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Yetişkin Düşük Dereceli Gliomlarda Sağkalım ve Prognostik Faktörler

Survival and Prognostic Factors in Adult Low-Grade Gliomas

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Özet

GİRİŞ ve AMAÇ: Pilositik olmayan düşük dereceli gliomlarda sağkalım değerlendirmek.

YÖNTEM ve GEREÇLER: 2003-2007 yılları arasında Ankara Onkoloji Eğitim ve Araştırma Hastanesinde (AOH) Düşük Dereceli Glial Tümör tanısıyla tedavi edilen 70 erişkin hasta geriye dönük olarak incelendi. Genel Sağkalım (GSK) tahminleri Kaplan Meier ile yapıldı.

BULGULAR: Ortanca yaş 37.5 (aralık; 20-73) ve erkek çoğunlukdaydı (erkek/kadın: 1.26). Ortanca takip süresi 39 aydı (aralık; 4-79). Cerrahi sonucu hastaların %54'ünün saf astrositom, %21'inin oligodendrogliom, %10'unun ise oligoastrositom olduğu belirlendi. Hastaların 44'üne (%63) subtotal rezeksiyon (STR), 19'una (%27) gross total rezeksiyon (GTR) ve 7'sine (%10) biopsi uygulandı. Başvuru şikayeti sıklık sırasıyla başağrısı, nöbet ve motor bozukluktu. Cerrahi ile radyoterapi arasındaki ortanca süre 7 hafta olup, 3 hafta ile 78 hafta arasında değişmekteydi. Ortanca GSK 71 ay (aralık, 4-80 ay) olarak bulundu.

TARTIŞMA ve SONUÇ: Sağkalım; yaş, cinsiyet, tümör boyutu, histolojik tip ve cerrahi sonrası radyoterapi başlama zamanından istatistiki olarak anlamlı derecede etkilenmemiştir. Karnofsky Performans skorunun (KPS) 70'in üstünde olması istatistiksel olarak anlamlı iyi prognostik faktördür ($p < 0.001$).

Anahtar Kelimeler: Düşük dereceli gliomlar, Radyoterapi, Prognostik Faktörler, Genel Sağkalım

Abstract

INTRODUCTION: The purpose of this study was to evaluate survival in patients with nonpilocytic low-grade gliomas (LGGs).

METHODS: Records of 70 adult patients with LGGs diagnosed between 2003 and 2007 at Dr Abdurrahman Yurtarslan Oncology, Education and Research Hospital (AOH), Ankara, Turkey, were retrospectively reviewed. The Kaplan-Meier method estimated overall survival (OS).

RESULTS: Median age at diagnosis was 37.5 years (range; 20-73) with a slightly higher male predominance (male / female: 1.26). Median follow-up was 39 (range, 4-79) months. Operative pathology revealed pure astrocytoma in 54% oligodendroglioma in 21%, and oligoastrocytoma in 10% of patients. Subtotal resection (STR) was achieved in 44 patients (63%), gross total resection (GTR) in 19 (27%), and biopsy only in 7 (10%). Presenting symptoms in order of frequency were headache, seizure and motor disturbances. Median time interval between surgery and radiotherapy was 7 weeks ranging from 3 to 78. Median OS was 71 months (range, 4-80 months).

DISCUSSION AND CONCLUSION: Survival was not significantly influenced by age, gender, extent of resection, tumor size, histology and time interval between surgery and radiotherapy. Statistically significant good prognostic factors for OS was Karnofsky Performance Status (KPS) > 70 ($p < 0.001$).

Keywords: Low-grade gliomas, Radiotherapy, Prognostic factors, Overall survival

INTRODUCTION

Low grade gliomas (LGGs) are World Health Organization (WHO) grade 1 and 2 tumors of neuroepithelial origin. They account up to 10-20% of primary central nervous system (CNS) tumors (1). Grade 1 tumors are well-circumscribed; they usually can be cured via surgical intervention and are not the subject for this report (2). The most common grade 2 gliomas are astrocytomas, oligodendrogliomas, and mixed tumors (3). They usually present with neurologic symptoms mainly headache and seizures between the second and fourth decades of life (4). A recently published study demonstrated the growing incidence of LGGs in elderly (5). T2-weighted or fluid attenuated inversion recovery (FLAIR) conventional magnetic resonance imaging (MRI) can best delineate the extent of disease and is the gold-standard (6).

