Table 4. Treatment-Related Neurotoxic Effects*

	No. in WBRT + SRS Group (n = 65)				No. in SRS-Alone Group (n = 67)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Acute toxic effects	2	1	1	0	3	3	2	0
Seizure	0	0	1	0	1	2	1	0
Other	2	1	0	0	2	1	1	0
Late toxic effects	3	0	2	2	1	0	0	2
Radiation necrosis	1	0	0	2	0	0	0	1
Leukoencephalopathy	1	0	2	0	0	0	0	0
Other†	1	0	0	0	1	0	0	1
Radiological leukoencephalopathy	2	3	2	0	1	1	0	0

Abbreviations: SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*From the National Cancer Institute's Common Toxicity Criteria version 2.0.[16]
†Other effects included 1 case of slight lethargy (grade 1) in the WBRT + SRS group and 1 case each of seizure (grade 4) and headache (grade 1) in the SRS-alone group.

Table 5. Univariate Analysis of Development of New Metastases at Distant Brain Sites

	Actuarial Rate, %		Log-Rank *P* Value
	6 mo	12 mo	
Treatment group			
WBRT + SRS	17.5	41.5	.003
SRS alone	49.9	63.7	
Age, y			
<65	34.5	55.9	.65
≥65	33.9	49.0	
Sex			
Male	32.7	51.5	.39
Female	36.3	55.9	
No. of brain metastases			
1	27.3	39.2	.03
2-4	42.4	69.9	
Primary tumor site			
Lung	29.5	52.0	.40
Other	43.1	55.9	
Primary tumor status			
Stable	32.8	44.8	.20
Active	37.1	69.6	
Extracranial metastases			
Stable	29.5	38.4	.02
Active	37.3	69.3	
KPS score			
70-80	43.2	57.4	.05
90-100	29.9	50.8	
Chemotherapy after brain treatment			
Yes	37.1	59.0	.33
No	32.9	50.0	

Abbreviations: KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

ing SRS alone ($P=.36$), including 1 and 2 patients with grade 3 toxicity, respectively, in each group. The symptoms developed a median of 6 days after initiation of treatment (range, 1-64 days) in the WBRT + SRS group and 10 days (range, 1-86 days) in the SRS-alone group. Symptomatic late neurologic radiation toxic effects were observed in 7 patients in the WBRT + SRS group and in 3 patients in the SRS-alone group ($P=.20$). Toxic effects were experienced for a median of 15.6 months (range, 6.7-59.4 months) in the WBRT + SRS group and 6.2 months (range, 5.8-8.1 months) in the SRS-alone group. There were 3 cases of radiation necrosis (grade 1, n = 1; grade 4, n = 2), 3 cases of leukoencephalopathy (grade 1, n = 1; grade 3, n = 2), and 1 case of slight lethargy (grade 1) in the WBRT + SRS group. In patients receiving SRS alone, the following effects were observed: 1 case of radiation necrosis (grade 4), 1 of seizure (grade 4), and 1 of headache (grade 1). Radiation necrosis was diagnosed using positron emission tomography or surgical resection in all cases. Radiological findings consistent with leukoencephalopathy were observed in 7 patients in the WBRT + SRS group and in 2 patients in the SRS-alone group ($P=.09$). Three of these 9 patients also experienced symptomatic leukoencephalopathy; the other 6 patients were asymptomatic.

Brain Tumor Recurrence

Brain tumor recurrence at either distant or local sites in the brain was observed in 63 patients (23 in the WBRT + SRS group and 40 in the SRS-alone group). The 12-month actuarial brain tumor recurrence rate was 46.8% (95% CI, 29.7%-63.9%) in the WBRT + SRS group and 76.4% (95% CI, 63.3%-89.5%) in the SRS-alone group ($P<.001$).

Fifty-five patients had new brain metastases at distant sites (21 in the WBRT + SRS group and 34 in the SRS-alone group). The 12-month actuarial rate of developing new brain metastases was 41.5% (95% CI, 24.4%-58.6%) in the WBRT + SRS group and 63.7% (95% CI, 49.0%-78.4%) in the SRS-alone group ($P=.003$) (Figure 2B).

The multivariate analysis revealed that WBRT + SRS was associated with a reduced risk of recurrence (hazard ratio, 0.32; 95% CI, 0.18-0.58; $P<.001$) (TABLE 5 and TABLE 6).

During the follow-up period, 122 patients (92% of the total patients enrolled) had at least 1 follow-up MRI scan performed. In total, 581 follow-up MRI scans were performed; of these, 87 scans (15%) demonstrated new brain metastases; these 87 "event scans" were obtained in 55 patients. Sixteen percent of these "event scans" (14/87) were associated with neurologic symptoms at the time of the MRI examination.

A total of 247 metastases received initial treatment with SRS (117 in the WBRT + SRS group and 130 in the SRS-alone group). Follow-up MRI was available for 210 metastases (85%). The actuarial local tumor control rate at 12 months was 88.7% (95% CI, 80.1%-97.3%) in the WBRT + SRS group and 72.5% (95% CI, 60.3%-84.7%) in the SRS-alone group ($P=.002$) (FIGURE 3). The histopathological type (adenocarcinoma vs others) was not shown to be a significant factor ($P=.90$). The multivariate analysis also showed significantly better tumor control by WBRT + SRS treatment (hazard ratio, 4.83; 95% CI, 2.00-11.65; $P<.001$).

Salvage treatment for progression of brain tumor was required significantly more frequently in patients receiving SRS alone (29 patients) than in the WBRT + SRS group (10 patients) ($\chi^2=12.33$; $P<.001$). Salvage WBRT was applied in 11 patients in the SRS-alone group but was not used in any patients in the WBRT + SRS group. Salvage SRS was used in 19 patients in the SRS-alone group and in 9 patients in the WBRT + SRS group.

Systemic and Neurologic Functional Preservation

Systemic functional preservation rates (KPS score ≥70) at 12 months were 33.9% (95% CI, 22.2%-45.4%) in the WBRT + SRS group and 26.9% (95% CI, 16.3%-37.5%) in the SRS-alone group ($P=.53$). The decrease in the KPS score to below 70 was attributed to neurologic causes in 17 patients (29%) in the WBRT + SRS group and 14 (22%) in the SRS-alone group.

The actuarial rates of neurologic preservation at 12 months were 72.1% (95% CI, 58.8%-85.4%) with WBRT + SRS and 70.3% (95% CI, 55.6%-85.0%) with SRS alone ($P=.99$) when neurologic preservation was defined as a lack of any worsening of the neurologic grade on follow-up examination, compared with the pretreatment grade. In total, 85 patients (38 in the WBRT + SRS group and 47 in the SRS-alone group) did not have neurologic symptoms when brain metastases were diagnosed (grade 0). Among the 47 patients who had a pretreatment grade of 1 to 3, an improvement in neurologic status was observed at least once in 9 patients and 10 patients in the respective groups ($\chi^2=1.32$; $P=.24$). Deterioration of neurologic function was observed in 43 patients, including 7 who initially experienced improvement after treatment (22 in the WBRT + SRS group and 21 in the SRS-alone group; $\chi^2=0.09$; $P=.75$). This deterioration was attributed to either original or distant brain metastases in 13 patients (59%) in the WBRT + SRS group and 18 patients (86%) in the SRS-alone group ($\chi^2=3.78$; $P=.05$). Late neurologic radiation toxic effects were the cause of deterioration in 4 and 2 patients in each group, respectively. Either meningeal dissemination or spinal cord metastases induced neurologic deterioration in 5 and 1 patient in each group, respectively.

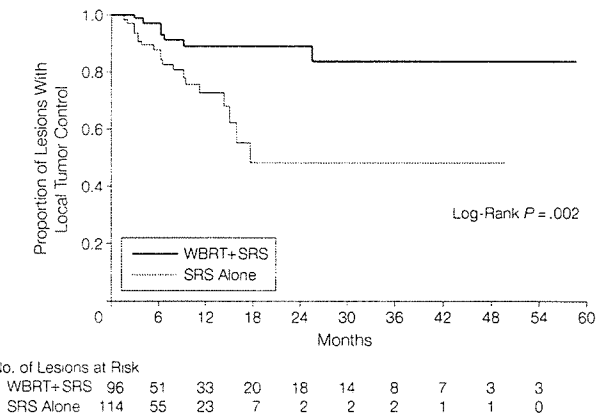
Neurocognitive function was optionally assessed using the Mini-Mental State Examination (MMSE). Among the 44 patients (25 in the WBRT + SRS group and 19 in the SRS-alone group) who lived 12 months or longer, MMSE data were available in 28 patients at least once (16 in the WBRT + SRS group and 12 in the SRS-alone group) at the median follow-up times of 30.5 months (range, 13.7-58.7 months) with WBRT + SRS and 20.7 months (range, 13.3-53.8 months) with SRS alone. The median MMSE pretreatment score was 28.0 (range, 23-30) in the WBRT + SRS

Table 6. Multivariate Analysis of Development of New Metastases at Distant Brain Sites

	Hazard Ratio (95% CI)	*P* Value
Treatment group (WBRT + SRS)	0.32 (0.18-0.58)	<.001
No. of brain metastases (2-4)	1.69 (0.97-2.93)	.06
Extracranial metastases (active)	2.06 (1.17-3.64)	.01
KPS score (70-80)	2.14 (1.17-3.93)	.01

Abbreviations: CI, confidence interval; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

Figure 3. Local Tumor Control



There was a statistically significant increase in local tumor control in patients receiving whole-brain radiation therapy (WBRT) plus stereotactic radiosurgery (SRS) ($P=.002$).

group and 27.0 (range, 23-30) in the SRS-alone group. The median score at the final follow-up was 27.0 (range, 21-30) in the WBRT + SRS group and 28.0 (range, 18-30) in the SRS-alone group.

COMMENT

Stereotactic radiosurgery is a method of delivering high doses of focal radiation to a tumor while minimizing irradiation of the adjacent normal tissue. This approach was originally developed by the Swedish neurosurgeon Lars Leksell as a substitute for direct surgical intervention.[21] Stereotactic radiosurgery is now available worldwide, and it is increasingly used to treat brain metastases because it is less invasive compared with direct surgical intervention, although a direct randomized comparison of the 2 modes has not been performed to date.

