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Prognostic factors in patients irradiated after incomplete excision of low-grade cerebral astrocytoma

Jadwiga Nowak-Sadzikowska

Introduction. Low grade astrocytomas account for 10-15% of primary adult brain tumours. The management of low-grade cerebral astrocytoma is controversial. Surgery is usually attempted and either biopsy or subtotal or total excision is undertaken. Complete surgical resection is potentially curative. After subtotal resection of the tumour, different polices are being pursued: planned immediate postoperative radiotherapy or retreatment by surgery or radiotherapy on progression of the disease. Material and method. One hundred and nineteen patients with incompletely excised low-grade astrocytomas (WHO grade II) irradiated between 1976 and 1993 at the Department of Radiation Oncology of Maria Skłodowska-Curie Memorial Canser Center in Kraków, were retrospectively reviewed. Fifty astrocytomas were classified as fibrillary, twenty two as protoplasmic and thirty seven as gemistocytic. All patients were treated with megavoltage gamma rays (^{60}Co). The total dose ranged from 50 to 64 Gy (mean: 59.23 Gy) delivered with daily fractions of 1.6-2.5 Gy. The three-field technique (parallel-opposed lateral portals with wedges and anterior portal), or anterior and lateral portals with wedges were used. The treatment volume covered the tumour residual with a margin of (1-2 cm). Factors analysed for prognostic significance included: age, gender, performance status, neurological function, length and nature of symptoms, tumour localisation, stage, histology, extend of surgery, interval from operation to radiotherapy and total dose.
Results. Toxicity was acceptable. The 5-year and 10-year overall actuarial survival rates were 39% and 24%, respectively. The following characteristics were associated with improved patient survival by univariate analysis: age (30, very good neurological function before radiotherapy, fibrillary or protoplasmic histology, female gender (p(0.05). Multivariate analysis showed that only age was correlated with survival time. Patients under 30 years of age carried the best prognosis.
Conclusion. 1. Combined surgery and postoperative radiotherapy in patients with incompletely excised low-grade cerebral astrocytoma results in obtaining 5-year and 10-year overall actuarial survival rates in 39% and 24% of cases, respectively. 2. The tolerance of radical radiotherapy with total doses of 50-64 Gy delivered with classical factions, covering the tumour residual with a margin, is good. 3. Age is the most significant variable determining the survival of patients with incompletely excised low-grade astrocytoma.

Czynniki prognostyczne u chorych na wysokozróżnicowane gwiaździaki mózgu, napromienianych po zabiegach nieradykalnych

Wstęp. Wysokozróżnicowane gwiaździaki stanowią 10-15% guzów mózgu u dorosłych. Postępowanie z chorymi na wysokozróżnicowane gwiaździaki mózgu jest przedmiotem kontrowersji. Podstawową metodą leczenia tych nowotworów jest neurochirurgia. W przypadku radykalnego usunięcia guza adiuwantowe napromienianie nie jest zalecane. Po nieradykalnym leczeniu operacyjnym stosowane są różne sposoby postępowania: planowane uzupełniające napromienianie lub odraczanie leczenia chirurgicznego czy napromienianiem do wystąpienia progresji guza.
Metodyka i materiał. Przeprowadzono retrospektywną analizę grupy 119 chorych na wysokozróżnicowane gwiaździaki mózgu, napromienianych po zabiegach nieradykalnych w Centrum Onkologii w Krakowie w latach 1976-1993. Do wysokozróżnicowanych gwiaździaków (WHO II°) zaliczono następujące postacie histologiczne: gwiaździak włókienkowy – 50 chorych, gwiaździak protoplazmatyczny – 22 chorych, gwiaździak tucznokomórkowy – 37 chorych. Napromienianie przeprowadzono w warunkach telegammaterapii Co-60. Dawka całkowita w badanej grupie wynosiła średnio 59,23 Gy i wahała się od 50 Gy do 64 Gy, frakcjonowana po 1,6-2,5 Gy raz dziennie. Stosowano następujące techniki radioterapii: trzy skrzyżowane wiązki (jedno pole przednie i dwa boczne z filtrami klinowymi) lub dwie wiązki skrzyżowane pod kątem 90°, z użyciem fil-