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LGGs have low proliferation index, heterogeneous clinical behavior and are infiltrative in nature (4, 7-12). Patients are 17-49% alive at 10 years (7). Optimal management is crucial for successful patient outcomes in terms of efficacy and long term safety and is still controversial (4). The effect of the extent of resection on survival remains uncertain despite decades of use, but it is at least necessary to provide tissue for histopathologic diagnosis (4).

The role of radiotherapy (RT) was well-defined with a few randomized trials. Immediate and higher doses of RT did not bring overall survival benefit (9-11). Chemotherapy (Procarbazine-Lomustine-Vincristine (PCV) and Temozolomide (TMZ)) can be used at progression and/or as an initial adjuvant treatment. Oligodendroglial and mixed histologies and apart from this 1p and 19q deleted ones are likely to respond well to chemotherapy (13-17). The rationale and potential role of targeted therapies are under investigation.

Several factors have been reported to affect the outcome. Some of these were age, performance status, tumor size, tumor location, extent of resection, history of seizures (4, 7-10). They were focused to some extent in different series.

We analyzed our own cohort of patients with grade 2 LGGs treated at AOH where adjuvant RT is a common practice in terms of survival function and prognosticators.

MATERIALS AND METHODS

In the present study, we reviewed retrospective analysis of 70 adult patients aged 18 years or older diagnosed as LGG (grade 2 according to 2007 WHO classification) treated with radiation therapy at Ankara Oncology Hospital Radiation Oncology Clinic between January 2003 and December 2007. Data was obtained from patients' medical charts and RT documents. Patients were included only if they had pathologic confirmation and had their follow-up at our institution. Since postoperative imaging was very scarce, the extent of resection was assessed mainly by the operation report of the neurosurgeon.

RADIATION THERAPY

During the study period, all the subjects were treated with surgery plus radiation therapy. RT was generally initiated within 2 months after surgery. All the patients were immobilized in a fixed position with custom-made thermoplastic masks. They received external beam radiotherapy (EBRT) with localized fields. A 2 cm margin was added to the low density area on preoperative computed tomography (CT) or high signal intensity area on T2-weighted MRI to obtain Clinical Target Volume (CTV). Total dose prescribed was usually 54 Gy in 27 fractions administered daily.

STATISTICAL ANALYSIS

Patient demographics, survival, prognostic factors, and timing of RT were analyzed. Survival was calculated from the date of pathologic confirmation to the date of last observation and death. The collected data were evaluated using Statistical Package for Social Sciences (SPSS) for Windows 11.5. Overall survival (OS) was estimated using Kaplan-Meier method. Because of the prognostic importance in prior studies, we examined age, gender, preoperative tumor size, extent of surgery, histologic subtype, and Karnofsky Performance Status (KPS) as potential prognostic factors affecting survival, and the difference was tested for statistical significance by the log-rank test. Cox regression analysis was used to evaluate association of radiotherapy timing with OS.

RESULTS

Demographic information, prognostic factors affecting survival for adult patients with LGG are presented in Tables 1 and 2.

Table 1 : Patient Demographics

Variable	Value (n = number of patients)
Gender:	
Male	n = 39 (56%)
Female	n = 31 (44%)
Age at Diagnosis	
Mean	39
Median	37.5
Seizures at Diagnosis	n = 35 (50%)
Headache at Diagnosis	n = 32 (45%)
Motor Deficit at Diagnosis	n = 21 (33%)
KPS	
≤ 70	n = 15 (21%)
> 70	n = 55 (79%)
Tumor Size (cm)	
≤ 5	n = 41 (59%)
> 5	n = 29 (41%)
Extent Of Surgery	
GTR	n = 19 (27%)
STR	n = 44 (63%)
Biopsy	n = 7 (10%)
Histology	
Astrocytoma	n = 38 (54%)
Oligodendrioglioma	n = 15 (21%)
Mixed Glioma	n = 7 (10%)
Subtype Undetermined	n = 10 (14%)
Radiotheraphy Timing	
Mean	10 Weeks
Median	7 Weeks
Range	3 - 78 Weeks
Total Radiation Dose	
Mean	52.8 Gy
Median	54 Gy
Range	4 - 60 Gy