Whole-brain radiation therapy has been a standard treatment for brain metastases for several decades.[1-4,6,7,17] In more recent years, the importance of focal aggressive therapy combined with WBRT has been increasingly recognized.[3,4,22-24] Andrews et al[4] recently reported the results from RTOG 9508, a multi-institutional phase 3 trial of 333 patients with 1 to 3 brain metastases who received WBRT with or without SRS boost. A statistically significant improvement in median survival with the addition of SRS was seen in patients with a single brain metastasis.

To reduce the risk of late radiation effects,[1,2,5] WBRT is increasingly being omitted from the initial management strategy.[6-13] There is not yet a general consensus regarding the risks and benefits of omitting up-front WBRT. One study showed a trend toward improved survival among patients who received SRS alone,[12] whereas another study showed a trend toward worse survival among patients who received SRS alone.[10] A retrospective multi-institutional review of SRS alone vs SRS with WBRT in 569 patients failed to show any difference in survival between the 2 groups.[7] In a single-institution prospective randomized trial comparing WBRT with observation in patients who underwent conventional surgery,[6] a large increase in intracranial relapse and a concomitant increase in death due to neurologic causes were identified in the non-WBRT group; however, no survival difference was identified in that study. In the present study, no significant survival difference was observed between the groups receiving WBRT + SRS and SRS alone, although the number of patients was not large enough to allow detection of any differences that were smaller than we had assumed. In addition, no significant difference in the frequency of death due to neurologic causes was observed. Moreover, these results were obtained in spite of the rather large increase in intracranial failure when WBRT was omitted. A further observation of note from the present trial was the significant increase in local failure with SRS alone, even though the radiation dose in these patients was considerably higher than that administered to patients receiving WBRT + SRS. We have adapted the 30% reduced dose of SRS in the WBRT + SRS group, which could have lowered local control of the brain metastasis in the WBRT + SRS group. However, we have observed opposite results in this study; the local control rate was significantly higher in the WBRT + SRS group than in the SRS-alone group. This observation lends merit to the value of fractionation, which might help overcome some radiation resistance mechanisms, such as hypoxia.

Also of concern in this context is that higher brain recurrence rates are associated with neurologic deterioration.[9] In a previous randomized study of surgery with or without WBRT,[6] the time to neurologic deterioration was dramatically longer in the WBRT group, although no difference in functional independence was observed. In the current study, no significant difference in the preservation of neurologic function was observed. However, the present study might have less ability to detect small differences, and the present assessment of neurologic function was not conducted with sophisticated measures that might have detected differences between patient groups.

Although surgery and SRS are both focal treatments, SRS is less invasive and may be repeated more often than surgical intervention.[11] The optimal timing of these interventions is an issue that remains open for debate. Our results suggest that the early detection of a brain recurrence and early salvage brain treatment may prevent neurologic deterioration and neurologic death, even when WBRT is not included in the initial treatment. However, study participants more frequently undergo physical and radiological examinations than do patients in the community. Given that the majority of new brain metastases were initially detected in asymptomatic patients, studies assessing the benefits of scheduled imaging should be conducted in the future.

In conclusion, our findings demonstrated that SRS alone without up-front WBRT was associated with increased brain tumor recurrence; however, it did not result in either worsened neurologic function or increased risk of neurologic death. With respect to patient survival, the control of systemic cancer might outweigh the frequent recurrence of brain tumors. Therefore, SRS alone could be a treatment option, provided that frequent monitoring of brain tumor status is conducted.

Author Contributions: Dr Aoyama had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: Aoyama, Tago, Kobashi
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> The only true hope for civilization—the conviction of the individual that his inner life can affect outward events and that, whether or not he does so, he is responsible for them.
> —Stephen Spender (1909-1995)

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CLINICAL INVESTIGATION **Spinal Cord**

SPINAL CORD GLIOMAS: A MULTI-INSTITUTIONAL RETROSPECTIVE ANALYSIS

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Purpose: To determine the impact of postoperative radiation therapy (POXRT) on outcome in spinal cord gliomas.
Patients and Methods: Data from 242 patients were collected retrospectively from six institutions using a standardized data sheet. Pathology specimens, when available, were centrally reviewed.
Results: A total of 183 patients were analyzed: 82 received surgery alone as initial treatment, whereas 101 had surgery and POXRT. Demographic, diagnostic, and treatment factors were analyzed for impact on progression-free (PFS) and overall survival (OS). PFS in ependymoma patients was 74%, 60%, and 35% at 5, 10, 15 years, respectively, and was significantly influenced by treatment type, race, age, tumor grade, and type of surgery on univariate analysis, with age being the only significant factor on multivariate analysis (MVA) ($p = 0.01$). OS of ependymoma patients was 91%, 84%, and 75% at 5, 10, and 15 years, respectively, and was significantly influenced by both complete resection ($p = 0.04$) and age ($p = 0.03$) on MVA. In astrocytomas, PFS was 42%, 29%, and 15% at 5, 10, and 15 years, and was significantly influenced by POXRT in low- and intermediate-grade tumors on MVA ($p = 0.02$). OS at 5, 10, and 15 years was 59%, 53%, and 32%, respectively, and was significantly influenced by grade on MVA ($p < 0.01$).
Conclusion: Postoperative radiation therapy reduced disease progression in low- and moderate-grade astrocytomas. In ependymomas, complete resection significantly influenced OS. © 2006 Elsevier Inc.

Spinal cord, Glioma, Radiation.

INTRODUCTION

Advances in surgical techniques and the widespread availability of improved imaging techniques have enhanced the ability of neurosurgeons to perform complete resections of these uncommon neoplasms. These changes have led to rapid evolution in the management of spinal cord gliomas. In all but patients with infiltrative tumors, total resections of these gliomas have become more attainable (1, 2). The role of postoperative radiation therapy (POXRT) for intramedullary gliomas has consequently evolved as well. However, heterogeneity in the treatment methods and pathology and the small number of patients complicate the development of unified treatment management recommendations (2–34). Furthermore, reports regarding the effect of radiation dose, extent of radiation field, and radiation technique on outcome have been conflicting (2, 3, 8, 11–13, 15–17, 20, 22, 24, 26–28, 32–34). The influence of the various prognostic factors on survival has also varied (2–9, 11–13, 15–34). An attempt to review patients treated for spinal cord gliomas at our institution and five others was made. The participation of six centers permitted the study of a large number of patients. The aim of this study was to report the overall (OS) and progression-free survivals (PFS) in this patient population. We also attempted to determine the influence of various clinical, topographic, pathologic, operative, and radiotherapeutic factors on long-term clinical outcome.

METHODS AND MATERIALS

Six institutions participated in this retrospective study. Only patients with the diagnosis of spinal cord glioma, ependymoma, or

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astrocytoma were included in the study. Clinical data were collected from medical records of spinal glioma patients operated between August 1953 and March 2000, using a standardized data sheet. Pathology slides were obtained for central pathology revision by two neuropathologists (B.W.S., O.Y.) who applied the 2000 World Health Organization (WHO) classification and grading scheme (35). Simulation and portal films, when available, were reviewed in irradiated patients. The information was then entered into a computerized database at the University of Miami/Jackson Memorial hospital. The retrieved data included gender, race, age at diagnosis, status at last follow-up, patterns of failure, presence and duration of sensory or motor signs and symptoms, pathology tumor subtype, tumor grade, and extent of surgery. If a complete resection was performed, then information regarding the method (whether piecemeal or en-bloc) was obtained. The number of surgeries, level of involvement, presence of brain or brainstem involvement, and number of cord segments involved were also documented.

Information regarding change in neurologic status after treatment, presence of pain, and type of pain medication used was collected. Documentation of available investigations such as computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, and cerebrospinal fluid analysis was also done. The presence or absence of cysts either inside or immediately adjacent to the tumor on radiography or operative note was documented. This was done in an attempt to study their prognostic implications. Other data retrieved included the overall radiation treatment time, techniques, field margins, and dose fractionation of radiation therapy.

Treatment

Surgery was in the form of complete or partial resection or biopsy. Radiation therapy was given to the site of the primary lesion with a margin of one to three vertebral bodies in patients receiving radiation to limited local fields. However, craniospinal or whole spine radiation was given in 10 patients based on the personal preference of the treating radiation oncologist. Craniospinal fields were given using parallel-opposed cranial fields matched to posterior spinal fields. The local field radiation was delivered via a posteroanterior field in most patients. Anteroposterior-posteroanterior, oblique, or lateral fields were used less often. All patients were treated using megavoltage equipment. Most patients were treated using photons alone, although 6 patients received electron beam treatments alone or in conjunction with photons. All but 1 patient were treated once per day. The median total radiation dose and dose per fraction were 49.5 Gy (range, 30–60 Gy) and 1.8 Gy (range, 1.33–2.27 Gy) for ependymoma patients and 50 Gy (range, 6.7–56 Gy) and 1.8 Gy (range, 1–2 Gy) for astrocytoma patients.

Pathologic evaluation

Confirmation of the pathology was attempted through a central pathology review by two neuropathologists (B.W.S., O.Y.) using the WHO 2000 classification (35). The reviewer-confirmed WHO tumor type was used in our analyses; however, in patients with no tissue available for review, original institutional diagnosis and grades were accepted. Among astrocytomas, pathologic subtypes encountered were pilocytic and diffuse or fibrillary tumors (Grades 2–4). Ependymomas were classified as myxopapillary (WHO Grade 1) and as cellular tumors (WHO Grade 2-3).