Department of Radiation Oncology
The Maria Skłodowska-Curie Memorial Cancer Center
and Institute of Oncology
Cracov, Poland
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trów klinowych. Teren napromieniany obejmował pozostałość guza z marginesem (1-2 cm). Oceniono wartość prognostyczną następujących czynników: wiek, płeć, stan neurologiczny, stan sprawności, czas trwania i rodzaj objawów, lokalizacja guza, zaawansowanie, utkanie mikroskopowe, doszczętność zabiegu, okres pomiędzy operacją a zabiegiem, dawka całkowita. Wyniki. Tolerancja leczenia była dobra. Odsetki prognozowanych przeżyć 5- i 10-letnich wynosiły odpowiednio 39% i 24%. W badanym materiale w analizie jednoczynnikowej wykazano prognostyczne znaczenie wieku chorych, płci, stanu neurologicznego przed wdrożeniem radioterapii oraz utkania mikroskopowego, wyróżniającego gwiaździaka tucznokomórkowego. W analizie wieloczynnikowej wiek najsilniej determinował rokowanie, najlepsze wyniki uzyskano w grupie chorych młodszych, poniżej 30 roku życia.
Wnioski. 1. Skojarzone leczenie chirurgiczne z pooperacyjnym napromienianiem chorych na wysokozróżnicowane gwiaździaki mózgu, po zabiegach nieradykalnych, pozwala na uzyskanie prognozowanych przeżyć 5- i 10-letnich, wynoszących odpowiednio 39% i 24%. 2. Tolerancja leczenia napromienianiem dawką, wahającą się od 50 Gy do 64 Gy, frakcjonowaną klasycznie, obejmującą pozostałość guza z marginesem, jest dobra. 3. Wiek jest najsilniejszym czynnikiem prognostycznym u chorych na wysokozróżnicowane gwiaździaki mózgu, napromienianych po zabiegach nieradykalnych.

Key words: low-grade astrocytoma, radiotherapy, prognostic factors
Słowa kluczowe: wyskozróżnicowane gwiaździaki, radioterapia, czynniki prognostyczne

Introduction

Low grade astrocytomas account for 10-15% of primary adult brain tumours [1-3]. The management of low-grade cerebral astrocytoma is controversial. Surgery is usually attempted and either biopsy or subtotal or total excision is undertaken [4, 5]. Complete surgical resection is potentially curative. After subtotaly resected tumour, different polices are being pursued: planned immediate postoperative radiotherapy [2, 6, 7] or retreatment by surgery or radiotherapy on progression of the disease [8, 9]. Stereotactic irradiation has been used more often in treatment of low-grade gliomas [10].

At some institutions, nonresectable low-grade astrocytomas located in the brain stem are treated by interstitial implants ^{125}J or ^{192}Ir [11]. Currently, there is no proven beneficial effect of chemotherapy in the treatment of adult patient with newly diagnosed low-grade astrocytoma [12].

Materials and methods

119 patients with incompletely excised low-grade astrocytomas (WHO grade II) [13] irradiated between 1976 and 1993 at the Department of Radiation Oncology of Maria Skłodowska-Curie Memorial Cancer Center in Kraków, were retrospectively reviewed. The parameters monitored to determine clinical response to therapy included neurological function and performance status (according to EORTC/MRC scale and Karnofsky scale) [14, 15].

