Low-grade Astrocytoma

A Retrospective Analysis of 102 Patients

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Acta Oncologica Vol. 38, No. 8, pp. 1051–1056, 1999

One hundred and two patients (57 males, 45 females, median age 17 years) with histologically proven low-grade astrocytoma (grades I, II) treated between 1978 and 1994 were retrospectively analyzed at the King Faisal Specialist Hospital & Research Center. Microscopic investigation showed 50 patients (48%) with grade I tumors as opposed to 52 patients (52%) with grade II tumors. Fifteen patients (15%) had complete surgical excision, 55 (52%) had partial excision and 32 (31%) had biopsy only; 68 patients (66%) received external radiotherapy with a median dose of 54 Gy (range 45–68.5 Gy). With a median follow-up of 3.3 years, the 5 and 10 years' overall actuarial survival rates were 78% and 62%, respectively while the progression-free survival rates at 5 and 10 years were 69% and 35%, respectively. Age and performance status were significant prognostic factors in terms of overall survival on univariate ($p = 0.05$ and 0.05, respectively) and multivariate analysis ($p = 0.005$ and 0.006, respectively).

Received 21 May 1999
Accepted 1 June 1999

Brain astrocytomas include a wide spectrum of tumors with different morphology and clinical behavior. Low-grade astrocytomas are a clinico-pathologically diverse group of central nervous system neoplasms, often referred to as benign, and are known to have a relatively prolonged natural history.

The management of low-grade astrocytoma is not clearly defined. Complete surgical resection, if feasible, is thought to be the treatment of choice (1–3). However, the role of radiation therapy in incompletely excised astrocytomas is still unclear (2, 4–10).

Several studies have investigated the indications for surgery and radiotherapy and the relative significance of factors affecting postoperative survival (3, 8–17), but the number of randomized studies has been insufficient to optimize the use of these two modalities. Current therapeutic recommendations are based on the limited number of retrospective studies that have been reported. The extent of surgery and the radiation techniques, including the radiation dose and volume, still needs to be defined for each tumor site.

The King Faisal Specialist Hospital & Research Center (KFSH) opened in 1975 and is a tertiary referral center for 174 public hospitals and numerous private clinics in Saudi Arabia. It is the main oncology center for the whole Kingdom of Saudi Arabia, covering a large geographic area. The median distance from sites of referral to KFSH is approximately 350 km, which explains the difficulty with follow-up. According to the 1997 hospital-based tumor registry, brain tumors account for 4.6% of all malignant tumors referred to the Oncology Service, 67% of which are astrocytomas. Brain tumors are actively treated with surgery at other local hospitals, but radiation therapy facilities are in short supply in almost all other hospitals and patients are subsequently referred to KFSH for further management. Around 40% of referred patients had surgery at the referring hospital, 50% of whom were subjected to a second surgical procedure at KFSH in order to achieve complete resection whenever it was considered possible. In this retrospective study, the efficacy of different treatment modalities and the effect of different potential prognostic variables influencing the disease outcome were analyzed.

MATERIAL AND METHODS

One hundred and two patients treated for low-grade astrocytomas of the brain at the KFSH & RC between 1978 and 1994 were analyzed retrospectively. Patients with optic glioma were excluded and are being reviewed in a separate study. All patients had a histologic diagnosis of astrocy-

 ISSN 0284-186X

toma grade I or II according to WHO criteria as assessed by our pathology department. Histologic slides were not re-reviewed for the purpose of this publication.

Medical records were reviewed for age, sex, performance status, presenting symptoms and signs, laboratory and radiological findings and treatment received. All patients had basic laboratory investigations including complete blood picture and screening profile. They all had CT scans of the brain at the time of diagnosis, some patients also had MRI of the brain. Follow-up CT scans and MRI were all evaluated for tumor response and detection of recurrence or tumor progression.

Survival analysis

Survival from the time of diagnosis was the endpoint of this study. The Kaplan–Meier method was used for survival analysis. Multivariate analysis was done using Cox's regression method. Patients still living at last the follow-up review were censored from the analysis as of the date last known alive.

RESULTS

The median age of the whole group of patients was 17 years (range 1–65 years) and the group included 57 males and 45 females with a male : female ratio of 1.2 : 1. Headache was the most common presenting symptom encountered in 70 patients (68%), followed by motor symptoms and vomiting in 41 (40%) and 38 patients (37%). Seizures were noted in 25 patients and behavioral changes in 8 patients.