Statistical methods

Because pathologic type is known to be one of the most significant prognostic factors affecting outcome (34), all statistical analyses were carried out separately for ependymomas and astrocytomas. The Cox proportional hazards method (36) was used to compare time to disease progression (PFS) and OS in patients treated with surgery alone to that of patients receiving POXRT. The definition of local disease progression or failure was as follows: an increase/progression in the size of the lesion as a whole or the enhancing portion on MRI/CT scan. Progression and survival were measured from date of surgery, and all deaths (any cause) were counted as events. The comparability of the two treatment groups was examined with respect to demographics (gender, race, ethnicity, and age), diagnosis (pathology subtype, tumor grade, presence of cysts, extent of cord involvement, number of segments), and treatment (date and type of surgery) using a chi-square test for categorical variables and Fisher's exact test for dichotomous variables. Next, we obtained univariate estimates of the effect of postoperative radiation and each of the demographic, diagnostic, and treatment characteristics on disease progression and survival. Multivariate Cox models were then developed to estimate the effect of postoperative radiation treatment (vs. surgery alone) after adjustment for factors identified on univariate analysis as having prognostic significance, taking the 15% level as a guideline for considering covariate inclusion. Models were tested for interaction to determine whether the estimated effect of postoperative radiation varied with the level of any included covariate. In instances of covariates with a substantial amount of missing data, we obtained results from a multivariate model without the covariate of interest and compared them with estimates from an adjusted model in the subset of patients for whom values of the additional covariate were available. We also examined the effect of radiation dose by modifying our multivariate models to compare each of two radiation groups—patients receiving a total dose of less than 5000 cGy after surgery and those treated with 5000 cGy or higher—against patients who had surgery only (reference group). Kaplan-Meier estimates were obtained for the proportion of progression-free and surviving patients over a 15-year period after surgery, in addition to the Cox models (36).

RESULTS

Information regarding 242 patients was submitted for inclusion in the study. Fifty-nine patients were excluded because of incomplete information. The remaining patients were excluded because of a lack of information on date of surgery, survival or disease status, or follow-up of less than 6 months. Thus, our study included information on disease progression and survival for 183 patients. One hundred and twenty patients had a diagnosis of ependymoma. Six had other gliomas (glioma not otherwise specified [NOS] or oligodendroglioma). Information was obtained from six study sites; the contribution of each site with regard to the ependymoma patients was as follows: 21 (17%) patients from the University of Miami; 12 (9%) from Thomas Jefferson University; 7 (6%) from Wayne State University; 28 (22%) from Barrow Neurologic Institute; 27 (21%) from Wake Forest University; and 31 (25%) from Hokkaido University. Similarly, data were obtained for 57 patients with astrocytic tumors as follows: 13 (23%) patients from the University of Miami; 3 (5%) from Thomas Jefferson University; 8 (14%) from Wayne State University; 2 (4%) from Barrow; 16

(28%) from Wake Forest University; and 15 (26%) from Hokkaido University.

Patients with ependymoma/NOS/oligodendroglioma

Demographic, diagnostic, and treatment characteristics: Patients were classified as ependymoma on the basis of central pathology review (92 patients) or by institutional site report if slides were not available for review (27 patients). One additional patient had a mixed ependymoma, four had a glioma NOS, and two had an oligodendroglioma. Eighty cases in which slides were available for review showed concurrence between central review and institutional site reported pathology. Grade was reported by study site investigators for only 82 (65%) of the 126 patients; in 93 of these patients, tumors were reviewed for grade using WHO criteria. Of the 64 patients with both reported and reviewed grade, only 24 (37.5%) were similarly graded and typed.

Fifty-seven patients had CT scans and 101 patients had MRI scans at the time of diagnosis. Thus, both studies were done in a subset of patients.

Although we attempted to obtain information regarding the duration of symptoms before diagnosis, information was not available in 64 of the 126 studied patients. Information for 41 patients in the surgery-only group showed a median duration of symptoms equal to 12 months (range, 1–120 months; mean, 20 months), whereas the 23 patients treated with surgery followed by radiation showed a median duration of symptoms of 6 months (range, <1–48 months; mean, 11.3 months).

Neurologic status improved after treatment in 27 patients (9 radiation, 18 surgery), was stable in 15 patients (6 radiation, 9 surgery) and was worse in 10 patients (4 radiation, 6 surgery). However, information was missing in 74 patients, making this information of limited use.

With regard to the 63 patients who underwent a complete resection, 15 had a piecemeal resection and 41 had an en-bloc resection (information was not available for the remaining patients).

Table 1 summarizes the demographic, diagnostic, and treatment characteristics of the ependymoma patients.

Survival analyses

Disease progression: Disease progression occurred in 38 of the ependymoma patients after a median follow-up of 22 months (range, 1 month to 14 years and 1 month). The 88 patients who remained progression-free were followed for a median of 5 years and 1 month (range, 4 months to 15 years). Kaplan-Meier estimates of the proportion of ependymoma patients alive without disease progression at 5, 10, and 15 years were 74% (95% CI, 66–83%), 60% (95% CI, 48–72%), and 35% (95% CI, 11–60%), respectively (Fig. 1).

Of the 38 instances of disease progression, 8 occurred in the group of 64 patients treated with surgery only; 3 of these 8 patients had complete resections, 1 partial resection, 2 biopsies only, and in 2 patients, the extent of surgery was unknown. There were 30 instances of progression among the 62 patients who received postoperative radiation; 4 of these patients had complete resection, 17 partial resection, 7 biopsy only, and in 2 patients, the extent of surgery was unknown. Infield failure was the main type of failure in the radiation patients in whom cause of failure was known. In radiation patients, infield failure alone was seen in 12 patients, with combined infield and distant spine failure seen in 2 patients. Two additional patients had concurrent infield and marginal failure. Patterns of failure in study cohort in general were as follows: 13 infield, 3 marginal, 1 distant spine, 2 brain, 1 outside the central nervous system, 2 combined infield and distant spine, 3 combined infield and margin, and the remaining 13 patients failed but the exact type of failure is unknown. Median total dose was 49.1 Gy (range, 40–55.8 Gy) for the 18 patients with infield failure and 48 Gy (range, 41.7–50 Gy) for 6 patients with other types of progression. Univariate analysis of factors potentially affecting PFS is seen in the upper panel of Table 2. Treatment, race, age, tumor grade (for both site-reported and reviewed-WHO), and type of surgery were significant, whereas ethnicity was marginally significant.

The lower panel of Table 2 presents a multivariate analysis of disease progression in which the effect of radiation treatment was adjusted for factors found to be significant on univariate analysis with the exception of grade, which entails a substantial amount of missing data. Adjustment for the remaining factors (type of surgery, age, and race) reduced the analysis set to 116 patients, including 33 of the 38 patients who experienced disease progression, but the median and range of follow-up were essentially unchanged. The resulting model indicates that postoperative radiation treatment as compared with surgery alone was not significantly associated with disease progression ($p = 0.11$). Age remained a significant prognostic factor in the multivariate model, with an estimated 27% reduction in the risk of disease progression for every 10-year increase in age ($p = 0.01$). Complete resection surgery was associated with a 60% risk reduction, which had marginal statistical significance ($p = 0.06$). (The effect of the extent of surgery on PFS is seen in the lower panel of Fig. 1.) The estimated doubling of risk for white patients as compared with other races was also of marginal statistical significance ($p = 0.08$). The multivariate model was further modified to consider the effect of radiation dose, but this did not result in evidence of a benefit even when comparing ependymoma patients who received high-dose postoperative radiation (≥50 Gy) with those who had surgery only (adjusted hazard ratio 1.3, $p = 0.67$, not shown).

Although univariate analyses indicated a significant risk associated with high-grade disease, data were not sufficient to include grade in the multivariate model. As can be seen from the upper panel of Table 2, adjustment for grade would reduce substantially both the number of patients and the number of events (disease progression). Furthermore, the number of high-grade patients is small, using either site-reported or WHO criteria, and most of these patients received radiation therapy (see Table 1). We note further that

Table 1. Characteristics of 126 ependymoma patients by treatment group

Characteristic		Postoperative radiation (62) *n* (%)	Surgery only (64) *n* (%)	*p* value*
Sex	Male	35 (56)	35 (55)	0.86
	Female	27 (44)	29 (45)	
Race	White	44 (72)	42 (68)	0.70
	Other	17 (28)	20 (32)	
	Missing	1	2	
Ethnicity	Hispanic	3 (5)	6 (10)	0.49
	Non-Hispanic	58 (95)	56 (90)	
	Missing	1	2	
Age at surgery	≤24 years	13 (21)	9 (14)	0.01
	25–54	41 (67)	33 (52)	
	≥55	7 (12)	21 (33)	
	Missing	1	1	
		Median, 36; range, 6–74	Median, 46; range, 3–76	
Pathology	Ependymoma	59 (95)	61 (95)	1.0
	Oligos and glioma NOS	3 (5)	3 (5)	
Subtype	Myxopapillary	9 (26)	8 (14)	0.31 (myxopapillary vs. cellular vs. tan/other)
	Cellular	19 (54)	39 (68)	
	Tanicytic	3 (9)	1 (2)	
	Other	4 (11)	9 (16)	
	Missing	27	7	
Grade, site reported	High (3)	8 (21)	0 (0)	<0.01 (high vs. low/moderate)
	Moderate (2)	7 (18)	4 (9)	
	Low (1)	23 (61)	40 (91)	
	Missing	24	20	
Grade, WHO	High (3)	3 (8)	1 (2)	0.29 (high vs. low/moderate)
	Moderate (2)	23 (64)	45 (79)	
	Low (1)	10 (28)	11 (19)	
	Missing	26	7	
Presence of cysts	Yes	21 (43)	20 (38)	0.69
	No	28 (57)	32 (62)	
	Missing	13	12	
Cord involvement	Cervical	17 (27)	26 (41)	0.11 (Cervical vs. thoracic vs. lumbar vs. con/other)
	Thoracic	14 (23)	9 (14)	
	Lumbar	5 (8)	10 (16)	
	Conus	2 (3)	3 (5)	
	Overlapping sites/other	24 (39)	15 (24)	
	Missing	0	1	
Number of segments	≤5	44 (75)	52 (87)	0.11
	≥6	15 (25)	8 (13)	
	Missing	3	4	
Surgery	Complete resection	12 (20)	51 (82)	<0.01
	Biopsy/partial resection/none	47 (80)	11 (18)	
	Missing	3	2	
Date of surgery	Pre-1980	12 (19)	1 (2)	<0.01 (Pre-1990 vs. later)
	1980–1989	24 (39)	5 (8)	
	1990 or later	26 (42)	58 (90)	
Radiation dose	<50 Gy	31 (53)	1	NA
	≥50 Gy	28 (47)	4	
	Missing/NA	3	59	

Abbreviations: NOS = not otherwise specified; NA = not available.
* Chi-square or Fisher's exact test.

only 2 patients were classified as high grade by both site report and central pathology review, whereas the following discrepancies and missing values were observed: 4 patients were reported as high grade but classified as moderate on review, 1 was reported as moderate and classified as high grade on review, 2 were reported as high grade but not reviewed, and 1 was determined to have high-grade disease by pathology review but did not have a site report.