There were 61 female (51%) and 58 male (49%) patients with a median age of 36 years (range: 15-68). Headache was the most common presenting symptom in 80 cases (67%) at pretreatment examination, followed by seizures in 68 cases (57%), sensory or motor deficit in 50 cases (42%), nausea and vomiting in 31 cases (26%) and disturbances of intellectual functions or personality in 18 cases (15%). The distribution of sites of involvement was as follows: frontal 49 patients (41%), temporal 46 patients (39%) and occipital 24 patients (20%). Tumour was located in one lobe in 79 patients (66%), while in 40 patients (39%) tumour extended beyond one lobe. All patients underwent surgical resection aiming to remove as much tumoral tissue as possible with preservation of neurologic function. 77 operations (65%) were considered as subtotal resections and 42 (35%) as partial resections. The distribution of histologic types in the study population was as follows: 60 fibrillary astrocytomas (50%), 22 protoplasmic astrocytomas (19%) and 37 as gemistocytic astrocytomas (31%).

Before radiotherapy, performance status and neurological function were assessed. Karnofski score was superior or equal to 80% in 35 cases (30%), 70%-50% in 81 cases (68%) and 40% or less in 3 cases (2%). Neurologic function was assessed as very good in 7 patients (6%), good in 77 patients (65%), moderate in 32 patients (27%) and poor in 3 patients (2%)

All patients were treated with megavoltage gamma rays (^{60}Co). Radiotherapy was started one to five months (median 2 months) after surgery. The total dose ranged from 50 to 64 Gy (mean: 59.23 Gy) delivered with daily fractions of 1.6-2.5 Gy. The three-field technique (parallel-opposed lateral portals with wedges and anterior portal), or anterior and lateral portals with wedges were used. The treatment volume covered the tumour residual with a margin of (1-2 cm). The techniques of radiotherapy according to the total and fraction doses are given in Table I.

Results

Tolerance

The tolerance to treatment was assessed according to the following criteria: very good – treatment without complications, good – periodic symptoms of increased intracranial pressure controlled pharmacologically with no breaks in irradiation, poor – the above symptoms which caused breaks in irradiation or its discontinuation. The treatment was generally well tolerated. In 93 patients

Tab. I. The techniques of radiotherapy according to total and fraction doses of 119 patients with low-grade astrocytomas

Techniques of radiotherapy	Total dose	Fraction dose	No. of patients	%
three-field technique	50-64 Gy	1.6-2 Gy	108	91
anterior and lateral portals	50-60 Gy	2-2.5 Gy	11	9

(78%) tolerance to treatment was assessed as very good, in 25 patients as good. One patient had poor tolerance and radiotherapy was discontinued after the dose 56 Gy in 28 daily fractions.

During radiotherapy, 29 patients (24%) showed improvement in neurological function, in 89 ones (75%) neurological function was assessed as steady. In one case neurological function became worse due to progression of tumour.

Survival

Length of survival was measured from the day of surgery. The survival was estimated by Kaplan-Meier method [16]. Prognostics factor analysis included univariate and multivariate analysis. The Kaplan-Meier method and log rank test were used for univariate analysis, the Cox regression model was used for multivariate analysis [17, 18].

The overall actuarial survival rates at 5 and 10-years were 39% and 24%, respectively (Fig. 1).

The following characteristics were associated with improved patient survival by univariate analysis: age ≤30, very good neurological function before radiotherapy, fibrillary or protoplasmic histology, female gender (test log rank p≤0.05, Figs. 2-5). There was no difference in survival in respect to Karnofsky performance status, type and duration of symptoms, tumour location and volume, extent of surgical resection, interval between the surgery and radiotherapy, total dose. In Table II a univariate analysis of prognostic factors is presented. Multivariate ana-

