Supratentorial Low-Grade Glioma in Adults: An Analysis of Prognostic Factors and Timing of Radiation

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Purpose: **To review the outcomes of patients with low-grade glioma diagnosed by modern imaging and treated at a center where postponing radiotherapy was common practice.**

Methods: **We reviewed the records of patients (age ≥ 18 years) with pathologically confirmed supratentorial low-grade fibrillary astrocytoma, oligodendroglioma, and mixed glioma treated at a regional cancer center in Canada between 1979 and 1995.**

Results: **Median survival for the entire group (N = 167; mean age 40.6 years) was 10.5 years with 5- and 10-year survival rates of 72% and 50%, respectively. Median progression-free survival was 4.9 years with 5- and 10-year progression-free rates of 50% and 12%, respectively. Overall and progression-free survivals were longer for patients with an oligodendroglioma or mixed glioma than with astrocytoma (median 13 *v* 7.5 years, *P* = .003; progression-free 5.6 *v* 4.4 years, *P* = .054). Age at diagnosis ≤ 40 years, seizures at presentation, minimal residual tumor after surgery, Karnofsky performance status ≥ 70, and oligodendroglioma or mixed glioma pathology were associated with significantly longer median survival on univariate and multivariate analyses. Radiotherapy deferred until tumor progression (*v* immediate radiotherapy) was associated with longer survival on univariate analysis, but an imbalance in other variables accounted for this advantage such that timing of radiotherapy was not an independent (favorable or adverse) prognostic factor on multivariate analysis.**

Conclusion: **Patients with low-grade glioma diagnosed by modern imaging can be expected to live a long time; timing of radiotherapy may be a less important determinant of survival than nontreatment variables and residual tumor bulk.**

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LOW-GRADE fibrillary astrocytoma, oligodendroglioma, and mixed glioma are CNS neoplasms that grow slowly and infiltrate widely. Many patients with these tumors are relatively asymptomatic on anticonvulsants, although some have intractable seizures or other disabling symptoms.[1,2] Often indolent initially, these types of low-grade glioma may progress to fast-growing high-grade tumors (ie, anaplastic glioma or glioblastoma multiforme); this transition occurs gradually in most instances.[2] Occasionally, patients are cured by aggressive surgical resection,[3,4] but typically these neoplasms are chronic illnesses that ultimately prove fatal. Retrospective studies[3-17] have identified a number of favorable prognostic factors, which, in addition to complete resection, include younger age at diagnosis, good performance status after surgery, and oligodendroglioma or mixed glioma histology. Most authorities recommend that a definitive diagnosis be established by early surgery whenever imaging studies reveal a supratentorial lesion that is compatible with a low-grade glioma, although watchful waiting, deferring surgery, may be an appropriate course of action for some patients.[18,19]

A critical question in the management of patients with supratentorial low-grade glioma centers on the timing of radiotherapy.[18-21] When in the natural history of low-grade glioma do the potential tumor-controlling benefits of radiation outweigh its potential toxicity? The risks of radiation may include cognitive impairment, neuroendocrine failure, cerebral necrosis, or second malignancy.[22,23] Hopefully, this question will be answered by the European Organization for Research and Treatment of Cancer (EORTC) randomized controlled trial that evaluates early versus delayed radiotherapy; however, for now clinicians must make treatment recommendations on a case-by-case basis guided by the results of retrospective studies. Many retrospective analyses have concluded that postoperative radiotherapy significantly prolongs overall and progression-free survival when compared with no radiotherapy,[4,14,24-26] but few have evaluated the relative merits of early versus delayed radiation for patients with supratentorial low-grade glioma.[11] The present report summarizes our experience managing patients with low-grade fibrillary astrocytoma, oligodendroglioma, and mixed glioma at a center where many patients underwent postoperative radiation, but a similar number had radiotherapy deferred until there was clinical or radiographic evidence of tumor progression.