Eighty patients had a performance status (WHO classification) of 0–2, while the remaining 22 patients had 3–4. Cerebral hemispheric tumors were encountered in 41 patients (41%), mainly in the frontal and the parieto-temporal regions (10 patients each). The thalamus was the second and the cerebellum the third most common sites for presentation, accounting for 24% (25 patients) and 20% (21 patients), respectively. Tumors of the brain stem accounted for 12.6% (13 patients). Two patients presented with pineal astrocytomas.

Seventy patients (70%) underwent surgery: 15 (15%) had complete surgical excision, 55 partial excision (52%), and 32 patients (31%) had biopsy only. VP shunts were placed in 48 patients (47%); 50 patients (48%) had grade I tumors and 52 (52%) had grade II tumors. Radiotherapy was delivered to 68 patients (66%): 29 patients were treated with radiation alone (after biopsy), whereas the remaining 39 patients received post-operative irradiation. Out of the 68 irradiated patients, only 2 had complete gross surgical excision. The radiation dose varied between 45 and 68.5 Gy with a mean dose of 54 Gy. Two parallel opposing fields were applied in 58 patients (85.5%) and a multiple-fields technique was used in 10 patients (14.5%). The radiotherapy treatment volume included the whole brain in 4/68 patients, whole brain followed by a localized boost in 10/68, while the remaining 54 patients received a localized field only.

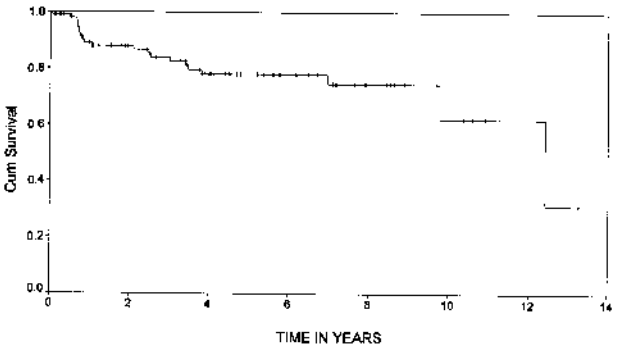

Fig. 1. Overall survival for the whole group (102 patients).

SURVIVAL ANALYSIS

The 5 and 10 years' actuarial overall survival rates (OS) for the whole group were 78% and 62%, respectively (see Fig. 1). While the progression-free survival (PFS) rates at 5 and 10 years were 69% and 35%, respectively (Fig. 2). Both survival endpoints were analyzed with respect to the different treatments applied and with the different prognostic factors.

Age was a highly significant factor in terms of overall survival ($p = 0.05$). Overall, younger patients did much better. In patients < 18 years of age, the 5 and 10 years' overall survival figures were 86% compared to 66% and 39%, respectively for older patients (Fig. 3). The corresponding PFS rates at 5 and 10 years were 71% and 44% for those < 18 years compared with 65% and 24%, respectively in older patients. However, this difference did not reach statistical significance ($p = 0.4$) (Fig. 4).

Patients with a better performance status had a significantly better outcome in terms of OS. Patients with a performance status of 0–2 had a 5- and 10-year survival of 81% and 65%, respectively compared with 63% and 0%, respectively in patients with performance status of 3-4 ($P = 0.05$). The same trend was observed for PFS (71%

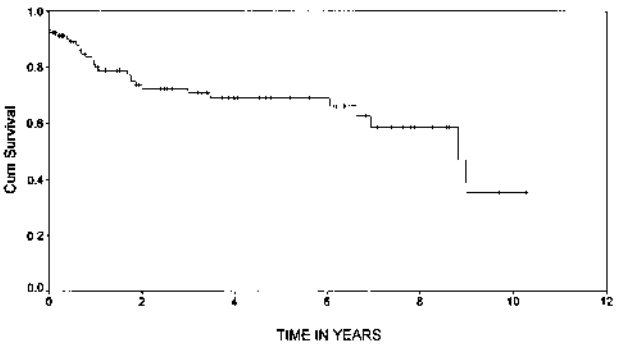

Fig. 2. Progression-free survival for the whole group.

