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# Low-grade gliomas in children: tumor volume response to radiation

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**Object.** The authors conducted a retrospective review to examine and document the frequency, degree, and timing of the radiologically confirmed response to radiotherapy of low-grade gliomas in children.

**Methods.** Between 1963 and 1995, 80 patients 17 years of age or younger were referred to the London Regional Cancer Centre in London, Ontario, after diagnosis of a low-grade glioma. All patients underwent surgical resection or biopsy procedures and 47 underwent radiotherapy (40 postoperatively and seven at the time of tumor progression). Nineteen patients with residual measurable lesions who received radiation therapy were selected for volumetric analysis of tumor response to this treatment. The extent and timing of response to radiation were determined by the process of comparing postoperative, preirradiation computerized tomography (CT) scans with postirradiation, follow-up CT scans. For one patient the comparison was made by using serial magnetic resonance images.

Residual tumor was found on postoperative CT scans in all cases. The mean preradiotherapy tumor volume was 17.1 cm<sup>3</sup>, and the postradiotherapy volume was reduced to a mean of 11.5 cm<sup>3</sup>. A reduction in tumor was demonstrated in eight patients by the time of their first postirradiation follow-up CT scan and in two patients a slower reduction in volume over time was shown, bringing the total number of "responders" to 10. In five of these 10 patients the tumor had shown a maximum response by the time of the first postirradiation CT scan; the median time to response was 3.3 months. A 25% or greater reduction in tumor volume was seen in eight (42%) of the 19 patients. A 50% or greater reduction was noted in five (26%) of the patients. A complete response was demonstrated at 7, 12, and 15 months, and 5 years, respectively, in four patients (21%). One responder's tumor eventually increased in size after radiotherapy and he died of his disease.

The magnitude of the radiographically demonstrated response to radiation did not correlate significantly with clinical outcome (that is, survival or symptom improvement).

**Conclusions.** On the basis of this CT scan analysis of the response of low-grade gliomas in children to radiotherapy, the authors suggest that these lesions respond to radiation, as demonstrated by tumor shrinkage on serial imaging. Major or complete responses occur occasionally. However, low-grade gliomas in children mimic other benign brain tumors such as pituitary adenomas and meningiomas in that, although growth is frequently arrested after radiotherapy, residual tumor can persist for many years, illustrating that tumor shrinkage may not be a good measure of treatment efficacy.

Nevertheless, radiation therapy can result in improvement of clinical symptomatology in association with or independent of visible tumor reduction. As radiation treatment techniques become increasingly conformal and because studies indicate that lower doses of radiation may be equally effective, improvement of symptoms may be an important consideration when weighing treatment options, particularly in patients with residual or unresectable disease.

### Key Words \* low-grade glioma \* radiation therapy \* children

Low-grade gliomas comprise the most common type of brain tumor in children. The role of radiation therapy in the management of low-grade gliomas remains controversial, although incompletely resected or recurrent low-grade gliomas are frequently treated with radiotherapy. Low-grade glioma cell lines demonstrate in vitro radiosensitivity,[23] and authors of retrospective clinical studies[11] have described radiotherapy as being effective in producing long-term survival and control of low-grade gliomas in children. However, the commonly held belief is that low-grade gliomas in the pediatric population, particularly pilocytic astrocytomas, are indolent and therefore, their size is unlikely to be affected by radiation. The response of these tumors in vivo as determined on radiological studies and the relationship of such response to clinical outcome have not been well documented.

This study is an attempt to analyze the patterns of the radiologically determined response of low-grade gliomas in children treated with radiotherapy to determine the extent and timing of such response.