Overall Survival: There were 15 deaths among the ependymoma patients after a median follow-up of 4.3 years (range, 8 months to 13 years and 5 months). The 111 patients who were alive at last contact were followed for a median of 5.7 years (range, 7 months to 15 years). Kaplan-Meier estimates of the proportion of ependymoma patients surviving to 5, 10, and 15 years were 91% (95% CI, 85–97%), 84% (95% CI, 75–92%), and 75% (95% CI, 60–

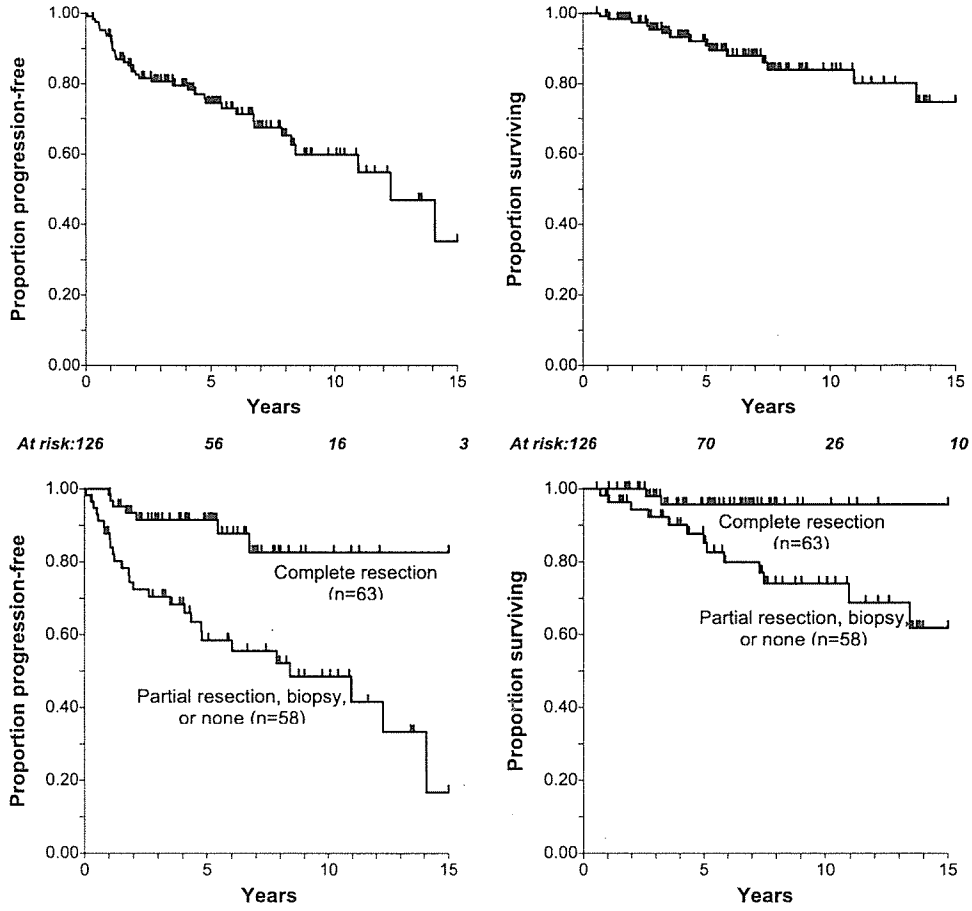

Fig. 1. Progression-free and overall survival in 126 ependymoma patients by type of surgery.

89%), respectively (Fig. 1). Three of the 15 deaths occurred in the group of 64 patients treated with surgery only; 1 of the deceased patients had complete resection, 1 partial resection, and 1 biopsy only. Twelve of the 62 patients who received postoperative radiation died, but only 1 of these patients had complete resection, whereas 8 had partial resection and 3 had biopsy only.

Univariate analysis, which is summarized in the upper panel of Table 3, identified age, grade, cysts, and type of surgery as significant prognostic factors, whereas treatment was marginally significant.

The lower panel of Table 3 presents the multivariate analysis of overall survival. The effect of radiation treatment was adjusted for type of surgery and age in the set of 119 patients for whom these covariates were known. After adjustment for these variables, there was no evidence that postoperative radiation treatment was associated with survival ($p = 0.99$). Age remained a significant prognostic factor for overall survival, with an estimated 34% reduction in the risk of disease progression (hazard ratio = 0.66) for every 10-year increase in age. (For example, the risk for disease progression for 30-year-old patients would be estimated as 34% lower than that of 20 year olds.) Complete resection was associated with a 72% reduction in risk of death (95% CI, 0.03–0.95).

As was the case with PFS, data were not sufficient to develop a multivariate model in which the risk of death was adjusted for high-grade disease. To determine whether our findings could be further explained by the presence of cysts, the multivariate model was applied to the subgroup of patients for whom this information was available. We found that presence of cysts was associated with an 88% risk reduction (hazard ratio 0.12; 95% CI, 0.02–0.97), whereas age again remained significant.

With respect to radiation dose, there was still no evidence of improved survival in a comparison of ependymoma patients given high dose postoperative radiation (≥50 Gy) with those having surgery only (adjusted hazard ratio 1.12, $p = 0.89$).

Patients with astrocytoma

Our study included information on disease progression and survival for 57 patients with a diagnosis of astrocytoma.

Demographic, diagnostic, and treatment characteristics of astrocytoma patients by treatment: Fifty-seven patients had astrocytomas. Patients were classified as astrocytoma on the basis of central pathology review (27 patients) or by institutional site report if slides were not available for review (30 patients). Of note is that 3 patients reported as having a mixed glioma were included in the astrocytoma group as well. Among the 25 patients in whom both central and institutional site report were available, 24

Table 2. Cox proportional hazards models for 15-year progression-free survival in 126 patients with ependymoma

Factors (univariate analysis)		Patients	Progression	Hazard ratio (95% CI)	*p* value (Wald)
Treatment	Postoperative radiation vs. surgery only	126	38	3.77 (1.71–8.28)	<0.001
Sex	Male vs. female	126	38	1.59 (0.82–3.08)	0.17
Race	White vs. others	123	38	2.67 (1.04–6.84)	0.04
Ethnicity	Non-Hispanic vs. Hispanic	123	38	0.42 (0.16–1.09)	0.07
Age	Per 10-year increase	124	37	0.76 (0.62–0.94)	0.01
Subtype	Cellular vs. myxopapillary	75	18	1.01 (1.36–3.39)	0.87
Grade, site-reported*	High vs. low	82	21	3.50 (1.16–0.54)	0.03
	Moderate vs. low			1.69 (0.54–5.31)	0.37
Grade, World Health Organization*	High vs. low	93	26	15.02 (3.20–70.52)	<0.001
	Moderate vs. low			0.77 (0.29–2.04)	0.60
Cysts	Present vs. not	101	29	0.69 (0.31–1.53)	0.36
Cord involvement	Lumber vs. conus	125	38	1.79 (0.38–8.44)	0.47
	Cord proper vs. conus			2.20 (0.52–9.27)	0.28
Segments	6 or more vs. 5 or fewer	119	35	0.97 (0.44–2.13)	0.93
Type of surgery	Complete vs. none/biopsy/partial	121	34	0.23 (0.10–0.54)	<0.001
Date of surgery	1980–1989 vs. pre-1980	126	38	1.39 (0.56–3.41)	0.48
	1990+ vs. pre-1980			0.57 (0.22–1.48)	0.25

Multivariate model†		Patients	Progression	Adjusted hazard ratio (95% CI)	*p* value (Wald)
Treatment	Postoperative radiation vs. surgery only	116	33	2.32 (0.83–6.49)	0.11
Type of surgery	Complete vs. none/biopsy/partial			0.40 (0.15–1.06)	0.06
Age	Per 10-year increase			0.73 (0.56–0.93)	0.01
Race	White vs. others			2.32 (0.89–6.05)	0.08

* High = 3/anaplastic, moderate = 2/cellular, low = 1/myxopapillary. Because numerical designations were not available for all cases, descriptors were used.

† $p < 0.001$ model fit.

(96%) were classified as astrocytoma by both data sources. With regard to grade, only 24 (42%) of the astrocytoma patients had review of grade by WHO criteria. Grade was reviewed centrally but not reported by the institution in 3 patients. Of the 21 patients with both reviewed and reported grade, only 9 were consistently classified into the low-, intermediate-, or high-grade groups by the two sources.

Thirty-nine patients had MRI scans and 30 patients had CT scans (some patients having had both imaging studies) done at the time of diagnosis.

Neurologic status improved after treatment in 14 patients (11 radiation, 3 surgery), was stable in 5 patients (2 radiation, 3 surgery), and was worse in 4 patients (3 radiation, 1 surgery). Unfortunately, information was lacking for the remaining 34 cases, thus rendering this information of limited use.

Thirteen patients underwent complete tumor resection, the method being known in 11 (4 en-bloc resections and 7 piecemeal resections).

Table 4 summarizes the demographic, diagnostic, and treatment characteristics of 39 astrocytoma patients who received radiation treatment after surgery and 18 who were treated by surgery alone.

Disease progression: Disease progression occurred in 33 of the astrocytoma patients after a median follow-up of 21 months (range, 4 months to 12 years and 4 months). The 24 patients who remained progression-free were followed for a median of 5 years and 7 months (range, 2 months to 15 years). Kaplan-Meier estimates of the proportion of patients alive without disease progression at 5, 10, and 15 years were 42% (95% CI, 28–56%), 29% (95% CI, 13–45%), and 15% (95% CI, 5–39%), respectively (Fig. 2). Median PFS was estimated as 44 months (95% CI, 24–110).

