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Visual Outcomes in Pediatric Optic Pathway Glioma After Conformal Radiation Therapy

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Abstract

Purpose—To assess visual outcome prospectively after conformal radiation therapy (CRT) in children with optic pathway glioma.

Methods and Materials—We used CRT to treat optic pathway glioma in 20 children (median age 9.3 years) between July 1997 and January 2002. We assessed changes in visual acuity using the logarithm of the minimal angle of resolution after CRT (54 Gy) with a median follow-up of 24 months. We included in the study children who underwent chemotherapy (8 patients) or resection (9 patients) before CRT.

Results—Surgery played a major role in determining baseline (pre-CRT) visual acuity (better eye: $P=.0431$; worse eye: $P=.0032$). The visual acuity in the worse eye was diminished at baseline (borderline significant) with administration of chemotherapy before CRT ($P=.0726$) and progression of disease prior to receiving CRT ($P=.0220$). In the worse eye, improvement in visual acuity was observed in patients who did not receive chemotherapy before CRT ($P=.0289$).

Conclusions—Children with optic pathway glioma initially treated with chemotherapy prior to receiving radiation therapy have decreased visual acuity compared with those who receive primary radiation therapy. Limited surgery before radiation therapy may have a role in preserving visual acuity.

Keywords

Vision; Pediatrics; Glioma; Radiotherapy

Introduction

The management of optic pathway tumors in children is complex and primarily governed by the child's age, the severity and rapidity of development of the child's symptoms, and consideration of the adverse effects of the various treatments and their ability to reverse vision loss or stabilize existing vision. Optic pathway tumors are rare. They are commonly low-grade astrocytomas with indolent or unpredictable growth patterns that can cause vision

loss long before diagnosis, and they are often seen in young children, for whom vision testing is unreliable. Because of their central location, optic pathway tumors may lead to additional neurologic complications, endocrine deficiencies, or cognitive impairment either by direct extension or through mass effect.

In the past, radiation therapy was most often chosen as the first treatment for patients with optic pathway tumors, and visual outcome information suggested that most patients were likely to experience stabilization of vision (1–3). Because of reports of radiation-related complications including endocrinopathy, vasculopathy, and cognitive decline in young children (4, 5), investigators have sought alternatives to radiation therapy, including chemotherapy and, in some cases, observation or surgery followed by observation or chemotherapy (6, 7). The current trend is to irradiate older symptomatic patients and to use chemotherapy as the primary (8) and second-line (9) treatment in younger children; the age range used to select chemotherapy is based on the preferences of the treating physicians or protocol guidelines. Because reports have suggested that patients who receive chemotherapy fare less well overall than those who receive primary radiation therapy (5, 10), we sought to investigate temporal changes in the visual acuity of patients irradiated by using conformal treatment methods and to assess visual outcome before and after irradiation as a function of prior therapy or clinical factors. Of great concern is the ability of radiation therapy to stabilize vision or reverse vision loss. Improved understanding of visual outcomes after radiation therapy and of the factors contributing to visual outcomes may support decisions on the use of radiation therapy in patients with optic pathway glioma.

In this prospective trial, we used conformal radiation therapy (CRT) with 54-Gy irradiation to treat optic pathway tumors in 20 children. We evaluated patients before and after CRT and documented visual outcomes by performing serial ophthalmologic examinations in groups of patients who had or had not undergone chemotherapy before CRT, who had or had not undergone surgical intervention before CRT, or who had or had not experienced symptomatic progression before CRT.

Methods and Materials

Patients

Between July 1997 and January 2002, 27 children with optic pathway glioma were treated at St. Jude Children's Research Hospital on a prospective trial of CRT that had received approval by the hospital's institutional review board. Written informed consent was obtained. Five patients were excluded from the analysis, including 3 who were followed for <3 months, 1 who was blind at the time of first examination, 1 who was too young for visual acuity testing, and 2 with neurofibromatosis type-1. The group analyzed comprised similar numbers of each sex and had a median age of 9.3 years (range, 3.2–14.6 years) at the time of irradiation. For the 20 patients included in the study, the diagnoses included juvenile pilocytic astrocytoma ($n=14$), ganglioglioma ($n=2$), and neuro-cytoma ($n=1$); the diagnosis was unspecified for 3 patients who did not undergo biopsy. All tumors were located within the region of the hypothalamus, optic chiasm, or optic tracts. Of the 17 patients who underwent a surgical intervention, 9 underwent subtotal surgical resection, and 8 underwent biopsy. Of 8 patients who received chemotherapy before radiation therapy, similar numbers underwent resection, biopsy, or no biopsy. Only 4 of the patients included in the analysis were treated on the basis of imaging findings; the remainder were treated on the basis of symptomatic progression (loss of vision). Three patients received steroids during radiation therapy. Two of the patients treated with chemotherapy before irradiation had evidence of vasculopathy before irradiation that was being closely followed with no impact on vision.