## CLINICAL MATERIAL AND METHODS

#### **Patient Selection and Treatment**

Between 1963 and 1995, 80 children (aged ¾ 17 years) in whom a low-grade glioma was diagnosed (astrocytoma, oligodendroglioma, or mixed glioma) were treated at the London Regional Cancer Centre in London, Ontario. All 80 underwent an initial surgical procedure ranging from biopsy sampling to gross-total resection. The patients who underwent gross-total resection did not receive radiotherapy, whereas 47 of the patients who underwent subtotal resection subsequently received this treatment (seven at the time of disease progression and 40 in the immediate postoperative period). Before 1970, there was a tendency to administer postoperative radiotherapy to all patients who underwent subtotal resections, but after 1970 the patient population receiving postoperative radiation treatment consisted primarily of those who were 4 years of age or older, who had undergone biopsy sampling or minor resections, and who had tumors of the optic tracts, hypothalamus, thalamus, or brainstem. Patients were selected for this volumetric study if they had received cranial radiation for residual or progressive low-grade glioma and if serial computerized tomography (CT) studies were available that demonstrated measurable residual tumor postoperatively, allowing objective tumor response assessment. Of 47 patients who received radiotherapy, 28 were excluded from analysis for the following reasons: 11 had nonmeasurable postoperative preradiotherapy tumor, in 13 no postoperative baseline CT scan had been obtained, and in four the scans were missing or unavailable.

Clinical information obtained from the patient's chart included age at diagnosis, sex, presenting symptoms and date of clinical presentation, estimated Karnofsky Performance Scale (KPS)[13] score, tumor location, date of surgery, type and extent of surgical resection, histological findings, radiotherapy details, progression of tumor and type of salvage therapy, last known disease status, and date of last known status. The extent of resection was estimated by comparing pre- and postoperative CT scans. Surgical resection consisted of a biopsy procedure in 12 patients, a minor resection ( $\frac{34}{4}$  50% of tumor) in four patients, and a major resection ( $\frac{94}{4}$  50% of tumor) in three patients. Tumor response was estimated by measuring the three largest tumor dimensions of the contrast-enhancing abnormalities or the low attenuation volume in nonenhancing lesions, in the anteroposterior (D<sub>1</sub>), superoinferior (D<sub>2</sub>), and transverse views (D<sub>3</sub>). Tumor volumes on postoperative CT scans obtained

before and after radiotherapy were compared to assess volume response to radiation (volume =  $\frac{1}{2}$ /6 D<sub>1</sub>D<sub>2</sub>D<sub>3</sub>). Tumor volume response was classified as stable (lt 25% decrease), minor (>= 25% to lt 50% decrease), major (>= 50% decrease), or complete (no measurable tumor observed on follow-up scan).[15] Progressive disease was defined by an increase of 25% or more in tumor volume and/or recurrence proven by biopsy findings.

#### RESULTS

# **Patient Demographics**

Demographic information for the 19 patients included in this study are presented in Table 1. The median age for the 19 patients in the study was 10 years (range 3-17 years) at presentation. There were seven girls and 12 boys. Sixteen patients had astrocytomas, of which at least six were a pilocytic subtype and one was a pleomorphic xanthoastrocytoma, two patients had oligodendrogliomas, and one had a mixed glioma. All patients received focal radiotherapy, which was administered postoperatively. The median dosage was 5400 cGy in 30 fractions delivered to the isocenter. Computerized tomography scans obtained before and after radiotherapy and during the follow-up period were compared with the postoperative baseline CT scans.

TABLE 1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WHO RECEIVED RT FOR LOW-GRADE GLIOMA*											
Case No.	Age at RT (yrs), Sex	Histological Findings	Tum or Location	Surgery	Post-RT Response on CT Scans	% Response	Time of Maximum Response	Response on Follow- Up CT Scan	Time Period	Present Status	
1 2 3	18, M 8, F 8, M	astro astro astro, pi- locvtic	frontal brainstem thalam us	subtotal biopsy biopsy	minor stable minor	42% at 6 mos 47% at at 1 mo	6 mos 8 mos	major not done majorre- sponse	3 yrs 3 mos 8 mos	Aw!D DofD dead	
4 5 7 8 9	10, F 10, M 4, F 9, M 16, M 9, F	oligo xantho oligo astro astro astro, pi- locytic	frontal parietal brainstem optic midbrain pons	subtotal subtotal biopsy biopsy biopsy biopsy	major stable stable stable stable stable	68% at 6 m os	6 mos	stable slow prog stable stable stable stable; enlarged cvst	6 yrs 6 yrs 5 yrs 5 yrs 4 yrs 3 yrs 4 yrs	AWD AWD AWD AWD AWD AWD	
10	14, M	astro, pi- locytic	mi dbralin	biopsy	stable, enlarged cvst			slow prog enlarged cvst	2 yrs	AwD	
11	9, F	astro	poins	biopsy	stable			stable	2 yrs	AW D	
12	10, M	astro	thalam us	biopsy	stable	100% at 5 yrs	5 yns	complete	5–8 yrs	D of D	
13	17, F	astro	cerebellum	subtotal	stable			fluctuating	3 yrs	AWD	
14	3, F	astro	suprasellar	subtotal	minor	42% at 3 m os	1 yr	complete	1 yr	A& W	
16	тэ, м 16, М	astro astro, pi- locytic	cerebellum su <b>p</b> rasellar	biopsy	stable major	53% at 1 mo	1 mo	stable	o yrs 3 mos	A wr D Dof D	
17	5, M locy	astro, pi- tic	mi dbræin	biopsy	minor	35% at 1 mo	11 mos	complete	15 m os	A&W	
18	3, M	mi×ed glioma	su <b>p</b> rasellar	subtotal	complete	100% at 6 m os	6 mos	complete	6 yrs	A& W	
19	5, M	astro, pi- locytic	mi dbratin	biopsy	minor	25% at 1 mo	1 mo	stable	10 m os	AWD	