Tab. II. Univariate analysis of prognostic factors

Factors	Relative risk	p	Actuarial 10-year survival	p
Age				
≤30 n=37	1.00	-	38%	0.0080
>30 n=82	1.85	0.0132	18%	
Gender				
female n=61	1.00	-	30%	0.0247
male n=58	1.62	0.0251	18%	
Performance status				
Karnofski ≥80 n=35	1.00	-	32%	0.0850
Karnofski <80 n=84	1.49	0.1032	20%	
Neurological function				
very good n=19	1.00	-	46%	0.0361
good.moderate.poor n=100	1.88	0.0605	20%	
Symptoms				
seizures n=68	1.00	-	24%	0.4256
others n=51	1.18	0.4264	22%	
Length of symptoms				
≥24 months n=36	1.00	-	19%	0.7585
<24 months n=83	0.93	0.7598	26%	
Localisation				
occipital n=24	1.00	-	33%	0.1342
frontal n=49	1.32	0.3571	23%	
temporal n=46	1.71	0.0816	21%	
Stage				
one lobe n=79	1.00	-	25%	0.9873
more than one lobe n=40	1.00	0.9875	24%	
Histology				
a. fibr. & protop. n=82	1.00	-	30%	0.0359
a. gemistocyticum n=37	1.62	0.0309	13%	
Surgery				
subtotal resection* n=77	1.00	-	27%	0.5179
partial resection** n=42	1.15	0.5216	19%	
Interval from operation to radiotherapy				
≤month n=51	1.00	-	22%	0.3350
>month n=68	0.81	0.3568	23%	
Total dose				
≥6000 cGy n=100	1.00	-	25%	0.9245
<6000 cGy n=19	0.97	0.9265	18%	

* subtotal resection: removal of the whole mass of tumour except that infiltrating deep brain structures

** partial resection: removal of only some parts of the tumour

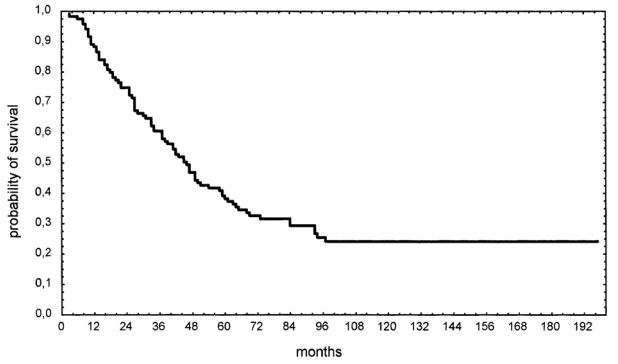

Fig. 1. Overall actuarial survival of 119 irradiated patients with incompletely excised low-grade astocytoma

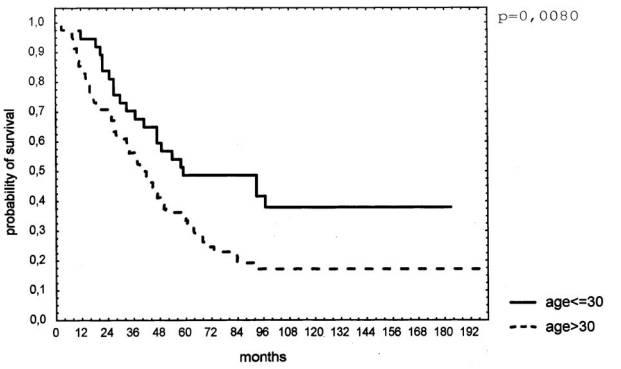

Fig. 2. Overall actuarial survival of 119 irradiated patients with incompletely excised low-grade cerebral astrocytoma according to age

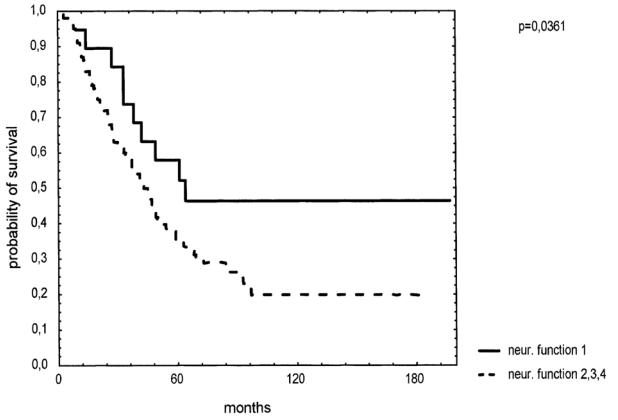

Fig. 3. Overall actuarial survival of 119 irradiated patients with incompletely excised low-grade cerebral astrocytoma according to neurological function (EOTRC/MRC scale)
neur. function 1 – very good neurological function
neur. function 2, 3, 4 – good, moderate and poor neurological function