METHODS

Case Selection

The medical records of all patients with a diagnosis of low-grade glioma who were treated at the London Regional Cancer Centre in

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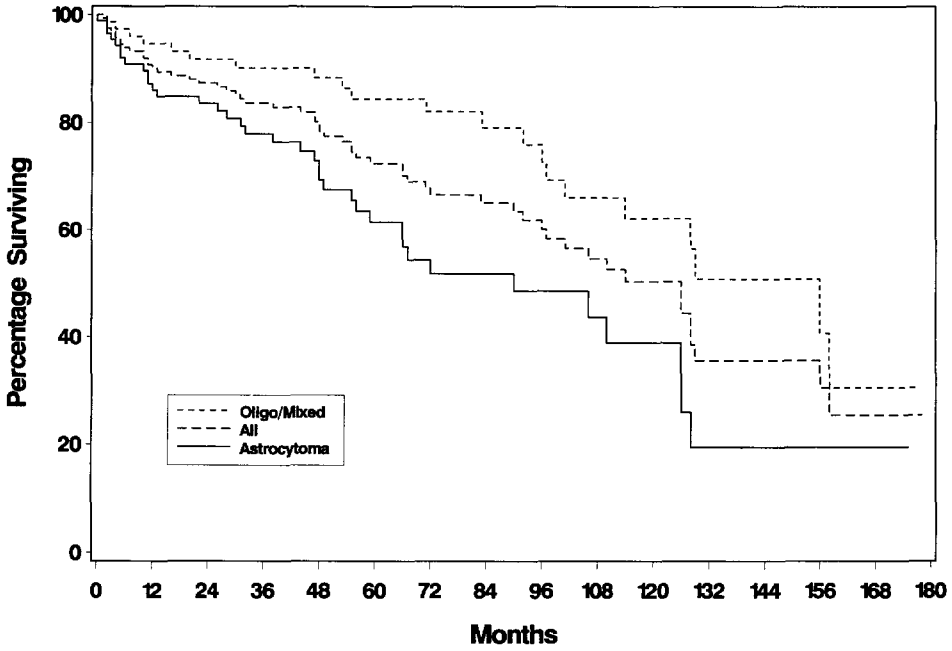

Fig 1. Actuarial survival curves depicting the overall survival of all patients, those with an astrocytoma, and those with an oligodendroglioma or mixed glioma.

London, Canada between January 1, 1979 and May 31, 1995 were reviewed. Adults (age ≥ 18 years) with a pathologically confirmed supratentorial low-grade fibrillary astrocytoma, oligodendroglioma, or mixed glioma (ie, oligoastrocytoma) were included in this analysis. Over the period of this review, Kernohan, modified Ringertz, and World Health Organization classification schemes for glial tumors were used at this center. Patients with other types of low-grade glioma, including those with pilocytic astrocytoma, gemistocytic astrocytoma, and incidental glioma-like lesions in corticectomy specimens removed during surgery for intractable epilepsy, were excluded from this study. Patients with incomplete radiation treatment records and all children with low-grade glioma also were excluded. Data abstracted from each patient's medical record included the following: sex; date of first symptom; date of first computed tomography (CT) or magnetic resonance (MR) scan that demonstrated a low-grade glioma; symptoms at presentation; date and age at tissue diagnosis; tumor location; presence of calcification or enhancement on the preoperative scan; extent of tumor resection based on imaging;