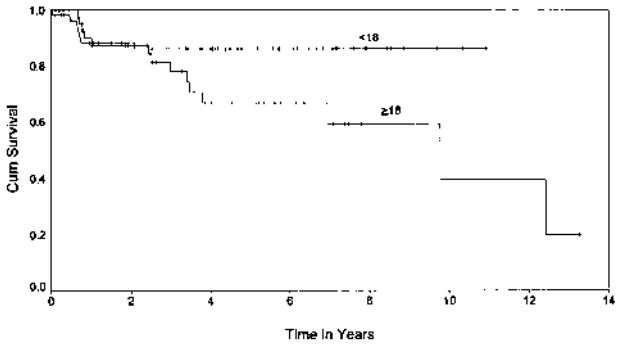

Fig. 3. Overall survival with age (< 18 years, n = 54; ≥ 18 years, n = 48)

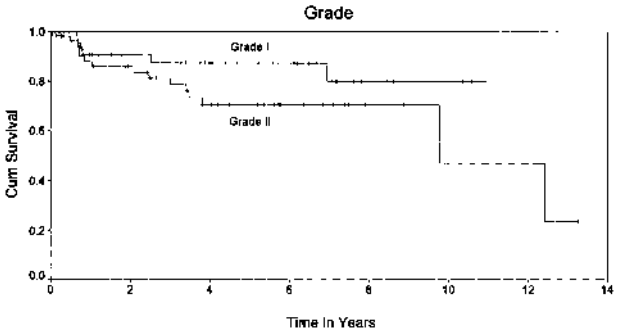

Fig. 5. Overall survival with histological grade (grade I, n = 50; grade II, n = 52)

and 35% vs. 67% and 0%, respectively) but with no statistical significance (p = 0.5).

Histological grade was not a statistically significant prognostic factor for OS and PFS, though patients with grade I tumors did better than patients with grade II tumors. Patients with grade I tumors had a 5- and 10-year OS of 87% and 80%, respectively, while patients with grade II tumors had a 70% and 47% OS, respectively (p = 0.1) (Fig. 5). The 5- and 10-year PFS were 76% and 31% for grade I and 62% and 36% for grade II, respectively, the difference not being statistically significant (p = 0.3) (Fig. 6).

Analyses of the OS and PFS were carried out in correlation with the treatment modality, patients treated with surgery alone did better in terms of OS (93% and 86% at 5 and 10 years, respectively) followed by patients treated with combined surgery and XRT (74% and 37%, respectively). The lowest OS figures were noted in patients treated with XRT alone (60% at 5 years and no survivors at 12 years). The difference between the three treatment modalities was statistically significant (p = 0.03). The same trend was observed in terms of RFS, however, with no statistically significant difference (p = 0.1).

On multivariate analysis, younger age and better performance status were the only two significant prognostic factors predicting for better overall survival (P = 0.005, 0.006 respectively).

Treatment results by tumor site

Thalamic tumors constituted 25% of this series (25 patients). They all underwent surgery: biopsy only (8), complete resection (3) and partial resection (14).

The median age for patients with cerebellar gliomas (n = 21) was 13 years (range 3–34 years). The treatment was primarily surgical. Eight patients had complete tumor excision and are still alive with no evidence of disease at 10 years.

Thirteen patients had brain stem glioma, 9 had biopsy and 4 had partial resection. Eleven patients received radical radiation with 54 Gy median dose (range 50–68 Gy). Overall, 6/13 (46%) patients were alive at 5 years with no survivors at 10 years with 36 months' median follow-up. The median time to disease progression/recurrence was 17 months from treatment.

In the 41 patients with hemispheric gliomas, 7 were treated with surgery alone and 34 patients irradiation following either biopsy (11), partial (20) or complete resection (3). Overall, 10/41 patients had recurrent/progressive disease.

The best results were obtained in patients with thalamic tumors with 90% and 81% OS rates at 5 and 10 years, respectively. For cerebellar tumors, the OS figures were 100% and 50% at 5 and 10 years, respectively. Cerebral hemispheric tumors had 69% OS at both 5 and 10 years.

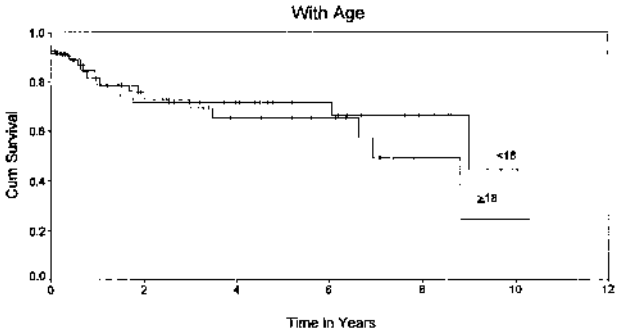

Fig. 4. Progression-free survival with age.