Twenty-two of the 39 patients treated with postoperative radiation had progression of disease; 1 of these patients had a complete resection, 11 partial resection, 9 biopsy only, and in 1 patient the extent of surgery was unknown. Eleven of the 33 instances of disease progression occurred in the group of 18 patients treated with surgery only; 2 of these 11 patients had complete resection, 5 partial resection, 1 biopsy only, and in 3 patients the extent of surgery was unknown. The pattern or type of failure was known in 21 patients and was mainly infield failure. Ten patients had infield failure as the only site of initial failure (6 in the radiation group, 4 in the surgery group). Two patients had failure both infield and in the distant spine/margin (1 patient from each group). Three patients had marginal failures (2 radiation, 1 surgery). The remaining failures occurred in the brain (4 radiation patients) and in the distant spine (2 radiation patients). Median total dose was 55 Gy (range, 40–55.8 Gy) for 9

Table 3. Cox proportional hazards models for 15-year overall survival in patients with ependymoma

Factors (univariate analysis)		Patients	Deaths	Hazard ratio (95% CI)	p value (Wald)
Treatment	Postoperative radiation vs. surgery only	126	15	2.95 (0.81–10.70)	0.10
Sex	Male vs. female	126	15	1.68 (0.57–4.92)	0.34
Race	White vs. others	123	15	1.27 (0.35–4.53)	0.72
Age	Per 10-year increase	124	15	0.69 (0.5–1.00)	0.03
Subtype	Cellular vs. myxopapillary	75	6	1.43 (0.17–12.3)	0.74
Grade, site-reported*	High vs. low	82	9	7.27 (1.82–29.13)	0.01
	Moderate vs. low			0.81 (0.09–7.41)	0.85
Grade, WHO	High vs. low	93	6	7.69 (1.07–55.33)	0.04
	Moderate vs. low			0.27 (0.03–1.92)	0.19
Cysts	Present vs. not	101	13	0.12 (0.02–0.94)	0.04
Cord involvement	Lumbar vs. conus	125	15	0.74 (0.07–8.23)	0.81
	Cord proper vs. conus			1.44 (0.19–11.1)	0.73
Segments	6 or more vs. 5 or fewer	119	15	0.82 (0.23–2.91)	0.76
Type of surgery	Complete vs. none/biopsy/partial	121	15	0.19 (0.04–0.83)	0.03
Date of surgery	1980–1989 vs. pre-1980	126	15	0.79 (0.22–2.85)	0.72
	1990+ vs. pre-1980			0.47 (0.12–1.89)	0.28

Multivariate model†		Patients	Deaths	Adjusted hazard ratio (95% CI)	p value (Wald)
Treatment	Postoperative radiation vs. surgery only	119	15	0.99 (0.23–4.25)	0.99
Type of surgery	Complete vs. none/biopsy/partial			0.18 (0.03–0.95)	0.04
Age	Per 10-year increase			0.66 (0.44–0.97)	0.03

* High = 3/anaplastic, moderate = 2/cellular, low = 1/myxopapillary. Because numerical designations were not available for all cases, descriptors were used.

† $p = 0.007$ model fit.

of the 12 patients with infield failure and 50.2 Gy (range, 16–56 Gy) for 8 patients with other types of progression.

As shown in the upper panel of Table 5, site-reported grade was the only factor identified as significant on univariate analysis of PFS. The risk of disease progression among patients with high-grade tumors was more than twice that of patients with low- or moderate-grade tumors: HR = 2.67 (95% CI, 1.15–6.20; $p = 0.02$).

The lower panel of Table 5 presents results from a multivariate analysis that considered radiation treatment in the context of site-reported grade and other additional factors found to be of marginal significance in the univariate analysis. In the resulting model, POXRT compared with surgery alone was associated with a significant reduction in risk of disease progression for patients whose tumors were reported to be of low or moderate grade (adjusted hazard ratio 0.24, $p = 0.02$). There was no evidence of a radiation benefit, however, in patients with high-grade tumors (adjusted hazard ratio, 1.42; $p = 0.67$). Type of surgery remained significant after adjustment for grade, treatment, and the identified interaction, with an estimated 84% reduction in risk of progression (hazard ratio, 0.16; $p = 0.01$) for patients who had a complete resection. (The effects of grade and treatment are illustrated in the lower panel of Fig. 2.)

Overall survival: There were 24 deaths among the astrocytoma patients after a median follow-up of 21 months (range, 2 months to 13 years and 8 months). The 33 patients who were alive at last contact were followed for a median of 5.8 years (range, 8 months to 15 years). Kaplan-Meier estimates of the proportion of surviving patients at 5, 10, and 15 years were 59% (95% CI, 46–73%), 53% (95% CI, 35–70%), and 32% (95% CI, 7–56%), respectively. Median survival could not be estimated with reasonable precision: the point estimate was 11 years, 8 months, but the lower bound of the corresponding 95% CI was only 47 months (Fig. 2).

Five of the 24 deaths occurred in the group of 18 patients treated with surgery only; 1 of the deceased patients had complete resection, 2 partial resection, 1 biopsy only, and 1 unknown. Nineteen of the 39 patients who received postoperative radiation died, but only 2 of these patients had complete resection, whereas 9 had partial resection and 8 had biopsy only.

Univariate analysis of OS, which is summarized in the upper panel of Table 6, identified site-reported grade as significant, whereas date of surgery was marginally significant. Results from the multivariate analysis of OS for astrocytoma patients are seen in the lower panel of Table 6. After adjustment for grade and age, POXRT did not significantly affect the risk of death as compared with surgery alone (hazard ratio, 1.64; $p = 0.38$). Grade remained significant in the multivariate model and age was marginally significant. There was still no evidence of a survival benefit when patients receiving higher doses of radiation (≥50 Gy) were compared with those treated with surgery only (adjusted hazard ratio, 2.66; 95% CI,

Table 4. Characteristics of 57 astrocytoma patients by treatment group

Characteristic		Postoperative radiation (39) *n* (%)	Surgery only (18) *n* (%)	*p* value*
Sex	Male	14 (36)	10 (56)	0.25
	Female	25 (64)	8 (44)	
Race	White	23 (59)	6 (40)	0.24
	Other	16 (41)	9 (60)	
	Missing	0	3	
Ethnicity	Hispanic	3 (8)	0	0.55
	Non-Hispanic	36 (92)	16 (100)	
	Missing	0	2	
Age at surgery	≤24 years	16 (41)	6 (38)	0.54
	25–54	14 (36)	8 (50)	
	≥55	9 (23)	2 (12)	
	Missing	0	2	
		Median, 30; range, 1–69	Median, 29; range, 1–66	
Subtype	Pilocytic	5 (38)	7 (50)	0.70 (Pilocytic vs. fib/ other)
	Diffuse fibrillary	5 (39)	4 (29)	
	Other	3 (23)	3 (21)	
	Missing	26	4	
Grade, site reported	High (3,4)	8 (23)	2 (13)	0.70 (High vs. low/moderate)
	Moderate (2)	13 (37)	6 (40)	
	Low (1)	14 (40)	7 (47)	
	Missing	4	3	
Grade, WHO	High (3,4)	1 (9)	3 (23)	0.60 (High vs. low/moderate)
	Moderate (2)	6 (55)	3 (23)	
	Low (1)	4 (36)	7 (54)	
	Missing	28	5	
Presence of cysts	Yes	10 (29)	6 (43)	0.50
	No	25 (71)	8 (57)	
	Missing	4	4	
Cord involvement	Cervical	14 (36)	4 (25)	1.0 (Cervical/thoracic vs. con/other)
	Thoracic	10 (26)	6 (38)	
	Conus	1 (2)	0 (0)	
	Overlapping sites/other	14 (36)	6 (38)	
	Missing	0	2	
Number of segments	≤5	25 (68)	12 (75)	0.75
	≥6	12 (32)	4 (25)	
	Missing	2	2	
Surgery	Complete resection	5 (13)	8 (53)	<0.01
	Biopsy/partial resection/none	33 (87)	7 (47)	
	Missing	1	3	
Date of surgery	Pre-1980	7 (18)	3 (17)	<0.02 (Pre-1990 vs. later)
	1980–1989	13 (33)	0	
	1990 or later	19 (49)	15 (83)	
Radiation dose	<50 Gy	13 (37)	1	NA
	≥50 Gy	22 (63)	3	
	Missing/NA	4	14	

Abbreviations: con = conus; fib = fibrillary.
* Chi-square or Fisher's exact test.

0.82–8.67; $p = 0.10$. PFS and OS of astrocytomas by grade and treatment are shown in Fig. 2.

DISCUSSION

The management of spinal cord gliomas continues to evolve. Because the low incidence of the disease in some patients, as well as the long natural history of the disease, the optimal management of these patients continues to be challenging. This multi-institutional study includes 183 patients; 101 of these patients received radiation as part of their initial management. Thus, this study is one of the larger studies dealing with radiation in spinal cord gliomas. Even so, this effort demonstrates the difficulty of obtaining data in a retrospective manner in this disease.

The extent of surgical resection has been shown in some studies to influence prognosis (33), with significantly better survival rates after complete resection compared with incomplete resection. In this study, complete resection significantly reduced the risk of disease progression in astrocy-