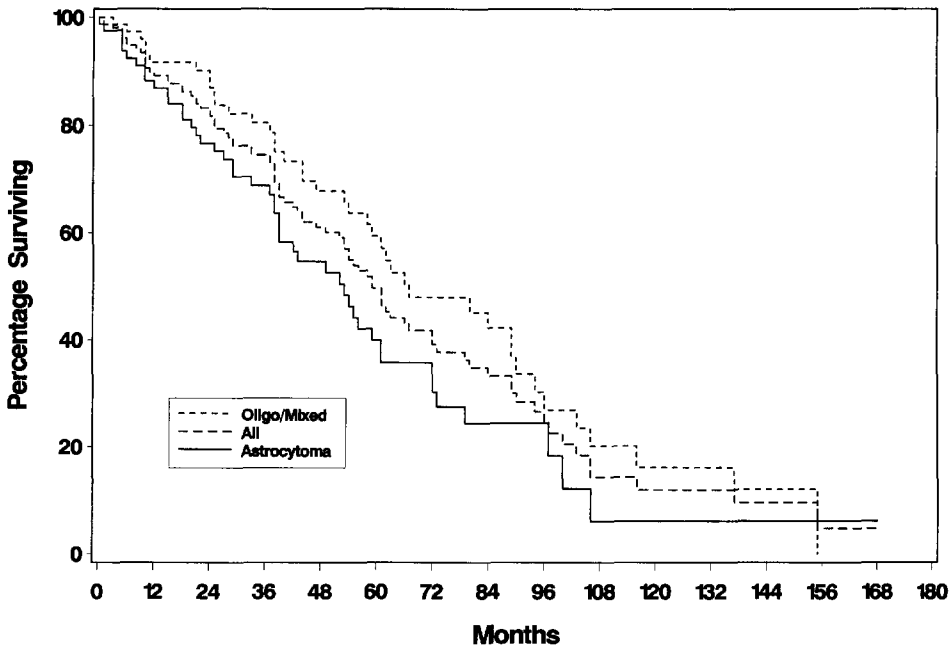

Fig 2. Actuarial survival curves depicting the progression-free survival of all patients, those with an astrocytoma, and those with an oligodendroglioma or mixed glioma.

Table 1. Overall Survival and 5- and 10-Year Survival Rates*

Prognostic Factor	Median Survival (months)	Univariate Analysis		Multivariate Analysis		5-Year Survival (%)	10-Year Survival (%)
		Hazards Ratio	P	Hazards Ratio	P		
Age (years)		2.032	.008	3 044	< .001		
≤ 40	128					79	61
> 40	97					64	36
Sex		0 847	538	—	NS		
Male	128					74	61
Female	97					70	34
Symptom duration (days)		1 837	036	—	NS		
≤ 30	156					79	63
> 30	97					70	41
Seizures		0.287	< .001	0 274	< 001		
No	55					44	21
Yes	128					81	60
Karnofsky score		0.408	001	0.358	< 001		
< 70	96					54	39
≥ 70	128					80	54
Residual tumor		2 065	.008	2 234	006		
Bulky	101					64	41
Minimal	128					82	59
Pathology		2.287	.003	1.802	.049		
Astrocytoma	90					62	39
Oligodendroglioma/mixed	156					84	62
Radiotherapy		2 329	.003	—	NS		
Postoperative	96					62	35
Delayed	156					84	70

Abbreviation. NS, not significant

*Five- and 10-year survival rates obtained from Kaplan Meier survival estimates

Karnofsky performance status after surgery; tumor type; timing of radiotherapy; radiation dose and technique; date of tumor progression; pathology at progression; treatment at progression; and last known status. The timing of radiotherapy was considered immediate if the patient received radiotherapy as an adjunct treatment after initial surgery and delayed if the patient was observed after initial surgery and irradiated for tumor progression. Patients in the immediate radiotherapy group were reimaged 6 to 8 weeks after completing treatment and then at 6 to 12 month intervals, or as clinically indicated. Patients in the delayed radiotherapy group were rescanned at 3 to 4 month intervals initially and then every 6 to 12 months, or as clinically indicated. The date of progression was determined retrospectively and qualitatively by two radiation oncologists (C.L. and B F.) and was based on symptomatic deterioration or radiographic worsening. CT and MR scans described as worse by a neuroradiologist were not reviewed again, and volumetric tumor measurements were not performed.