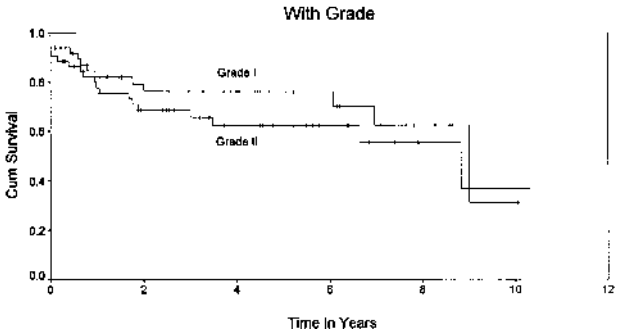

Fig. 6. Progression-free survival with histological grade.

Table 1

Disease progression with treatment modality

	Patients n	Progressed n	%
Complete excision + XRT	2	0	0
Incomplete excision + XRT	37	14	38
Biopsy only + XRT	29	9	30
Complete excision + no XRT	13	1	8
Incomplete excision + no XRT	18	7	33
Biopsy only + no XRT	3	1	33
Total	102	32	100

The lowest survival figures were seen in tumors of the brain stem, with 46% at 5 years and no survivors at 10 years.

Tumor progression and treatment modality

Out of the 102 patients, 32 patients had disease progression of their tumors. This was correlated to the different treatment modalities (results are shown in Table 1).

DISCUSSION

The primary treatment of low-grade astrocytomas is complete surgical excision whenever feasible. In most centers, it is generally agreed that postoperative radiation therapy is not indicated following gross total resection (2, 3, 6, 10, 14, 18, 19). However, in the case of incomplete excision, the proper management is still unclear. A confounding issue is the indolent history of some of these tumors, which may remain stable for long periods with incomplete surgery alone or even without therapy. This is particularly true in the pediatric age group. Furthermore, many of the published retrospective analyses lump the treatment results of different sites, despite the variations in tumor behavior and outcome according to the site and anatomic location, making the data difficult to interpret (7, 10, 17, 18). The value of adjuvant radiation therapy after subtotal resection is not clearly defined and remains controversial. Whereas a number of reports demonstrate a beneficial effect of postoperative radiation following incomplete excision (2, 4, 6–9, 18), others failed to demonstrate this effect (2, 5, 14, 18, 19). While the impact of radiation upon survival is suggested in unresected central diencephalic tumors (6, 7, 19–21), in most series no radiotherapy advantage could be demonstrated in low-grade cerebellar and cerebral hemispheric gliomas (5, 10, 12, 14, 19, 20, 22). In fact, recent reports indicate total resection in up to 90% of hemispheric low-grade gliomas and low recurrence rates (3, 20). The beneficial effect of postoperative radiation after subtotal excision in supratentorial low-grade glioma was difficult to demonstrate, except in a few studies where a survival advantage was limited to adult patients above the age of 40 (2, 3, 8, 18). To the best of our knowledge, no prospective randomized study comparing adjuvant postoperative radiotherapy to delayed radiotherapy for treatment of progression or recurrence has been completed.

In the present study, only 15% of our patients had complete surgical excision, while the remaining 85% had either biopsy alone or incomplete excision. Radiation therapy was delivered to 68 patients and was the sole mode of treatment following biopsy in 29 patients. Only 2 patients with complete surgical excision received postoperative radiotherapy. Our results show a better 5- and 10-year overall survival for patients who had surgery alone (total or subtotal resection) compared to those treated by surgery followed by postoperative irradiation or biopsy plus radical radiotherapy. These findings are similar to those reported in other retrospective analyses (3, 8, 10, 15–17, 23). These results, however, are likely to be biased and should be interpreted with caution, since patients treated by surgery alone tend to have selectively smaller resectable tumors, typically peripherally situated, and also a better performance status, rendering complete surgical excision much more likely. On the other hand, patients referred for radiation are likely to have large and more centrally located tumors and to have had less extensive surgical procedures. For the latter type of tumors, some authors advocate a stereotactic biopsy only followed by radical radiotherapy and claim similar survival results to those achieved by a more radical surgery (11, 12). Applying this philosophy to the treatment of low-grade astrocytomas, Lunsford et al. (11, 12) reported a median survival of >10 years. Laws et al. (2) reported in their series of 461 adults and children with low-grade supratentorial astrocytomas that total resection was related to a much higher survival rate than biopsy or subtotal removal. Similarly, Leibel et al. (6) reviewed 108 patients with incomplete resection and noted that the overall recurrence-free survival rate for incomplete resection plus radiotherapy was 46 vs. 19% for incomplete resection alone.