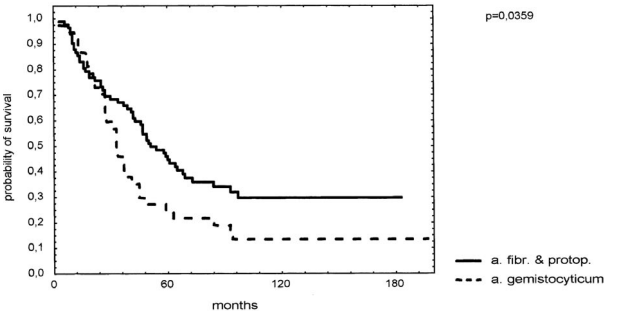

Fig. 4. Overall actuarial survival of 119 irradiated patients with incompletely excised low-grade cerebral astrocytoma according to histology

lysis showed that only age was correlated with survival time. Patients under 30 years of age carried the best prognosis. The definitive results of the Cox model are given in Table III.

Recurrences

Clinical progression was observed in 81 patients (68%). In 70 cases it was documented by CT and in 11 cases assessed only by neurological examination. Median time to recurrence was 34 months (range: 1-97 months). 10 patients underwent second operation. Malignant transformation occurred in 7 patients, radiation necrosis was found in one case, and in two cases the tumour was histologically similar in appearance to the specimen removed at the first operation.

Tab. III. The definitive Cox model

Factor	Relative risk	P-value	Confidence interval
Age ≤30	1.00	-	-
>30	1.85	0.0132	1.14-3.02

Discussion

The 5-year overall survival of all 119 patients in this series was 39%. This is worse, compared to survival rates reported by other institutions, which ranges from 44-65% (Table IV). Variability in the reported survival rates is likely due to patients heterogeneity. In most series, patients with pilocytic astrocytoma, low-grade oligodendroglioma and oligoastrocytoma were included, which carried better prognosis [1, 11, 19-23]. Some studies assessed adults as well as children and supratentorial or infratentorial localisation [1, 19, 21, 24]. Present materials consisting

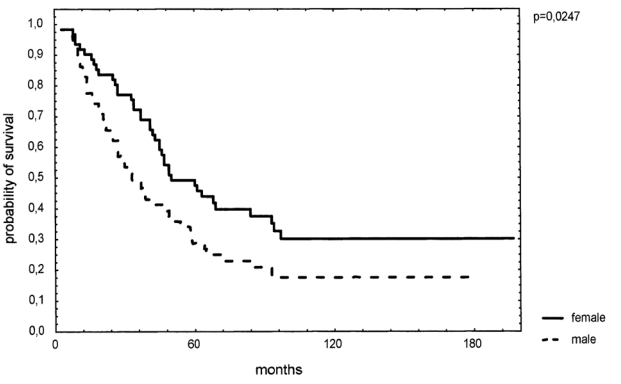

Fig. 5. Overall actuarial survival of 119 irradiated patients with incompletely excised low-grade cerebral astrocytoma according to gender

Tab. IV. Results of postoperative radiotherapy of patients with low grade astrocytomas

Author	No of patients	Total dose	Survival (%)	
			5-year	10-year
Leibel et al. 1975 [19]	71	35-50 Gy	46	35
North et al. 1990 [21]	66	50-55 Gy	55	43
McCormack et al. 1992 [20]	53	24-68 Gy	64	48
Shibamoto et al. 1993 [25]	101	41-66 Gy	60	41
Touboul et al. 1995 [11]	26	45-57.5 Gy	65	37
Bahary et al. 1996 [1]	43	50-60 Gy	67	-
Leighton et al. 1997 [24]	80	54 Gy	62	35
Rudoler et al. 1998 [33]	30	46.4-64 Gy	50	-
Present series	119	50-64 Gy	39	24

of patients with known negative prognostic factors may show relatively decreased survival.