All patients received 54 Gy irradiation at 1.8 Gy per day delivered 5 days per week (Monday through Friday) for 6 weeks. The radiation therapy parameters we used included a clinical target volume margin of 1 cm (ie, a volume encompassing the tumor with a 1-cm margin), a planning target volume margin of 5 mm, and multiple static, and noncoplanar beams delivered using cerrobend or multileaf (4–10 mm leaf width) collimation (11). Treatment planning objectives included maximizing conformity while sparing the supratentorial brain (eg, temporal lobes) and cochlea.

The median time from the onset of symptoms to diagnosis was 7.15 months (range, 1 week to 3.8 years), and the median time from the onset of symptoms to radiation therapy was 30.55 months (range, 1.8–99.5 months). This latter interval was a median of 58 months for the 8 patients who received chemotherapy before irradiation and a median of 2 months for the 12 patients who received immediate irradiation. The median follow-up period was 30 months (range, 8–62 months).

Patients were examined before radiation therapy and serially at 3- to 6-month intervals after treatment. Each patient received a detailed ophthalmologic examination before treatment and at scheduled follow-up intervals. These evaluations included slit-lamp examination, measurement of Snellen visual acuity (except when too young), and tests for visual field (by using a Goldman perimeter or a Humphrey computerized automated perimeter), afferent papillary defect, and color vision. Indirect fundoscopic examination was performed on each patient. Snellen visual acuity measures were converted to the logarithm of the minimal angle of resolution (logMAR) (12–14) for statistical analysis. For example, a Snellen visual acuity of 20/20 has an equivalent logMAR = 0; for 20/40 visual acuity, logMAR = 0.301; for 20/100, logMAR = 0.698; for 20/200, logMAR = 1; and for 20/400, logMAR = 1.3. Therefore, the higher the value of logMAR, the poorer the visual acuity. For each subgroup of patients (eg, chemotherapy vs. no chemotherapy) we plotted the mean value of logMAR from the fitted model for the eye with better vision and the eye with worse vision against time. Our analysis included the data obtained at the time of diagnosis and data obtained during the interval between diagnosis and the initiation of radiation therapy (Table). We evaluated the anatomic location of the tumors in this series and confirmed that 3 were limited to the optic chiasm; 2 had involvement of the hypothalamus, chiasm, and proximal optic nerves; and the remainder were largely hypothalamic/chiasmatic lesions. The distribution did not permit statistical treatment.

For statistical analysis, we used a mixed (random and fixed effects) model (15, 16) to estimate the longitudinal trends of visual acuity from approximately 10 months before irradiation to last follow-up examination. The response variable of the model is the logMAR value (ie, the logarithm of visual acuity). Clinical or treatment-related factors such as chemotherapy, surgical treatment, and symptomatic tumor progression before irradiation were included as covariate variables (separately) in the model. The statistical package SAS (17) was used for all analysis.

Results

Two hundred eight visual acuity examinations were performed on the 20 patients included in the study. The median number of visual acuity exams was 11 (range, 2–17). Examinations included ranged from 25 months before the start of CRT to 40 months following CRT. At the initial evaluation, 1 patient was limited to only light perception in both eyes, 1 patient was limited to light perception in 1 eye with normal visual acuity in the other, 1 patient had light perception in 1 eye with decreased visual acuity in the other, and 1 patient had no light perception in 1 eye but normal visual acuity in the other. Visual acuity before radiation therapy was influenced by a number of patient and treatment-related factors including

surgical intervention, chemotherapy, and symptomatic progression before the initiation of radiation therapy (Figs. 1–3).

In the eye with better vision, there was no difference in baseline or longitudinal visual acuity based on the use of chemotherapy before irradiation, preirradiation progression, or steroid use. Patients who underwent surgery had improved baseline vision (logMAR = 0.2426) compared with those who did not (logMAR = 1.3566, $P=0.0431$). The effect did not depend on the extent of resection.

In the eye with worse vision, visual acuity was significantly worse at baseline in patients with preirradiation progression (logMAR 1.8646 vs 0.2657, $P=0.0220$) and those treated with preirradiation chemotherapy (logMAR 2.1695 vs 1.1146, $P=0.0736$). The effect of chemotherapy was borderline significant. Visual acuity was improved at baseline in those treated with subtotal resection vs those who did not undergo resection (logMAR 2.1871 vs 2.4016, $P=0.0032$). When preirradiation chemotherapy and surgery were combined in a model, there was no effect on baseline; however, vision appeared to improve over time in patients who did not receive preirradiation chemotherapy (LogMAR $-0.02314/\text{year}$, $P=0.0289$).

Discussion

Our results show that patients with optic pathway tumors who receive radiation therapy as their first treatment are more likely to have useful vision before and after treatment (acuity range 20/40–20/80 in the better eye, 20/200–20/300 in the worse eye) than are those who failed chemotherapy as initial treatment and received radiation therapy as salvage treatment (visual acuity 20/200–20/300 in the better eye, limited to counting fingers in the worse eye). These results show that stabilization of vision after radiation therapy is possible. The benefit of early intervention with radiation therapy was demonstrated by Pierce et al (3), who showed stable or improved visual acuity in 91% of patients for whom treatment was initiated before their vision declined severely. Similar reports that vision loss can be minimized with the early use of irradiation include those of Grabenbauer et al (2) and Horwich et al (18), in which 22 of 25 patients and 28 of 30 patients, respectively, had stable or improved vision after irradiation.