Abbreviations: KPS; Karnofsky Performance Status

Table 2. Prognostic factors effecting survival

Variables	N	Crude Survival	1-Year	5-Year	Mean life expectancy (95% Confidence Interval)	Log-Rank	P
Age						0.81	0.369
≤ 40	42	48.3	93.1	60.6	54.5 (44.0 -64.9)		
> 40	28	47.1	64.7	47.1	43.5 (28.2 - 58.7)		
Gender						0,01	0,945
Male	39	48.0	88.0	58.1	51.3 (40.2 -62.1)		
Female	31	47.6	76.2	52.4	48.9 (34.5 -63.4)		
Resection Type						2.86	0,091
GTR	19	61.4	100.0	74.6	65.5 (52.6 -78.4)		
STR	44	41.9	77.4	48.4	44.5 (33.7 -55.4)		
Biopsy	7	0.0	-	-	9.0 (9.0 -9.0)		
Tumor Size						1.47	0.226
≤ 5 cm	41	54.5	90.9	72.7	58.9 (47.1 -70.7)		
> 5 cm	29	44.4	83.3	40.4	45.1 (31.4 -58.7)		
Histology						0.01	0.993
Pure astrocytoma	38	50.0	80.8	52.0	48.8 (36.9 -60.7)		
Oligodendroglioma	15	41.7	75.0	58.3	48.2 (31.7-64.7)		
Oligoastrocytoma	7	50.0	100.0	50.0	-		
KPS						22.8 <	0.001
≤ 70	15	11.1	44.4	-	17.0 (8.7 -25.3)		
> 70	55	60.0	94.3	70.1	60.2 (51.2 -69.2)		

Abbreviations: N;Number of patients, GTR; gross total resection, STR; subtotal resection, KPS; Karnofsky Performance Status

Total of 70 adults with LGG WHO grade 2 treated at AOH were reviewed. The median follow-up

was 39 months (range, 4-79) and median OS was 71 months (range, 4-80 with 95% CI). The 1 and 5-year OS rates were 85% and 57%, respectively. Median age at diagnosis was 37.5 years ranging from 20 to 73. Male to female ratio was 39 / 31 and male gender was slightly predominant. According to the largest diameter measured on preoperative CT images, 59% of the patients (n = 28) had tumors smaller and/or equal to 5 cm. All of the patients had supratentorial tumors, and the parietal lobe was the most frequent (38%) site followed by the frontal lobe. All of the cohorts had definite LGG diagnosis pathologically and among them astrocytoma was the largest histologic subgroup (n = 38, 54%), followed by oligodendroglioma (n = 15, 21%) and mixed glioma (n = 7, 10%). Procedure types as determined by the neurosurgeon were subtotal resection (STR) (n = 44, 63%), gross total resection (GTR) (n = 19, 27%) and biopsy (n = 7, 10%). Before the radiation therapy, functional status was evaluated according to KPS scale. KPS was ≤ 70 in 15 patients and > 70 in 55.

EBRT was used in 2 Gy/fraction to a total dose of median 54 Gy (range, 4-60) after surgery within a median of 7 (range, 3-78) weeks. During the follow-up, 10 patients had recurrence, and they either had surgery (n = 7) or re-irradiation (n = 3). None of the patients received chemotherapy.

Age, gender, extent of resection, tumor size, histological subtype, and performance scores were analyzed for their association with survival. Sixty percent of the patients (n = 42) were younger than 40 years of age. One and 5-year OS rates for patients under age 40 were 93% and 61% and over age 40 were 65% and 47%, respectively. There was no significant difference between the age groups (p = 0.369).

Gender was examined as a prognostic factor and no significant difference in survival was found by Kaplan-Meier log-rank test.

The impact of the extent of resection on survival was analyzed for subtotal, gross total resected and biopsied patients. One and 5-year survival in total excision group were 100% and 75% compared to the 77% and 48% in subtotal resection patients (p = 0.091).

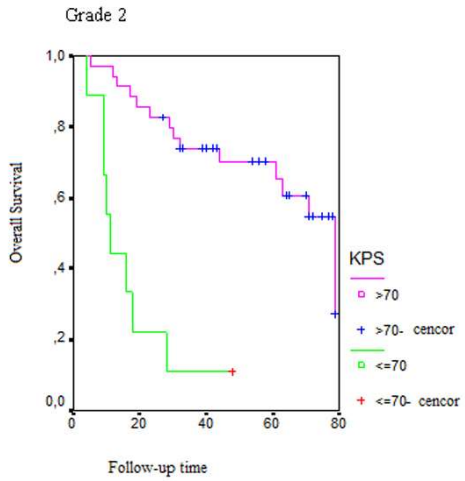
Preoperative CT was the main radiological imaging modality, 61 patients had CT scan (87%) and 9 had MRI (13%). Data obtained from MRIs were considered missing because assessment of tumor size was done primarily by hypodense, nonenhancing tumor on diagnostic CT scans. One and 5-year survival were 91% and 73% in patients with tumor size ≤ 5 cm; 83%, and 40% in patients with tumor size > 5cm, which is not statistically significant (p = 0.226).