\* A & W = alive and well no evidence of tumor; astro = astrocytoma; A w/D = alive with disease; D of D = dead of disease; oligo = oligodendroglioma; prog = progression; RT = radiation therapy; xantho = xanthoastrocytoma. † Malignant recurrence.

A comparison of the study group of patients whose tumors responded to radiotherapy and the total population of patients with low-grade glioma is detailed in Table 2. The two groups displayed very similar characteristics except that, not surprisingly, more biopsy procedures than resections were performed among the 19 patients in the group studied.

TABLE 2 COMPARISON OF CLINICAL CHARACTERISTICS FOR STUDY GROUP AND TOTAL PEDIATRIC POPULATION WITH LOW-GRADE GLIOMA								
Characteristic	Study Group (19 patients)	Total Population (80 patients)						
sex (M/F) median age	12:7 10 yrs	39:41 7 yrs						
presentation (%)	26	43						
focal neurological deficit	47	60						
cerebral	16	22						
cerebellar brainstem	10 42	28 15						
ventricular optic-hypothalamic	0 21	11 17						
thalamic bistological findings (%)	11	7						
astrocytoma	85	87						
oligodendroglioma.mixed glioma	15	13						
resection (%) gross total	0	12						
subtotal biopsy	37 63	50 37						
overall survival rate (%)	94	83						
10-yr	80	76						
progression-mee survival rate (%) 5-yr 10-yr	88 68	77 68						
10-yr	00	00						

## Tumor Response

The median radiological follow-up period was 3.1 years, and the median clinical follow-up duration was 5.6 years. The first posttreatment scan was obtained at a median of 3.3 months (range 0-11 months) after completion of radiotherapy. An average of six follow-up CT studies (range 1-12 scans) were obtained in these patients. The mean pretreatment tumor volume was 17.1 cm<sup>3</sup> (range 0.5-42.1 cm<sup>3</sup>), and the mean posttreatment volume was reduced to 11.5 cm<sup>3</sup> (range 0-47.7 cm<sup>3</sup>). The mean volume decrease was 5.4 cm<sup>3</sup> (range 0-40 cm<sup>3</sup>), resulting in a mean 31% decrease. The maximum tumor response was judged as complete in four cases, major in four cases, minor in two cases, and stable in nine. Of the 10 patients with tumors that responded to radiotherapy, the maximum response was seen on the first follow-up scan in five. Five patients had protracted responses; their tumors continued to decrease in size between the end of radiation treatment, from 7 months to 5 years later. The mean time to maximum response for the 10 responders was 14.4 months.

No significant difference in histological findings, age of the patient, or estimated pretreatment KPS score was noted among responders compared with nonresponders in our small series of cases. The median age was 9.3 years for responders and 11.5 years for nonresponders. Seventy percent of responders had astrocytomas compared with 80% of the nonresponders. There were six patients with pilocytic astrocytomas and four of these were responders. The mean estimated pretreatment KPS score was 46 for responders and 50 for nonresponders.