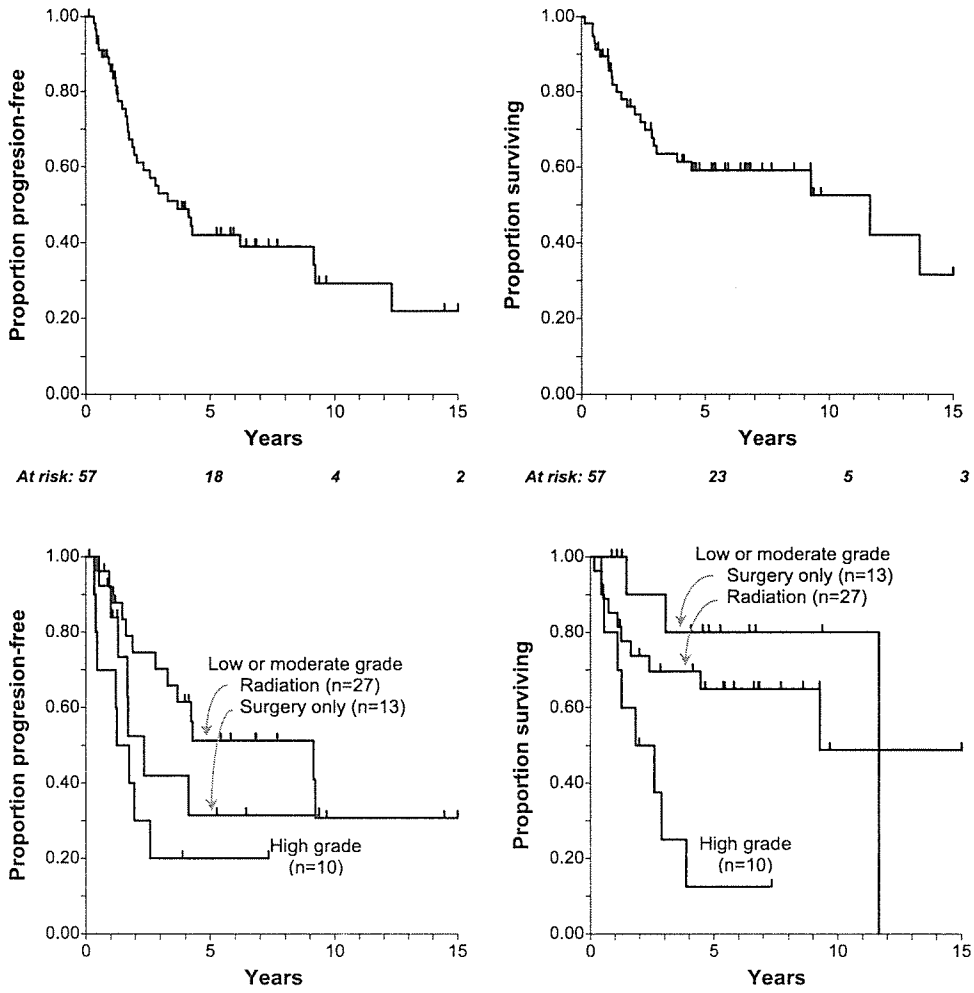

Fig. 2. Progression-free and overall survival in 57 astrocytoma patients by tumor grade and treatment.

tomas. The effect was marginal in ependymomas, but OS was significantly improved by complete resection in this patient group. The method of complete resection may also be important. Tumors removed in a piecemeal fashion have been reported to have higher failure rates compared with those who had their tumor removed en-bloc, and postoperative radiation is recommended as adjuvant therapy to improve outcome (32). The method of complete resection could not be adequately studied in this series because of the small number of patients with this information.

Radiation significantly reduced the risk of disease progression in low- and moderate-grade astrocytomas in this study. However, evaluation of the effect of radiation dose on survival revealed the absence of a significant difference in this series. This may be due to the fact that only 6 of 39 astrocytomas and 14 of 62 ependymoma patients received doses less than 45 Gy—too small a number to show a dose–response. In the literature, a dose–response was seen by Garcia (11) at dose levels ≤40 Gy vs. >40 Gy. In the study by Kopelson *et al.* (14), a dose–response was seen at a time–dose factor of 65 Gy for ependymomas. Dose responses were not detected at higher dose levels commonly used for these gliomas (45 Gy or greater) (16, 19, 26).

Ependymomas

OS in our series for ependymomas was 91% and 84% at 5 and 10 years, respectively. This was consistent with the ranges quoted in the literature that are between 50–100% at 5 years and 50–95% at 10 years. A higher 15-year survival of 75% was seen in this series, as compared with 25–62% in the literature (9, 21).

In our current series, race and age influenced 15-year PFS, but only age influenced OS of ependymomas. Although Read (21) also found age to be a significant factor, with children doing worse than adults, the series combined intracranial and spinal ependymomas, with spinal ependymomas comprising 15% of these tumors. On the other hand, although Sgouros *et al.* (37) and Whitaker *et al.* (33) also found age to be a significant factor on univariate analysis, they found that younger patients (<40 years of age) did better than older patients. This was different from some series that showed that age was not a significant factor in determining survival (31). Grade was found to be a significant prognostic factor in other series (31) and significantly affected OS and disease-free survival of ependymomas at 15 years on univariate analysis in the current series. The prognostic effect of grade in ependymoma patients was

Table 5. Cox proportional hazards models for 15-year progression-free survival in 57 patients with astrocytoma

Factors (univariate analysis)		Patients	Progression	Hazard ratio (95% CI)	*p* value (Wald)
Treatment	Postoperative radiation vs. surgery only	57	33	0.89 (0.43–1.84)	0.75
Sex	Male vs. female	57	33	1.10 (0.55–2.20)	0.79
Race	White vs. others	54	30	0.52 (0.25–1.11)	0.09
Age	Per 10-year increase	55	31	1.10 (0.90–1.32)	0.26
Grade, site-reported*	High vs. low/moderate	50	28	2.67 (1.15–6.20)	0.02
Grade, WHO	High vs. low/moderate	24	10	0.91 (0.18–4.51)	0.91
Cysts	Present vs. not	49	27	0.49 (0.18–1.29)	0.15
Cord involvement	Lumbar/conus vs. cord proper	55	31	1.20 (0.46–3.12)	0.72
Segments	6 or more vs. 5 or fewer	53	30	0.95 (0.43–2.08)	0.90
Type of surgery	Complete vs. none/biopsy/partial	53	29	0.33 (0.10–1.09)	0.07
Date of surgery	1980–1989 vs. pre-1980	57	33	1.77 (0.58–5.45)	0.32
	1990+ vs. pre-1980			1.84 (0.67–5.06)	0.24

Multivariate model†		Patients	Progression	Adjusted hazard ratio (95% CI)	*p* value (Wald)
Treatment	Postoperative radiation vs. surgery only	48	26		
	Low/moderate grade			0.24 (0.08–0.79)	0.02
	High grade			1.42 (0.28–7.26)	0.67
Type of surgery	Complete vs. none/biopsy/partial			0.16 (0.04–0.66)	0.01

* High = 3, 4; moderate = 2; low = 1.
† $p = 0.008$ model fit; treatment adjusted for type of surgery and grade, allowing for treatment-grade interaction ($p = 0.08$).

inconclusive on multivariate analysis—the limited site reporting of tumor grade (82 of 126 ependymoma patients) may have contributed to lack of significance.

On reviewing the ependymoma patient population in this series, it is evident that the group that received radiation as a component of their initial therapy had a more adverse prognostic factor profile that may ultimately influence outcome. For example, they were less likely to undergo complete resections (20% vs. 82%; $p < 0.01$). Furthermore, only 42% of radiation patients in this study were treated in 1990 or later, when optimal treatment techniques and imaging became more widely available, compared with 90% of the surgery-only group ($p < 0.01$). None of the patients who received surgery alone had high-grade disease as compared with a significant percentage (21%) of the radiation patients with this poor prognosticator ($p < 0.01$).

Table 6. Cox proportional hazards models for 15-year overall survival in patients with astrocytoma

Factors (univariate analysis)		Patients	Deaths	Hazard ratio (95% CI)	*p* value (Wald)
Treatment	Post-operative radiation vs. surgery only	57	24	2.08 (0.78–5.58)	0.15
Sex	Male vs. female	57	24	0.99 (0.44–2.23)	0.98
Race	White vs. others	54	22	0.85 (0.35–2.07)	0.73
Age	Per 10-year increase	55	23	1.17 (0.96–1.44)	0.13
Grade, site-reported*	High vs. low/moderate	50	21	4.06 (1.60–10.30)	<0.01
Grade, WHO	High vs. low/moderate	24	6	1.93 (0.32–11.50)	0.47
Cysts	Present vs. not	49	18	0.66 (0.22–2.02)	0.47
Cord involvement	Lumbar/conus vs. cord proper	55	23	1.09 (0.32–3.70)	0.89
Segments	6 or more vs. 5 or fewer	53	22	1.06 (0.43–2.60)	0.90
Type of surgery	Complete vs. none/biopsy/partial	53	23	0.49 (0.15–1.66)	0.25
Date of surgery	1980–1989 vs. pre-1980	57	24	3.39 (0.90–12.74)	0.07
	1990+ vs. pre-1980			1.40 (0.37–5.22)	0.62

Multivariate model†		Patients	Deaths	Adjusted hazard ratio (95% CI)	*p* value (Wald)
Treatment	Postoperative radiation vs. surgery only	50	21	1.64 (0.54–4.96)	0.38
Grade, site-reported	High vs. low/moderate			4.86 (1.83–12.88)	<0.01
Age	Per 10-year increase			1.23 (0.99–1.54)	0.06

* High = 3, 4; moderate = 2; low = 1.
† $p = 0.006$ model fit.

Univariate analysis demonstrated that radiation may have an adverse effect on PFS but not on OS, which may reflect the effect of the dominance of adverse prognostic factors in the radiation group.

Multivariate analysis was limited by the large number of patients who had missing data regarding grade. Even so, only age was found to significantly affect PFS at 15 years, with extent of resection being marginally significant ($p = 0.06$), which is contrary to observations by other authors (2, 38) and suggests that the unequal distribution of various prognosticators between the two study groups in this study. As for OVS, age and extent of resection determined outcome in these patients. The same two factors were the only significant factors with regard to OS. Radiation did not confer any significant protection in terms of survival, consistent with Sgouros *et al.* (37). Other authors, however, have championed radiation postoperatively in ependymomas after incomplete removal of ependymomas and in those with aggressive histopathologic features (39).

Astrocytomas

Gender, race, and age were not found to significantly influence 15-year PFS or OS in astrocytomas in this series on univariate analysis. However, an age of <18–20 years was found to be associated with an increase in recurrence free survival (23, 40). In some series, however, age older than 20 years was a favorable prognosticator (19).

The radiation group had less complete resections as compared with the surgery alone group (13% vs. 53%; $p < 0.01$). Furthermore, only 49% of radiation patients in this study were treated in 1990 or later, compared with 83% of the surgery-only group ($p < 0.01$).

On univariate analysis, grade was the only significant factor affecting PFS and OVS at 15 years. Completeness of resection and grade were the only significant factors for PFS on multivariate analysis. OVS was affected only by grade on multivariate analysis. This was consistent with the findings of Kim *et al.* (41).

Certain limitations were unavoidable in this retrospective analysis, most importantly the selective use of radiation therapy in patients with poor prognostic factors as determined by standard clinical practice. Thus, the desired comparison of outcomes on the basis of whether or not patients received postoperative radiation necessarily relies on covariate adjustment rather than baseline comparability of the two groups. In addition, central pathology review was not possible in all patients and grade review was even less complete. Thus, analysis of grade in conjunction with radiation therapy and other risk factors was limited. In the case of ependymoma patients, adjustment for grade was possible only in a subset of 82 (65%) patients for whom site-reported grade was available. This is a very important factor that may influence study outcomes. Another limitation of our study was the lack of sufficient information on all of the potentially eligible patient records, leading to their elimination from the study.