Statistical Methods

Overall and progression-free survival times and actuarial 5- and 10-year survival rates were estimated for all eligible patients using the Kaplan-Meier method and were measured from the date of tissue diagnosis. The following parameters were assessed for prognostic significance: sex; age at tissue diagnosis ≤ 40 years or more than 40 years; duration of symptoms ≤ 30 days or more than 30 days; seizures at presentation; calcification on the preoperative CT scan; contrast enhancement on the preoperative CT or MR scan; estimated extent of resection (≥ 90% resected *v* < 90% resected); postoperative Karnofsky performance status less than 70 or ≥ 70; tumor type (astrocytoma *v* oligodendroglioma or mixed glioma); and timing of radiotherapy (postoperative radiation *v* delayed radiation). Univariate and multivariate analyses were performed using the Cox proportional hazards model; multivariate analysis was performed in a forward and backward stepwise manner. The distribution of prognostic variables and rates of malignant degeneration between the immediate and delayed radiotherapy groups was compared using the χ^2 test. *P* values ≤ .05 were significant, based on two-tailed tests.

RESULTS

Demographics—All Cases

One hundred seventy-two adults had a pathologically verified supratentorial fibrillary astrocytoma, oligodendroglioma, or mixed glioma, and 167 (103 men and 64 women, age 18 to 84 years; mean age at diagnosis, 40.6 years) met all the eligibility criteria for this study; five (3%) were excluded because of inadequate radiation treatment records. For eligible patients, the median interval from the initial symptom attributable to the tumor to the first CT/MR scan that visualized the tumor was 2 months (range, 0 to 365), and from the first scan that visualized the tumor to the date of tissue diagnosis was less than 1 month (range, 0 to 119). Seventy-eight percent of patients had seizures at presentation, 31% had focal neurologic deficits, and 29% had headache. Cognitive or behavioral change (11%) and papilledema (9%) were uncommon. The tumor was located predominantly in the frontal lobe in

Table 2. Progression-Free Survival and 5- and 10-Year Progression-Free Rates*

Prognostic Factor	Median Progression-Free Survival (months)	Univariate Analysis		Multivariate Analysis		5-Year Survival (%)	10-Year Survival (%)
		Hazards Ratio	P	Hazards Ratio	P		
Age (years)		1.691	.017	2.236	< .001		
≤ 40	72					56	17
> 40	54					39	5
Sex		0.798	.314	—	NS		
Male	63					55	11
Female	54					41	18
Symptom duration (days)		0.876	.542	—	NS		
≤ 30	59					48	9
> 30	61					51	16
Seizures		0.955	.868	—	NS		
No	54					43	28
Yes	61					52	9
Karnofsky score		0.759	.277	—	NS		
< 70	58					46	12
≥ 70	61					51	13
Residual tumor		1 374	.149	—	NS		
Bulky	58					46	10
Minimal	62					53	15
Pathology		1.522	.054	1.781	.014		
Astrocytoma	53					40	6
Oligodendroglioma/mixed	67					59	16
Radiotherapy		1.049	.825	—	NS		
Postoperative	54					44	19
Delayed	61					56	4

Abbreviation: NS, not significant.

*Five- and 10-year survival rates obtained from Kaplan Meier survival estimates.

55% of patients, in the temporal lobe in 23%, in the parietal lobe in 19%, and in the occipital lobe in 3%; it exhibited some degree of contrast enhancement in 28% and was calcified in 20%. Fifty-one percent of patients had bulky residual tumor after surgery, 72% had a Karnofsky performance status ≥ 70, 53% had an astrocytoma, and 52% had delayed radiotherapy.

Radiotherapy

Radiotherapy was given immediately after surgery in 80 patients (48%) and deferred in 87 (52%). Thirty of 87 patients (34%) in the deferred treatment group had radiation subsequently when the tumor was judged to have progressed (total irradiated, 110 patients). The most frequently prescribed treatment regimen was 54 Gy in 30 fractions over 6 weeks; photon energies ranged from cobalt 60 to 6 Mv. Sixty-seven percent of patients were treated with a lateral parallel opposed photon pair, 28% with a wedged pair and 5% with other beam arrangements. Although this study was not designed to evaluate radiation toxicities, the following treatment-related side effects were noted in patient records: four deaths on treatment (two suicides, one lung abscess, one cardiac arrest); increasing headache or seizures (four patients); chronic otitis media with permanent hearing impairment (one patient); delayed hypopituitarism (four patients); and delayed cognitive impairment (five patients).