No significant difference in survival was noted between the patients with astrocytoma, oligodendroglioma, and mixed group by log-rank test. One and 5-year OS rates were 81% and 52% (n = 38); 75% and 58% (n = 15); 100% and 50% (n = 7), respectively.

KPS was scored postoperatively at admission to the Radiation Oncology Clinic. Our data showed that performance status is a prognosticator of survival (p < 0.001). The patients with minimal or no deficits (KPS > 70) had better prognosis. Kaplan–Meier curve of survival difference according to a performance status (KPS) was presented in figure 1.

Time interval between surgery and the first day of RT was analyzed for its effect on survival. Delaying RT does not impact survival. (RR = 1.002 (0.962-1.043 CI:95%))

Figure 1: Kaplan-Meier curve for OS by KPS performance status



DISCUSSION

In the present study, we report an analysis of data of supratentorial LGGs in 70 adult patients with the primary aim to evaluate the prognostic factors of LGGs on OS.

In our study, all the patients underwent surgical intervention at least for histologic confirmation and had postoperative radiotherapy.

The 5-year OS rates of LGGs in randomized studies range from 58% to 72% (8-10). Patients can survive up to 20 years according to the Surveillance, Epidemiology, and End Results (SEER) data collected between 1973-2001 (18). Despite decades of its use, there are still concerns about long-term toxicity of postoperative RT. Some advocate early RT because they respond well to radiation (19), which makes it therapeutic in case of symptomatic patients complaining mass effect and seizures (19, 20).

Different variables were described as potential factors affecting survival (6, 7, 11). Low-risk and high-risk prognostic grouping was done in European Organization for Research and Treatment of Cancer (EORTC) trials (8, 9). Risk factors from the EORTC prognostic index were: histology, tumor size, neurologic deficit, age, and tumor crossing the midline. The high-risk group was defined as patients with more than two risk factors. Median OS for low-risk patients were 7.8 years, and it was 3.7 years for high-risk ones.

LGGs occur in patients with a median age of 40 years. Younger age was found to be as a positive prognostic factor in many retrospective series (7, 11, 18, 20) and prospective series (8-10). The 5-year OS in the present study was 59.4% for age younger than 40, and 54.5% for older. However, the difference was not statistically significant probably because of the relatively smaller number of the patients enrolled in this study.

Although some survival benefit was achieved towards GTR, we found no statistically significant correlation with the type of resection. In many retrospective and 3 large prospective series, survival advantage was noted with increased extent of resection (7). Because of the non-enhancing nature of LGGs and scarcity of postoperative tumor volume determination with imaging technics, the extent of resection is mainly evaluated by the neurosurgeon.. To date, no randomized trials have been conducted regarding the role of early versus delayed surgery, and it does not seem possible in the future from the ethical point of view. Nonetheless, total excision was possible only in 56/156 of patients, where the extent of resection was measured by the use of intraoperative MRI (24). However, surgery is mandatory for accurate histologic subtype, grade and to determine the molecular status, which is therapeutic and prognostic. Under these circumstances, the use of brain mapping techniques are well advised in terms of increased extent of resection and decreased post-operative deficits (25-27).

Role of RT was investigated in a few randomized studies. EORTC 22844 and North Central Cancer Treatment Group (NCCTG) questioned different schemes of radiation (8-10). They showed no survival advantages and increased toxicity for higher versus lower doses. EORTC 22845, which is known as 'Non-Believers Trial', investigated the timing of RT: early or delayed (9). Background for this phase 3 randomized trials was because of the indolent nature of the disease and long-term side effects of radiation; some clinicians advocated delaying RT until the time of progression (9). At the end of median 7.8-years follow-up, early RT lengthened progression free survival, controlled seizures but did not impact OS. Our data are

consistent with the findings of EORTC trial, where delaying RT had no impact on OS. It must be noted that LGGs are slow growing tumors, and the survival may be observed to be different from the disease-free survival only after years of follow-up.

The findings of our cohort have reaffirmed the importance of performance status as a previously identified prognostic variable in other series. The results of completed and ongoing prospective trials with long-term follow-up will help to understand gliomagenesis so that best treatment strategy could be achieved.

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