The lack of standard treatment techniques may have adversely influenced the effectiveness of the postoperative radiation such as low total doses, doses per fraction, or unconventional techniques. Another potential flaw is the fact that MRI or CT scans were not centrally reviewed. An attempt was made to minimize the impact of this on results by establishing a uniform definition of progression of disease that was agreed on from the onset of the study.

In conclusion, our findings indicate that ependymoma patients whose tumors are completely resected have a more favorable prognosis with respect to both disease progression and OS than do those whose surgical treatment is limited to partial resection or biopsy. Contrary to expectation, we did not find evidence that radiation treatment is beneficial in these patients. With regard to overall survival in astrocytomas, high-grade tumors were the only significant risk factor, whereas age had a marginally significant effect. Although POXRT did not affect OS, it significantly reduced the risk of disease progression in astrocytoma patients whose tumors were reported to be of low or moderate grade, compared with treatment consisting of surgery alone. We did not find evidence of a similar effect on the progression of disease in high-grade astrocytoma; however, our study included only 10 such patients. Complete resection surgery was also significant in reducing the risk of disease progression in astrocytomas. We recommend the establishment of a national database of spinal cord tumors with pathology blocks being stored for subsequent review. This will allow sufficient numbers of treated patients to look at grade and better define the indications for adjuvant therapy.

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Clinical–patient studies

Hypofractionated radiotherapy boost for dose escalation as a treatment option for high-grade spinal cord astrocytic tumor

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Key words: astrocytoma, ependymoma, glioma, hypofractionated radiotherapy boost, radiotherapy, spinal cord

Summary

Purpose: To retrospectively analyze the outcome of post-operative radiotherapy for spinal cord glioma with the emphasis on the hypofractionated radiotherapy boost for dose escalation as a treatment option for high-grade spinal cord astrocytic tumors.

Materials and methods: Forty-one patients with spinal cord glioma received post-operative radiotherapy between 1979 and 2003. The median age was 34 years (range, 10–66 years). Median follow-up was 49 months (range, 5–291 months). There were 12 low-grade astrocytic tumors, 11 high-grade astrocytic tumors, 16 low-grade ependymal tumors and 2 high-grade ependymal tumors. Among 11 patients with high-grade astrocytic tumors, 5 with anaplastic astrocytoma and 1 with glioblastoma received hypofractionated radiotherapy boost for dose escalation. The median total dose of the conventional radiotherapy was 45.5 Gy in 19 fractions (range, 30.0–60.0 Gy). The median normalized total dose (using daily dose of 2.0 Gy and an α/β ratio of 2.0) of the hypofractionated radiotherapy boost was 131 Gy_2 (range, 85 249).

Results: The Kaplan Meier survival rates at 10 years from the date of the first surgery were 64% for the entire group, 47% for the astrocytic tumors and 84% for the ependymal tumors, respectively ($P=0.009$). Among 11 patients with high-grade astrocytic tumors, the actuarial survival rate at 10 years was 35%. The actuarial survival rates at 10 years were 67% for those who received hypofractionated radiotherapy boost for dose escalation, and 20% for those who did not ($P=0.47$).

Discussion: The results for ependymal tumors and low-grade astrocytic tumors were comparable to those reported in the literature. Hypofractionated radiotherapy boost for dose escalation may help to prolong the survival of patients with high-grade astrocytic tumors.

Introduction

Spinal cord glioma is a rare disease with an expected 5-year overall survival rate of 54–82% [1,2]. Survival strongly depends on the pathological grade and subtypes of the disease. Long-term motor and sensory function is related to the extent of the surgical removal, and possibly to the adjuvant post-operative radiotherapy. Spinal ependymal tumors usually have a low-grade histology, and a 5-year survival rate of 83–100% [3,4]. Astrocytic tumors are often malignant and have a 5-year survival rate of 50–64% [1,4,5]. The benefits of post-operative radiotherapy in reducing relapse of the tumor after partial resection has been suggested by retrospective analyses both for ependymal tumors [4,6] and astrocytic ones [7,8], but its value has been questioned for children with astrocytic tumors [8]. It would be worthwhile to publish the long-term outcome of post-operative radiotherapy for spinal gliomas.

High-grade astrocytic tumors have a worse outcome, with a 5-year overall survival rate of 0–24% [1,9–12]. The benefits of chemotherapy in addition to radiotherapy are still under investigation [13]. Meanwhile hypofractionated radiotherapy boost for dose escalation for high-grade brain gliomas has been suggested to prolong the progression-free survival compared to the conventional dose radiotherapy albeit with increased toxicity [14–16]. The hypofractionated radiotherapy boost is far beyond the tolerance dose of the spinal cord, which means that sensorimotor function will deteriorate if a high dose is used for spinal cord glioma. However, the sensorimotor function of patients with spinal high-grade astrocytic tumors is usually very poor at the time of initial diagnosis, before treatment has begun [4,13]. Because of this pre-existing dysfunction, patients with high-grade astrocytic tumors would lose little sensorimotor function after hypofractionated radiotherapy boost. After conducting an ethics evaluation, we adopted hypofractionated radiotherapy boost as an option for patients with high-grade astrocytic tumors at the thoracic or lumbar spinal cord.

In this study, we have updated the long-term outcome of radiotherapy for spinal cord glioma. In addition, the efficacy and adverse effects of hypofractionated radiotherapy boost were investigated.

Materials and methods

Study group

Forty-one patients were treated with post-operative irradiation for spinal cord glioma at our institution between 1979 and 2003. Twenty were male, and 21 female. The median age was 34 years (range, 10–66).

Tumor characteristics

Pre-operative and pre-radiotherapeutic radiological investigation varied according to the time period during which the investigation was performed. A magnetic resonance imaging (MRI) was performed in 33 patients, a computed tomography (CT) in 2, a CT-myelogram in 2, and a myelogram in 4. The main location of the tumors was the cervical spinal cord in 15 patients, the thoracic in 12, the conus medullaris in 9, and the cauda equina in 5. All patients had histopathological confirmation of their diagnosis by neuropathologists. The patients were classified into four groups according to the World Health Organization classification: 12 low-grade astrocytic tumors (1 pilocytic astrocytoma, 10 diffuse astrocytomas, 1 oligoastrocytoma), 11 high-grade astrocytic tumors (10 anaplastic astrocytomas, 1 glioblastoma), 16 low-grade ependymal tumors (4 ependymomas, 11 myxopapillary ependymomas, 1 ependymoma with astrocytoma) and 2 high-grade ependymal tumors (2 anaplastic ependymomas). There were 2 patients who were initially diagnosed with a low-grade astrocytic tumor, and experienced recurrence within a year. Since the surgical specimens in the second operation for these 2 patients showed high-grade glioma, the 2 patients were included in the high-grade group.

Surgical treatment

All patients underwent a surgical procedure prior to the initial radiation therapy; 5 patients underwent a gross total resection, 32 a subtotal or partial resection, and 4 a biopsy.

Radiation therapy

Conventional radiation therapy excluding the hypofractionated radiotherapy boost for dose escalation

Treatment was given to the primary tumor site with or without additional irradiation to the entire spine or entire central nervous system. In general, the gross tumor volume (GTV) was a gadolinium-enhanced area on MRI as well as high-intensity areas on T2-weighted MRI. The clinical target volume (CTV) was determined by adding 2–4 cm margins to the cranial and caudal sides to the GTV. The planning target volume (PTV) margin was 1 cm for each side. Treatment was delivered with mega-voltage X-ray (4, 6, or 10 MV), except in 2 patients who had been treated by cobalt gamma ray 13 and 19 years ago. Local irradiation was given using single posterio-anterior and/or oblique wedge-pair fields. For the low-grade astrocytic tumors and low-grade ependymal tumors with post-operative residual disease, we treated the patients with 40–46 Gy in 20–23 fractions. For the patients who received conventional radiotherapy, the median total dose was 46 Gy in 23 fractions (range, 35 Gy in 14 fractions to 50 Gy in 20 fractions) in the low-grade astrocytic tumors and 40 Gy in 20 fractions (range, 30 Gy in 12 fractions to 50.4 Gy in 28 fractions) in the low-grade ependymal tumors. In routine practice, the patients with high-grade glioma were treated with 50–54 Gy in 25–27 fractions. The median total dose was 50 Gy in 25 fractions (range, 46 Gy in 23 fractions to 60 Gy in 24 fractions) in the patients with high-grade gliomas who were treated with the conventional radiation therapy.

Hypofractionated radiotherapy boost for dose escalation

After conducting an ethics evaluation, the following research was conducted for patients with high-grade astrocytic tumors. Patients were candidates for hypofractionated radiotherapy boost for dose escalation if the high-grade astrocytic tumors existed in the thoracic or lumbar spinal cord and the upper edge of the PTV did not involve the cervical spinal cord or the spine at a higher level. Patients with a disseminated tumor were not candidates for this treatment. The definitive loss of function that would occur after this treatment was explained to all patients and their families in detail. In all cases, the treatment was applied only with the written informed consent of the patients and their families.

The hypofractionated radiotherapy boost was delivered using the supra-tolerable dose for the spinal cord. We used various dose fractionation schedules depending on the length of the field, surrounding critical organs, and the general condition of the patient. We defined an irradiation dose of more than 70 Gy_2 or more in normalized total dose (NTD) assuming a 2 Gy daily dose with α/β of 2.0 as the hypofractionated radiotherapy boost for dose escalation. We used 6 or 10 MV X-rays with two to three portals to reduce the spread of the dose to surrounding normal tissue, except in one patient who received posterior single portal irradiation. All treatments were given to the involved areas with the same margin as conventional radiotherapy.

Adverse effect assessment

Neurologic motor function was scored and classified into four groups (excellent, good, fair, or poor/dead) at the time of initial diagnosis based on our previous study [4] (Table 1), and these scores were compared to those obtained at the patient's last visit. Other adverse events were scored according to the National Cancer Institute

Table 1. Neurological motor function classification

Excellent	Intact or minimal neurological deficit, no functional impairment
Good	Mild neurological deficit, ambulating without braces or aid, no functional impairment
Fair	Moderate neurological deficit, ambulating with braces and/or aid, significant functional impairment
Poor	Quadriplegic or paraplegic, wheel chair dependent, significant functional impairment

Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE v3.0).