Survival Results and Prognostic Factors

The median follow-up time from tissue diagnosis to last known status was 50 months (mean, 59; range, 1 to 178). One hundred twenty-five of 167 eligible patients (75%) were monitored for at least 2 years. At last assessment, the tumor had progressed in 20 of 42 patients who were followed-up for less than 2 years and was unchanged in 22 (13%). For eligible patients, the median survival duration was 126 months (10.5 years), the 5-year survival rate was 72%, and the 10-year rate was 50%; the median progression-free survival duration was 59 months (4.9 years), the 5-year progression-free survival rate was 50%, and the 10-year progression-free rate was 12%. For patients with an astrocytoma (n = 89), the median survival duration was 90 months (7.5 years), the 5-year survival rate was 62%, and the 10-year rate was 39%; the median progression-free survival duration was 53 months (4.4 years), the 5-year progression-free survival rate was 40%, and the 10-year progression-free rate was 6%. For patients with an oligodendroglioma or mixed glioma (n = 78), the median survival duration was 156 months (13 years),

the 5-year survival rate was 84%, and the 10-year rate was 62%; the median progression-free survival duration was 67 months (5.5 years), the 5-year progression-free survival rate was 59%, and the 10-year progression-free rate was 16%. Because there was no difference in median survival (log-rank, $P = .787$) or progression-free survival (log-rank, $P = .697$) between patients with an oligodendroglioma (n = 57) and those with an oligoastrocytoma (n = 21), these subgroups were combined and analyzed together. Because pure and mixed tumors have common molecular derangements distinct from those in fibrillary astrocytic neoplasms, combining pure and mixed oligodendrogliomas can be justified on other grounds as well. Overall survival and progression-free survival curves for all patients, for those with an astrocytoma, and for those with an oligodendroglioma or mixed glioma are illustrated in Figs 1 and 2.

Univariate analysis demonstrated that age at tissue diagnosis ≤ 40 years, seizures at presentation, minimal residual tumor after surgery (≥ 90% resected), postoperative Karnofsky performance status ≥ 70, oligodendroglioma or mixed glioma pathology, and delayed radiotherapy were associated with significantly longer overall survival ($P < .05$; Table 1) and higher 5- and 10-year survival rates. Age at tissue diagnosis ≤ 40 years and oligodendroglioma or mixed glioma pathology were associated with significantly longer progression-free survival ($P < .05$; Table 2) and higher 5- and 10-year progression-free survival rates. On multivariate analysis, timing of radiotherapy was not a significant independent prognostic variable; patients selected for delayed treatment had other characteristics that could account for their longer overall survival and higher 5- and 10-year survival rates. Patients with a short duration of symptoms, nonseizure symptoms at presentation, bulky residual tumor after surgery, and astrocytoma pathology were more likely to have received immediate postoperative radiotherapy, whereas those with a long duration of symptoms, seizures at presentation, minimal residual disease after surgery, and oligodendroglioma or mixed glioma pathology were more likely to have had radiation deferred ($P < .05$; Table 3). In this study, tumor calcification and contrast enhancement did not have a significant effect on patient survival.

Disease Progression

Tumor progression occurred in 90 of 167 patients (54%; median time to progression, 50 months): 46 of 80 patients in the postoperative radiation group (median time to progression, 49 months) and 44 of 87 in the deferred group (median time to progression, 52 months). Seventy-one of 90 patients (79%) had a tissue diagnosis at progression (Table 4). Rates of malignant degeneration were not significantly different between the immediate and delayed radiotherapy groups (χ^2 test, $P = .909$) or between astrocytic and oligodendroglial tumors (χ^2 test, $P = .556$). The median duration of survival after tumor progression was 39 months: 16 months (1.3 years) for patients with an astrocytoma and 60 months (5.0 years) for those with an oligodendroglioma or mixed glioma.

