment for WHO III astrocytoma and could also have been a second primary.

DISCUSSION

With a median follow-up of 79 months, which seems sufficient for LGG, the results concerning the overall and progression free survival are in accordance with other data from computerised tomography era. The five-year survival in patients with LGG treated since the 1980s ranged from 50% to 80% [8,20,12,9,21,22,23,10, 14,24].

The strongest prognostic impact of seizures is one of the most interesting findings in our study. Improvement of survival with seizures at presentation in LGG have also been reported by others [25,8, 9,11]. In contrast, some authors point out that epilepsy as a presenting symptom is related to a smaller tumour volume and thus leads to a selection of cases for early diagnosis [10,26]. The prevalence of seizures decreases significantly with increasing histological grade of gliomas. Epilepsy is considered to be a marker for less aggressive tumour biology within the high-grade [26]. In our study, the presence of seizures was not correlated either with a smaller tumour size or with a shorter duration of symptoms before diagnosis. Thus, seizures remained really the strongest independent prognostic factor, possibly related to the inherent less aggressive biological behaviour of the tumour.

Like other data [8,9,21,23,14,27] in our study the WHO performance status appeared to be a better predictor than the neurologic status. The performance status depends strictly on the presence of neurologic deficits. Therefore, some authors claim that the use of a neurological performance scale instead of the performance status scores improves the stratification of patients with brain tumours for clinical trials [12, 28]. In our study, the retrospective use of the neurologic performance score could have been to some extent subjective and inappropriate.

The longer duration of symptoms before diagnosis, characterising more indolent behaviour of tumours especially in older reports was considered to be a factor related to improved survival [29]. More recent studies have usually included pts with a short duration of symptoms, because of rapid implementation of diagnostic tools, so this factor has been loosing its predictive value [30]. Our group of patients was very heterogeneous with respect to this variable. The duration of symptoms ranged from 1 to 190 months. Therefore, it was possible to show its prognostic importance.

Age is not a questionable prognostic factor for primary brain tumours. However, for statistical purposes the finding of an optimal cut point differentiating between two prognostic subgroups remains a problem. Some authors report that even at the early age of 30-35 years the survival of pts with LGG rapidly decreases [32,33]. For others, 40 or 50 years is an optimal cut point differentiating between two prognostic groups [6,8,9,10, 31,21]. We found 45 years to be a cut point after having tested various values and then selecting the one giving the minimum P-value. We have also tested age as a continuous parameter in the MA and we found similar results. According to Recht et al. [34], in pts >45 years of age the observation strategy of non-enhancing lesions is not safe because of rapid increase in anaplasia. The increased risk of finding malignancy in primarily diagnosed LGG in pts >45 years of age may explain the poorer prognosis with age in such tumours [35].

The extent of resection as a prognostic factor is more questionable, particularly if it is based exclusively on the opinion of a surgeon. The extent of resection estimated by a surgeon often loses its prognostic value [8, 28, 21, 24]. Although our estimation of resection was based on the neurosurgeon's opinion, we found a statistically significant difference in the survival between pts with total and subtotal resections and those with partial resections and biopsies. Similar results concerning this variable based only on the neurosurgeon's opinion are reported by others [20,31,10,36,17,29]. As shown in the UA the improvement in treatment results with a smaller tumour size after surgery additionally reinforces the opinion about the positive influence of surgical tumour sterilization on survival.

Improved survival of pts with an oligodendroglial component in brain gliomas as compared with those with pure astrocytomas has been largely reported [37,9, 23,17,27]. In some reports no such difference has been found. This may be the result of differences between various centers of the definition of oligodendroglioma and particularly of mixed gliomas. No worse survival in gemistocytic astrocytomas in our study is in disagreement with most studies [33,38]. This may be due to the high percentage of non-classified astrocytomas (28%) which may have contained tumours with a gemistocytic component. Some authors indicate a rapid malignant progression of this type of LGG and some others include gemistocytic astrocytomas in grade III of malignancy [38].

Seven pts with radiotherapy delayed until recurrence had the same survival as 151 pts with immediate radiotherapy, which, according to some authors, suggest no indication for immediate PRT. A small number of pts with delayed radiotherapy, as well as the retrospective character of the study did not allow us to draw any conclusions about the optimal time for the implementation of radiotherapy in LGG. This problem has been studied in a randomized EORTC trial no 22845. Preliminary results show inferior progression free survival in pts with delayed radiotherapy as compared with those immediately irradiated [39].

The percentage of malignant transformation of recurrences amounting to 70% in our study is similar to other reports [40]. The study concerning the localization of recurrences included 73 pts and was the largest one among those dealing with this problem [15,10,16,14,29]. However, there are two possible pitfalls in the methodology. One is that the study of the pattern of failures was conducted by one investigator and only in case of serious doubt a second opinion was sought. The differences in the definition of targets in treatment planning are well known [41]. The risk of committing errors in a complex procedure such as tracing projections of tumours from CT scans to simulator films could have been additionally exacerbated. Another possible pitfall in this study was the lack of relation to a 3-D- planning system. The localisation of relapse within the radiation field visualised on a simulator film does not necessarily indicate a real occurrence of failure within the area of the prescribed dose. Therefore, recurrences in the fall-off dose area could have been missed and considered as total dose failures. Despite these two limitations in our study, by taking into account the large size of the group and collective deci-

sions in case of doubt, we think that recurrences in LGG were closely related to the initial tumour site and the irradiation volume.

The high percentage of strictly local failures as well as the improvement in survival with sterilization of the tumour (a larger extent of resection, complete response on combined treatment) suggest a need for intensification of local treatment. Limitations of surgery due to many tumour locations and the infiltrating type of the growth are well known. More intensive use of new methods of radiotherapy such as conformal or stereotactic techniques opens us prospects for future studies.

CONCLUSIONS

- Ten-year actuarial progression free survival in 29% of patients is a proof of low long-term efficacy of surgery followed by radiotherapy using doses of 44-66 Gy in management of LGG.
- The prognostic factors such as: seizures, performance status, symptom duration, age and extent of surgery should be taken into account in therapeutic decisions and planning of clinical studies in LGG.
- Localisation of failures in all but one patient within the irradiation field is a proof of the low effectiveness of radiotherapy using conventional techniques and doses. Thus, intensification of local treatment is needed.

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