Statistics

Follow-up time was calculated from the first date of the surgery. The median follow-up time for the entire group was 53 months (range, 5–291), and that of the 6 patients who received hypofractionated radiotherapy boost, 19 months (range, 8–124). Survival rates were determined with the Kaplan–Meier method. Univariate analyses were performed using the log-rank test.

Results

Entire group

By the time of the last follow-up, 13 patients had died. The actuarial survival rates of the entire group at 5 and 10 years from the date of the first surgery were 73% and 64%. The actuarial survival rates at 5 and 10 years were 54% and 47% for astrocytic tumors, and 94% and 84% for ependymal tumors, respectively ($P=0.009$) (Figure 1). Among the 23 patients with astrocytic tumors, the 5- and 10-year actuarial survival rates were 68% and 57% for low-grade tumors, and 40% and 40% for high-grade ones ($P=0.056$) (Figure 2). The 5- and 10-year actuarial survival rates were 100% and 88% for low-grade ependymal tumors. There was a significant difference in survival between low-grade ependymal tumors and low-grade astrocytic tumors ($P=0.05$). The 2-year actuarial survival rates and progression-free rates were 53% and 18% for high-grade astrocytic tumors. The median survival for the high-grade astrocytic tumors was 21 months (range, 5–221).

For 11 patients with myxopapillary ependymoma, the actuarial 5- and 10-year survival rates were 100% and 80%, respectively. For 5 patients with ependymoma,

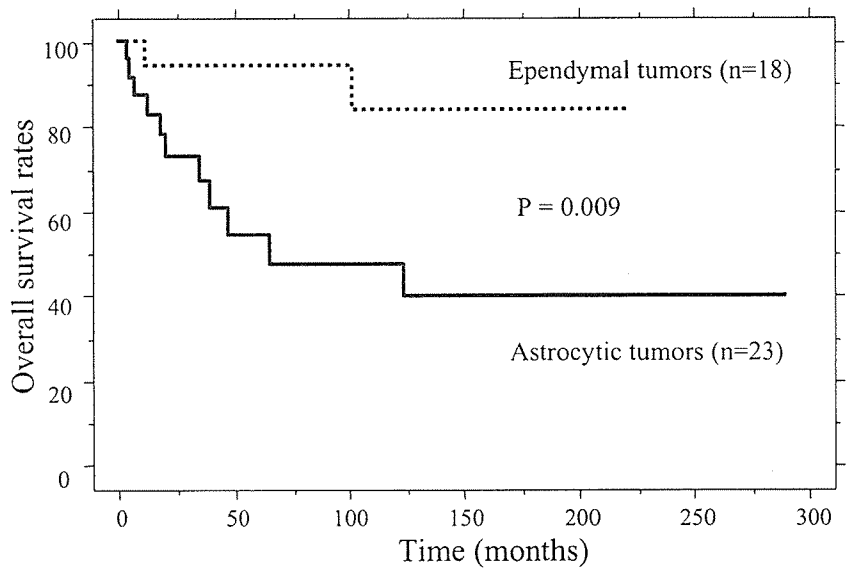

Figure 1. The actuarial survival curves for astrocytic tumors and for ependymal tumors.

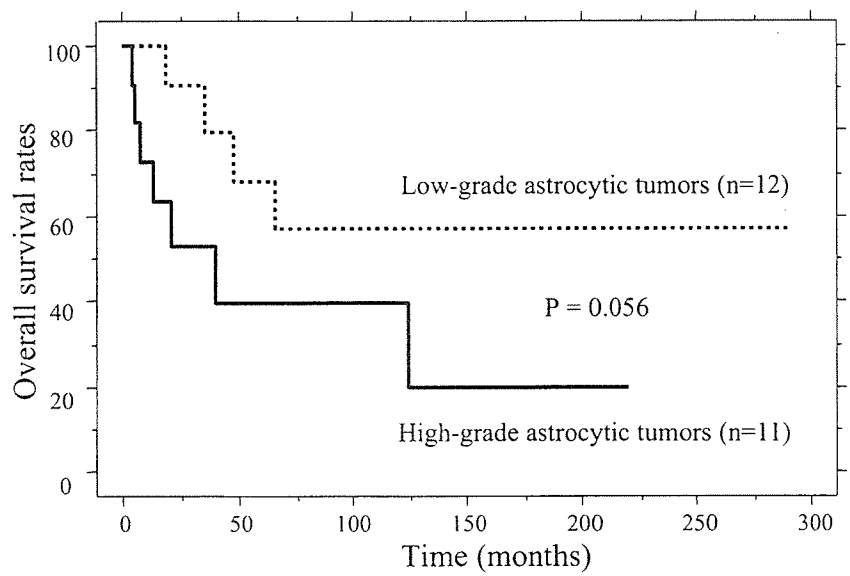

Figure 2. The actuarial survival curves for low-grade astrocytic tumors and for high-grade ones.

those rates were 100% and 100%. Tumor relapse at the cauda equina after radiotherapy was observed in a single patient with myxopapillary ependymoma, for whom the irradiation field had not included the cauda equina. In two with anaplastic ependymoma, one patient died at 12 months, and the other lived for 224 months.

The results of neurological assessment are shown in Table 2. Motor function at the time of initial diagnosis was excellent in 5, good in 23, fair in 7, and poor in 6 patients. At the last follow-up, motor function was scored as excellent in 10, good in 3, fair in 2, poor in 5, dead in 13, and unknown in 8. Improvement of motor function was observed in 9 patients, of whom 8 had good function and 1 fair at the initial diagnosis. No patient with poor function at the initial diagnosis showed improvement of motor function.

Hypofractionated radiotherapy boost for dose escalation

Of the 6 patients who received hypofractionated radiotherapy boost for dose escalation, there was 1 glioblastoma, and 5 were anaplastic astrocytomas as shown in Table 3A. The characteristics of 5 patients with anaplastic astrocytoma who did not receive hypofractionated radiotherapy boost are also shown in Table 3B. The median total NTD of the hypofractionated radiotherapy boost was 131 Gy_2 (range, 85–249 Gy_2). The actuarial 3-, 5- and 10-year survival rates were 67%, 67% and 67% for the patients who received a hypofractionated radiotherapy boost, and 40%, 20% and 20% for the others with high-grade astrocytic tumors ($P = 0.47$) (Figure 3).

Table 2. Result of neurological assessment

	Initial diagnosis	Last follow-up
Excellent	5	10
Good	23	3
Fair	7	2
Poor	6	5
Dead	-	13
Unknown	-	8
Total	41	41

Effectiveness of the treatment was evaluated radiologically and histopathologically in one patient who suffered from marginal relapse. The patient had thoracic anaplastic astrocytoma (Table 3A, No. 6) and treated with 40 Gy in 10 fractions after 46 Gy in 23 fractions with the margin of field at the edge of high intensity in T2-weighted image, that is, the junction of C7 and T1 (C7/T1). The patient experienced marginal relapse at C7/T1. Surgical resection of the relapsed tumor showed that tumor relapse was observed also at the level of T3/4 which had received 80% of the prescribed dose but no tumor cell was detected at the level below T5 where more than 90% of the prescribed dose had been irradiated. Hypofractionated radiotherapy boost was interrupted for 6 days in one patient who experienced a severe decline in bowel movements during the treatment. NCI-CTCAE v3.0 Grade 3 leukopenia was seen in 2 patients during hypofractionated radiotherapy boost. No patients suffered from radiation-induced skin necrosis throughout the follow-up period. One patient treated by a single posterior field experienced severe subcutaneous induration and pruritus starting 3 years after the treatment. The patient was treated with a single posterior field, and was the initial patient for this treatment in our series. Two patients experienced severe lower limb pain for 3–6 months, which began at 6 months after the treatment, and decreased in intensity afterwards. Regarding neurologic motor function, one patient had good function and the rest poor before treatment. After the hypofractionated radiotherapy boost for dose escalation, the one with good function pre-treatment had been ambulant for 10 months, and was alive, using a wheelchair, and fully employed at 45 months after the treatment at the time of analysis. The poor function of the other 5 remained after treatment.

In the same patient who experienced marginal relapse, pathological examination of the normal structure was also performed which shoed that the spinal cord and meningus below the level of T5 was severely atrophied.

Table 3. Patients characteristics of high-grade astrocytic tumors treated with (A) hypofractionated radiotherapy boost for dose escalation; (B) conventional radiotherapy

No.	Sex	Age	Pathological diagnosis	Site	Treatment	NTD[a] (Gy_2)	Follow-up time (mo)	Final status	Cause of death
(A)									
1	M	54	Anaplastic astrocytoma	T7-10	40 Gy/16f + 40 Gy/4fr	165.0	123.9	Dead	Unknown
2	F	12	Anaplastic astrocytoma	T7-10	46 Gy/23f + 18.75 Gy/3fr	84.7	13	Dead	Dissemination
3	M	37	Glioblastoma	T1-4	9 Gy/6f + 40 Gy/4fr	127.9	8	Dead	Dissemination
4	F	31	Anaplastic astrocytoma	T12-L1	14 Gy/7f + 60 Gy/10fr	134.0	45	Alive	-
5	M	54	Anaplastic astrocytoma	T10-L2	40 Gy/16f + 42 Gy/7f + 40 Gy/4fr	249.0	29	Alive	-
6	F	23	Anaplastic astrocytoma	T1-T12	46 Gy/23fr + 40 Gy/10fr	106.0	18	Alive	-
(B)									
1	M	37	Anaplastic astrocytoma	T11-L1	52.5 Gy/23fr	57.2	21	Dead	Dissemination
2	F	34	Anaplastic astrocytoma	C1-C7	45.5 Gy/19fr	50.4	221	Alive	-
3	M	11	Anaplastic astrocytoma	T11-L1	50 Gy/20fr	56.3	5	Dead	Dissemination
4	F	34	Anaplastic astrocytoma	C4-C6	46 Gy/23fr	46.0	40	Dead	Dissemination
5	M	19	Anaplastic astrocytoma	C1-C4	50 Gy/25fr	50.0	5	Dead	Dissemination

[a]NTD (Gy_2): Normalized total dose using a daily dose of 2.0 Gy and α/β ratio of 2.0.