DISCUSSION

We evaluated survival and other outcomes in a large group of patients with supratentorial low-grade fibrillary astrocytoma, oligodendroglioma, and mixed glioma diagnosed since 1979 who were treated at a regional cancer center in Canada. Long durations of survival were observed: the median survival duration exceeded 10 years, the 5-year survival rate was 72%, and the 10-year rate was 50%. Long durations of tumor control also were observed: the median progression-free survival duration was 6 years and the 5-year progression-free survival rate was 50%. The 5- and 10-year survival rates documented in this study were superior to those observed in similar analyses of patients with low-grade glioma diagnosed and treated before 1980 (Table 5). Longer survival durations and higher rates of tumor control in this and other contemporary series may reflect improvements in therapy—especially safer, more radical surgical resection—but earlier diagnosis made possible by CT and MR imaging, creating a lead time bias, could also explain better outcomes in modern series.[10-12,14,27] The lower rates of papilledema in recent series, 9% in this study, are indicative of smaller tumor volumes at presentation and support the view that low-grade gliomas are diagnosed earlier now than 30 years ago. Furthermore, this retrospective analysis reaffirmed the prognostic importance of age, symptoms at presentation, extent of resection, postoperative performance status, and tumor type. Age at diagnosis ≤ 40 years, seizures at presentation, minimal residual tumor after surgery, postoperative Karnofsky score ≥ 70, and oligodendroglioma or mixed glioma pathology were independent prognostic variables, each associated with significantly longeroverall survival. Age at diagnosis ≤ 40 years and oligodendroglioma or mixed glioma pathology also were associated with significantly longer progression-free survival. Nontreatment variables and residual tumor bulk had profound effects on the duration of survival of patients with supratentorial low-grade glioma.

Several influential retrospective low-grade glioma studies have concluded that overall and progression-free survival times are enhanced by immediate postoperative radiation,[4,14,24-26] although other similar analyses have been unable to demonstrate a survival benefit attributable to early treatment.[11,12,15,27,28] Our practice of individualiz-

Table 3. Clinical Parameters and Timing of Radiotherapy

Variable	Postoperative Radiation (n = 80) No	%	Radiation Delayed (n = 87) No	%	P*
Age (years)					
≤ 40	46	58	51	59	.883
> 40	34	42	36	41	
Sex					
Male	52	65	51	59	.397
Female	28	35	36	41	
Duration of symptoms (days)					
≤ 30	23	29	36	41	.088
> 30	57	71	51	59	
Seizures at presentation					
No	24	30	12	14	012
Yes	56	70	74	86	
Residual tumor					
Bulky (< 90% resected)	51	64	33	38	.001
Minimal (≥ 90% resected)	29	36	53	62	
Karnofsky performance status					
< 70	22	28	23	27	.834
≥ 70	56	72	63	73	
Pathology					
Astrocytoma	54	68	35	40	.001
Oligodendroglioma/mixed glioma	26	33	52	60	
Overall survival (months)	96		156		
Progression-free survival (months)	54		61		

*χ^2 test; comparison to detect an unequal distribution of variables between postoperative and delayed radiation.

ing treatment decisions, including deferred radiotherapy in many instances, afforded an opportunity to evaluate whether the timing of radiotherapy influenced the survival of patients with low-grade glioma diagnosed at this center since 1979. We observed that timing of radiotherapy was a less important determinant of survival outcome than other variables. Although patients in the delayed radiotherapy group had longer overall and progression-free survival times and higher survival rates at most time points, timing of radiotherapy was not a significant independent prognostic factor. The postoperative and delayed radiotherapy groups were dissimilar, and these differences contributed to better outcomes in the deferred group; patients with bulky residual disease and astrocytic tumors were more likely to have had immediate postoperative treatment, whereas those with complete resections and oligodendroglial or mixed glial pathology were more likely to have had radiation deferred.