The optimum radiation dose administered is another important factor that could affect the prognosis (2, 3, 23, 24). Dose-response data indicate improved disease control beyond 45–50 Gy (24). In our study, the mean radiation dose was 52.5 Gy with a range between 45 and 68.5 Gy. This value could be considered suboptimal by some investigators. Shaw et al. (3, 15) showed that patients receiving total radiation doses >53 Gy had significantly better 5- and 10-year survival rates when compared to those receiving <53 Gy. In the present study as well as in some other series (6, 8), multivariate analysis showed that neither the radiation volume nor total doses >45 Gy demonstrated any significant association with survival. Some recent studies, however, suggest that precision volume radiation techniques, including fractionated radiosurgery, three-dimensionally planned conformal therapy, or stereotactic iridium implants, may improve the results of radiation therapy in central gliomas (16, 25).

In the current study, as in many other series (2, 18), the histologic grade had no impact on survival, with little difference in survival between grade I and II astrocytomas.

In our series, age and performance status proved to be the two most important prognostic factors, affecting overall survival in multivariate analysis. This is in complete agreement with other series in which better survival is related to good performance status, young age and a lack of major postoperative neurologic deficits (2, 3, 5, 6, 9, 18, 23). In the Mayo Clinic series (2) these variables were all significant, but age was found to have an overwhelming effect on outcome, eclipsing all other variables and all forms of management. It appears that these tumors have a different biological behavior in a young host.

The median age in our series is 17 years, which reflects the fact that 50% of the population in Saudi Arabia are under the age of 16. This in itself may have contributed to a better survival rate for the whole study group. The age distribution in our patient population also explains the preponderance of infratentorial tumors.

Analysis of our survival data according to tumor site showed a high survival rate for patients with thalamic tumors as compared to the reported 33–60% survival in other series (21, 24, 26, 27). This can be explained by the fact that all thalamic tumors in the current series were verified histologically to be low-grade gliomas. Recurrence was not seen in patients with completely resected thalamic tumors. As in other series (1, 10), there appears to be no difference in survival between patients with partially resected tumors and those with biopsied tumors, nor between patients who did or did not receive irradiation. Whereas a number of reports demonstrate a beneficial effect of radiation therapy in thalamic low-grade gliomas (6, 7), no clear-cut benefit of radiation therapy could be demonstrated in other series (26, 27). This has led some authors to advocate radiation therapy only for patients with evidence of disease progression (6).

In cerebellar low-grade glioma, therapy is primarily surgical. The cure rate with complete resection is high and recurrence is rare (5, 18, 22, 28). For patients with partial/subtotal resection, there is no advantage in disease-free or overall survival for those who received postoperative irradiation.

Within the brain stem low-grade gliomas, patients with mid-brain tumors did better than those with pontine or medullary tumors. This finding is in agreement with other series (4, 19, 27, 29). The median time to recurrence was 10 months.

The 5- and 10-year actuarial overall survival rates obtained in our series (78% and 62%, respectively) are in accordance with the figures published in the recent literature (3, 13, 16–18). However, these figures are notably higher than those reported in most of the older series (i.e. before 1975) (6). In our opinion, apart from the age factor mentioned already, this survival improvement is mainly attributed to the widespread use of modern imaging techniques such as CT scanning and MRI in the diagnosis and follow-up of these patients. Recent advances in micro-surgical techniques not only have permitted more resections, but also have substantially reduced the operative risks and mortality (2, 3, 24, 30). Furthermore, the inclusion of cerebellar astrocytomas may have contributed to the higher survival in the current series compared to some other series reporting only on supratentorial gliomas.

In conclusion, the progress of patients with low-grade astrocytoma is generally favorable. No new insights have been gained in recent years, and further improvement in the treatment results will be possible only through well-designed, prospective studies and a better understanding of the biology and pathogenesis of these tumors.

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