Numerous prognostic factors have been reported for low-grade astrocytomas such as age, sex, performance status, neurological function, length and nature of symptoms, localisation, stage, histological subtype, proliferative potential of tumour, p53 mutations, markers of angiogenesis, CT contrast enhancement, extent of surgery, postoperative radiotherapy – but no consensus has been obtained [1, 19, 25-34].

Our results indicate that age is the principal variable determining the survival times of patients with low-grade astrocytomas. It was the only significant factor in multivariate analysis. The actuarial 10 year survival rates were 18% and 38%, respectively, for patients at ages above 30 years and 30 years or less ($p=0.008$). Several other studies had demonstrated better results in younger patients (the cut-off point seems to lie somewhere between 20 and 45 years of age), and confirmed the importance of age in treatment outcome [1, 21, 22, 24, 25, 30, 35-37]. In the series of 461 patients with supratentorial low-grade gliomas reported by Laws et al., 5- and 15-year survival rates were, respectively, 83% and 71% for patients at the age of 20 years or less compared to 35% and 11% for patients in age between 20 to 49 years ($p<0.0002$) [30]. An attempt has been made to explain favourable prognosis in younger patients by better tolerance of treatment: surgery as well as radiotherapy.

The parameters of neurological status showed prognostic influence on survival in univariate analysis of our series. Patients with very good neurological function before radiotherapy had better prognosis than others. The actuarial 10-year survival rate was 46% for patients with very good neurological function and 20% for patients with good, moderate and poor neurological function ($p=0.0361$). These findings agree with many other reports [20, 33, 34, 38]. However, comparison of own results with others is difficult due to differences of criteria used in assessment of neurological status. Correlation between neurological status and outcome indicates that treatment should not be delayed until progression.

In our material, the Karnofsky performance status did not significantly affect survival, similary to the results of Janny's et al. series [26]. On the other hand, there are a few reports, which point to the status performance as one of the most significant prognostic factors [11, 21, 22, 24, 35, 37]. We observed that performance status was a less important determinant of survival outcome than neurological function. This is consistent with result of randomised EORTC trial [38]. Assessment of status in patient with brain tumour by the Karnofsky score or WHO scale seems to be insufficient compared with neurological status. Neurological status appears to be more precise than performance status, which is assessed secondary to neurological function.

In the current series, in univariate analysis, sex was a statistically significant prognostic indicator, females fared better than male patients ($p=0.0247$). Some authors have also found gender to be a prognostic factor with improved survival times in females, while other reports have failed to find any significant impact of sex [1, 7, 21, 24, 26].

In the present study, patients with gemistocytic astrocytoma carried worse prognosis compared to patients with fibrillary or protoplasmatic astrocytomas. The actuarial 10-year survival rates were 13% and 30% respectively, for patients with gemistocytic astrocytoma and fibrillary or protoplasmic astrocytomas ($p=0.0359$). The gemistocytic astrocytoma has been associated with poor survival times in many others series, most likely due to the high incidence of dedifferentiation and malignant transformation [7, 19, 29]. In gemistocytic astrocytes, p53 mutations and low expression of bcl-2 are more often observed [39].

In the presented series seizures had no influence on prognosis. This is consistent with the study of Lote et al. who found that epilepsy was not a significant prognostic factor in patients with low-grade gliomas [40]. In con-

trast, North et al., Leighton et al. and Piepmier et al. reported that seizures as a presenting symptom were associated with better outcome [24, 34, 41]. Small tumours may cause epilepsy years before any other symptoms, and patients diagnosed with smaller tumours may be expected to live longer.

Length of symptoms did not result in any differences in survival (within the assessed range), similarly to other studies [11, 20, 21, 24, 37]. Some authors observed length of symptoms to have influence on outcome [23, 41]. Piepmer et al. found that patients presenting symptoms for more than 2 years had a significantly longer time to recurrence ($p=0.0001$) and survival ($p=0.0028$) compared with those with symptoms for less than 2 years [41].

Tumour localisation did not show a significant difference in outcome. Pipemer et al. studying a series of 55 patients with low-grade astrocytoma, observed that temporal lobe localisation was associated with significantly longer time to recurrence ($p=0.05$), but they failed to find significance for length of survival [41].