Table 4. Malignant Degeneration and Treatment at Diagnosis

Timing of Radiotherapy	High-Grade at Progression	Low-Grade at Progression	No Biopsy at Progression	Total Progressing/ Total at Risk (%)
Immediate	19	18	9	46/80 (58)
Delayed	17	17	10	44/87 (51)
Total	36	35	19	90/167 (54)

Radiotherapy is prescribed for most patients with low-grade glioma, only the timing of treatment is debated. Some clinicians favor immediate postoperative treatment[21] because low-grade gliomas respond to radiation[29] and because they often progress; others favor delayed treatment because radiation may have toxic effects in long-term survivors[22,23] and because some low-grade gliomas are remarkably indolent. Those who advocate immediate treatment argue that radiation will be more effective at diagnosis. Those who recommend delayed treatment assume that modern conformal radiotherapy will be associated with the same frequency and spectrum of toxicities that were observed in patients with malignant glioma after whole brain or large parallel opposed radiation fields.[30-32] Although both points of view have merit, it must be acknowledged that radiation may be an effective salvage treatment for some patients with low-grade glioma and that modern focal radiotherapy may be far less toxic than feared. The utility of radiotherapy as a salvage treatment for low-grade glioma was noted by Piepmeier et al[11] in a recent retrospective analysis of astrocytomas, but was also suggested by the long postrecurrence survival (ie, 5.0 years) of the oligodendroglioma/mixed glioma group in this study. The relative safety of modern radiotherapy has been highlighted by two recent prospective analyses. Taphoorn et al[33] evaluated cognitive function and mood

Table 5. Major Retrospective Studies of Low-Grade Glioma

First Author	Study Interval	No of Patients	Percent Survival			
			5-Year		10-Year	
			Surgery	Surgery + RT	Surgery	Surgery + RT
Laws[4]	1915-1975	326	34	49	18	20
Leibel[25]	1942-1967	108	19	46	11*	35*
Garcia[24]	1950-1979	80†	21	50		
Soffietti[15]	1950-1982	86	30	9-25		
Jubilier[28]	1957-1987	38	53‡	49 3‡		
Shaw[26]	1960-1982	126	32	54	11	27
Whitton[17]	1960-1985	60		36		26
Shibamoto[14]	1965-1989	119	37	60	11	41
North[10]	1975-1984	77		66		43
McCormack[8]	1977-1988	53		36		26
Philippon[12]	1978-1987	179	65	55		
Bahary[27]	1974-1992	63	66	67		42
Present study	1979-1995	167	84	62	70	35

Abbreviation: RT, radiotherapy

*Fifteen-year survival.

†Seventy-eight patients had tumors with some anaplastic features.

‡Median survival in months

over 2 to 3 years in three groups: irradiated and nonirradiated patients with low-grade glioma and patients with low-grade hematologic malignancies. They observed significant intellectual and psychologic difficulties in patients with glioma, but found no difference in performance between the irradiated and nonirradiated brain tumor cases. Viglianis et al[34] evaluated cognitive function in two groups of patients with low-grade glioma, one group observed and the other maximally resected and irradiated; there were no significant differences over 4 years within or between the groups. Although it may still be necessary to irradiate significant volumes of normal tissue when treating patients with large or deep-seated tumors with resulting toxic effects, in the years ahead, better tumor localization and improved conformal radiotherapy techniques can be expected to enhance the therapeutic ratio for patients with low-grade glioma.

The present analysis addresses an important clinical question in neuro-oncology: when in the natural history of low-grade glioma do the potential tumor-controlling benefits of radiotherapy outweigh its potential risks? We draw the following conclusions regarding patient management from this study: immediate postoperative radiotherapy to prevent neurologic deterioration may be the appropriate treatment strategy for patients with poor prognostic factors (eg, older age, bulky residual disease, astrocytic pathology, etc) who are likely to have early tumor progression and relatively short survival. Delayed radiotherapy to avoid or postpone any possibility of neurotoxic effects from treatment may be an appropriate course of action for patients with favorable prognostic factors (eg, younger age, complete resection, oligodendroglial pathology, etc) who are likely to have long survival times. Recht et al,[19] in a cohort-style study, and Piepmeier et al[11] have concluded that delayed treatment together with clinical vigilance may be a safe therapeutic option for some patients with supratentorial low-grade glioma. Large randomized clinical trials will be necessary to clarify these issues further, but for now, our study helps to delineate a group of patients for whom delayed radiotherapy may be an acceptable management strategy.

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