#### **Clinical Outcomes**

The 10-year actuarial survival rate was 80% for the 19 patients studied and 76% for the entire group, and the 10-year disease-free survival rate was 68% for both groups. The Kaplan-Meier curves for actuarial and

disease-free survival were not significantly different for the study group (p = 0.52) than for the total group of 80 patients with low-grade gliomas (p = 0.29).

Fifteen patients did not develop tumor progression. Nine of these 15 children demonstrated focal neurological deficits before receiving radiotherapy, and seven of these nine patients showed significant improvement of their focal neurological deficits despite the fact that only four of them were "responders" (had visible tumor reduction on serial imaging studies). Figure 1 comprises serial CT scans obtained in a child with a pilocytic astrocytoma whose tumor responded to radiation. Preradiation, the boy was hemiplegic and was confined to a wheelchair, but by 6 months postirradiation, his neurological examination was normal. However, clinical improvement in neurological function was not confined to responders only. Three of six patients with stable disease and no visible evidence of a change in tumor size on CT scans also demonstrated reversal of focal neurological deficits. All three patients with preirradiation cranial nerve deficits and one patient with corticospinal tract signs demonstrated complete reversal of their deficits during several months postirradiation. These patients have been followed for 5 years or more and have demonstrated stable tumor volume and no recurrence of neurological deficits. Seizure control secondary to radiotherapy could not be assessed independent of antiepileptic medication.



Fig. 1. Serial CT scans of a low-grade glioma demonstrating response to radiotherapy in an 8-year-old boy who underwent stereotactically guided biopsy of a thalamic pilocytic astrocytoma. The histological diagnosis was confirmed at autopsy. Left: Axial CT scan obtained before radiotherapy. Center: Axial CT scan obtained 1 month after radiotherapy. Right: Axial CT scan obtained 6 months after radiotherapy.

# Local Tumor Control

Four patients exhibited tumor progression after radiation treatment; the median interval was 2.5 years. Two of these patients developed enlargement of the cystic component of their tumors only. In one of these cases, the tumor itself showed a minimal reduction in size at 2 years postirradiation and in the other the tumor remained stable postradiotherapy. Four patients died, three as a result of tumor progression and one secondary to an infection.

## DISCUSSION

We have encountered a number of difficulties in assessing the value of radiotherapy in the management of low-grade gliomas in children. The long natural history, particularly of pilocytic astrocytomas, makes the value of radiotherapy difficult to define. The radiographically determined response of low-grade gliomas to radiotherapy has not been well documented because it has been assumed that low-grade gliomas in children are

indolent and unresponsive to radiotherapy, as assessed by tumor shrinkage. On the basis of our CT scan analysis, we suggest that low-grade gliomas in children can demonstrate shrinkage on radiographic studies in response to radiotherapy, but that such shrinkage is not directly related to tumor control or necessarily to improvement of symptoms. Forty-seven percent of the tumors studied exhibited a volume reduction of 25% or more following radiation treatment. Our study also demonstrated that response to radiation, when it occurred, was not always evident on the first follow-up scan obtained after radiation treatment. Although the group studied is a highly selected one, comparison of the overall survival rates in this group from the time of radiotherapy demonstrated no significant difference in comparison with the larger pediatric population with low-grade glioma from which it was drawn.

Confounding factors in the assessment of tumor volume changes include resolution of postoperative changes and steroid administration. In this particular study the majority of patients had contrast-enhancing tumors, which made the distinction between tumor and edema or hemorrhage more reliable. Also, the majority of patients had undergone biopsy procedures as opposed to resections, minimizing the probability that major postoperative changes would occur. The time to maximum tumor response was quite long (mean 14.4 months). In relation to this time frame, postoperative changes and steroid administration tended to be more short-term events for these children.

Patient age,[2,6,8] extent of resection,[6,21] tumor grade,[3] tumor location,[8,14,16,18] and radiation dosage[6] have been reported to be variables having prognostic significance in low-grade gliomas, but response to radiation has never been examined as a prognostic factor in this patient group. However, chemotherapeutic agents are often evaluated in terms of response rates. Packer, et al.,[19] have reported their response rate findings after using chemotherapy to treat low-grade gliomas, noting that 23 of 37 patients with low-grade glioma who were newly diagnosed as diencephalic and 12 of 23 patients with recurrent disease experienced a 50% or greater reduction in tumor volume. Gajjar, et al.,[7] reported a response rate to chemotherapy of 57% in 14 children with progressive low-grade gliomas, although it is not known whether response to chemotherapy correlates with improved survival. Over the follow-up period for our patient group, 47% of the tumors responded to radiation, with 44% demonstrating a 50% or greater volume reduction over time.