There were no differences between survival times in patients with tumour limited to one lobe and patients with tumour extended beyond one lobe. North et al. showed different results, patients with involvement of two or more lobes fared significantly worse than patients with involvement of only one lobe ($p=0.016$) [21]. According to Berger et al. a strong correlation between size of tumor and risk of recurrence and histological progression is observed [4]. Staging classification assessing the number of involved lobes seems to be imperfect, as it does not estimate diameter of tumor, crossing the midline and encroaching on the ventricular system. Karim et al. in a randomized trial, found that the „T" of the TNM classification appears to be one of the most important prognostic factors ($p<0.00001$) on multivariate analysis. The T parameter was significantly discriminant for prognosis of overall survival ($p<0.0001$) as well as prognosis free survival ($p<0.0001$) [38]. However, others did not find differences in survival according to tumor size [7, 26, 32].

The usefulness of surgery in the management of low-grade astrocytomas remains disputable. Some authors do not find advantage in removing them, whereas others do and emphasise the relationship between the survival time and the extent of resection [1, 4, 7, 11, 21, 24, 25, 37, 42, 43]. The impact of the extent of surgery is difficult to ascertain. Differentiation between gross total or subtotal operation is subjective and conducted with high risk of error. The extend of resection assessed by surgeons very often does not correlate with postoperative CT scans. The majority of patients with low-grade gliomas die of malignant transformation [31, 44]. About 13-85% of low-grade gliomas recur at a higher histologic grade [7, 9, 11, 21, 30]. Berger et al. suggest that the risk of recurrence is minimised when less residual tumour volume is present after surgery [4]. In our series, patients who underwent subtotal resection did not survive longer than those in whom the tumor was partially removed. It should be noted, however, that all operations were non-radical.

The interval from operation to radiotherapy (within the assessed range) had no influence on survival time in our series. The question whether to irradiate immediately after surgery or to delay treatment until progression, remains unsolved. The optimal treatment and its time for patients with low-grade gliomas is still controversial, but all these opinions are based on the results from retrospective clinical studies [1, 7-9, 19, 24, 29, 36, 41, 44, 45].

No differences in survival were found in patients who were treated with less than 60 Gy of radiation when compared with those treated with 60 Gy or more. This finding is consistent with the result of prospective randomised trial on dose-response in radiation therapy of low-grade cerebral glioma EORTC no 22844. For this study, 379 adult patients were included to receive irradiation postoperatively or postbiopsy, with either 45 Gy in 5 weeks or 59.4 Gy in 6.6 weeks, with daily fractions of 1.8 Gy. There was no significant difference in terms of 5-year survival (58% for the low-dose arm and 59% for the high-dose arm) or the 5-year progression free survival (47% and 50%), between the two arms of the trial [38].

The absence of dose-response and time-response may indicate that postoperative radiotherapy in patients with low-grade astrocytomas is ineffective, but only prospective study can assess the value of radiotherapy in this group. Currently, two prospective randomised trials (EORTC no 22845, RTOG no 9802) are in progress, which have been designed to define the role of postoperative radiation therapy for patients with supratentorial low-grade gliomas and to characterise any dose-response relationship.

Conclusion

1. Combined surgery and postoperative radiotherapy in patients with incompletely excised low-grade cerebral astrocytoma results in obtaining 5-year and 10-year overall actuarial survival rates in 39% and 24% of cases, respectively.
2. The tolerance of radical radiotherapy with total doses of 50-64 Gy delivered with classical factions, covering the tumour residual with a margin, is good.
3. Age is the most significant variable determining the survival of patients with incompletely excised low-grade astrocytoma. Patients under 30 years of age carried the best prognosis.

Jadwiga Nowak-Sadzikowska M.D.
Department of Radiation Oncology
The Maria Skłodowska-Curie Memorial Cancer Center
and Institute of Oncology
Garncarska 11
31-115 Cracov, Poland

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