Regarding malignant gliomas in adults, several authors [1,4,9] have reported response rates of 30 to 40% but there is controversy as to whether response rates translate into longer survival times.[9] Eyre, et al.,[5] examined the response rates of subtotally resected low-grade gliomas in adults. They defined response as an improvement in neurological function together with a 50% or greater decrease in the product of the largest perpendicular tumor diameters on CT scans and found these to be moderately radioresponsive lesions, with a 63% response rate in 54 tumors. In contrast, in our study of low-grade gliomas in children, there was a fairly even ratio between those tumors that did not respond to radiation but remained stable in size and those that shrank, either immediately or over time. Response, when it occurred, was very slow, taking years in many cases, but was usually demonstrable to some extent on the postradiation scan. The majority of patients continued to display visible residual tumor on CT scans for many years after therapy: only four of the patients achieved a complete response. Other types of central nervous system tumors, such as meningiomas and pituitary adenomas, tend to have a similar pattern of very slow, minimal response to radiation but very high long-term control rates.[10] Conversely, some radioresponsive tumors such as central nervous system lymphomas recur rapidly. Therefore, tumor shrinkage may not be the only or most important measure of tumor control. Prospective studies in which tumor response is evaluated might be made more meaningful by the inclusion of information about disease-free survival or symptom improvement.

The radiotherapeutic management of subtotally resected low-grade gliomas is even more controversial in children than in adults because progression-free survival rates tend to be higher and cognitive and endocrine effects more significant. Some authors have reported higher survival rates with the addition of postoperative radiotherapy,[17] whereas others have not confirmed a survival benefit.[20,21] Pollack, et al.,[21] reported

actuarial survival rates at 5, 10, and 20 years of 95%, 93%, and 85%, respectively, in 71 patients with low-grade gliomas; no significant survival difference was conferred by the addition of radiotherapy. Studies of radiotherapy in the treatment of pediatric low-grade gliomas have tended to focus on prolongation of survival as an endpoint while ignoring other potential benefits such as tumor response and symptom improvement. The management trend for low-grade gliomas in children (particularly with the increasing use of chemotherapy) is toward deferral of radiation treatment because of its toxicity and the lack of a conclusive survival benefit. However, as radiation delivery becomes more conformal because of techniques such as fractionated stereotactic radiosurgery or three-dimensional planning, and because there is some evidence that lower radiation doses may be equally effective,[12] the long-term risks of this treatment may well be reduced and the risk/benefit ratio may then have to be reanalyzed. Such an analysis should include assessments of tumor response and symptom improvement as well as survival rates. Results from our small series indicate that radiation may offer benefits in terms of tumor reduction and symptom improvement, leading us to suggest a continuing role for radiation, particularly in unresectable or symptomatic tumors, independent of the survival issue.

Although tumor response did not correlate directly with patient survival, such a relationship would be difficult to identify because of the very high rate of control of these tumors following radiation treatment. What is clear is that symptomatic improvement of neurological deficits did occur in the majority of patients who received radiotherapy, independently of tumor response. Rogers, et al.,[22] have previously reported reduced seizure frequency in medically intractable epilepsy in patients with low-grade glioma treated with cranial radiation.

## CONCLUSIONS

This retrospective review of radiographically demonstrated tumor response shows that pediatric low-grade gliomas in children can be radioresponsive but that the decrease in size is often slow (mean time to maximum response 14.4 months). No clinical correlation could be demonstrated; stability and shrinkage after radiotherapy were both correlated with long-term control. Symptomatic improvement of focal neurological deficits may occur independently of radiation response, indicating that radiation should continue to play a role in the treatment of symptomatic tumors. Tumor response and symptom reduction should be examined along with survival and long-term side effects in future studies involving radiation treatment of low-grade gliomas in children, particularly as radiation techniques become increasingly uniform.

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