Because of the hypothetical risk of cognitive impairment in patients given radiation therapy at an early age, chemotherapy, primarily with carboplatin-based regimens, has been used to delay the use of radiation therapy in young children with optic pathway tumors. This hypothesis is supported by data on the age-related effects of conventional radiation therapy on cognition (19), but insufficient data are available on psychometric and visual outcomes to demonstrate the relative merits of delaying radiation therapy through the use of chemotherapy for younger patients. Using a regimen of alternating procarbazine/carboplatin, etoposide/cisplatin, and vincristine/cyclophosphamide every 3 weeks, Laithier et al (8) achieved a radiotherapy-free survival rate of 61% at 5 years. Janss et al (5) used chemotherapy to delay giving radiation therapy to children younger than 5 years for a median of 51 months; 87% of the patients in this study experienced tumor progression (symptomatic or shown by imaging), and most required radiation therapy. Of the patients given radiation therapy, 42% had progressing symptoms or imaging changes after therapy; this finding suggests that event-free survival after irradiation will be shorter for patients treated with chemotherapy. Although Janss reported deterioration of vision in only 8 patients, serial measurements were limited to 27 of 42 patients. These data provide insufficient evidence to support the rationale for delaying radiation therapy. Prospective treatment of LGA with chemotherapy has been demonstrated to have a PFS as high as 68%

at 3 years; however, no correlation of tumor reduction with visual acuity was mentioned (20).

Differences in visual outcome, related to the visual acuity in the better or worse eye, may be difficult to explain given the small number of patients included in this series. It is even more difficult to relate the number and degree of surgical intervention to visual outcomes as the neurosurgeon often uses visual acuity in decision making. We found that patients treated with limited surgery before irradiation had better visual acuity in both eyes at the start of radiation therapy than did those who did not undergo surgery. In addition, limited surgery may have a role in preserving long-term vision in the worse eye. These results would support surgical intervention aimed at reducing mass effect of tumor to improve vision.

Current opinion also favors surgical resection only for optic nerve tumors, because tumors involving the chiasm and optic pathways present a more difficult challenge. Some have advocated the use of subtotal surgical resection followed by observation (7), but the data of Jenkin et al (1) do not support the use of this treatment regimen: patients who underwent subtotal resection and observation had a 5-year relapse-free survival rate of 33% compared with those who underwent subtotal resection and radiation therapy (5-year relapse-free survival rate of 49%). Surgical intervention has been shown to have a positive role in cases of globular involvement of the chiasm in which subtotal resection might alleviate symptoms, including hydrocephalus or neurologic complications, but the risks associated with surgical treatment, which include blindness, endocrine disorders, and vascular complications, make even conservative resection questionable (21).

In this study, patients with symptomatic progression before radiation therapy had significantly worse visual acuity in their worse eye before radiation therapy than did those who received CRT prior to disease progression. Disease progression was not found to affect vision in the better eye. In the past, patients at our institution who experienced rapidly deteriorating vision have been given steroids. In this study, patients who received steroids during radiation therapy were likely to be those with the worst acuity bilaterally at the start of treatment; this finding reflects the practice of administering steroids on the basis of perceived and measured acuity. Because patients given steroids do not fare better than those not given steroids according to our data and because of the potential long-term complications arising from steroid use, including cataract formation, endocrine deficiencies, and avascular necrosis, we have chosen to avoid giving steroids to most patients unless they have other significant clinical symptoms such as headache or nausea that cannot be controlled with other medications.

Although radiation therapy has been shown to have a positive effect on vision (2, 3, 18, 22, 23), the adverse effects associated with radiation therapy have prevented its use in younger children, especially those <5 years (3, 18, 20, 24–27). Because there have been no reports of the effects of radiation on cognition or of the benefits associated with primary chemotherapy in patients with optic pathway tumors, we do not know whether the risks of cognitive impairment are uniform or whether reducing the irradiated volume will decrease the effects of irradiation in some patients. There are, however, data showing that patients with optic pathway glioma are at risk of endocrine deficiencies and vascular malformations, including moyamoya syndrome, cognitive losses and memory loss, and development of secondary tumors (3, 18, 21, 24–28). Deficiency in anterior pituitary hormones after radiation therapy has ranged from 20%–70% (2, 4, 18, 27), with younger patients appearing to be at increased risk of endocrine effects. Grabenhauer (2) similarly reported pituitary deficiency in 69% of children aged <10 years who received radiation therapy. Because of the high rate of preexisting endocrine deficiencies in this patient population (29), we do not use the potential for endocrine deficiencies as a reason to delay or avoid irradiation.

The rarity of optic pathway tumors precludes the use of statistical power to detect subtle differences in visual outcomes based on clinical characteristics and treatment maneuvers intended to preserve vision. The present study included 4.9 patients per year (22 patients in 4.5 years), a number that parallels or exceeds those in previous studies, which range from 1–1.6 patients per year (2, 3, 18, 20, 21, 23, 30, 31). The small number of patients and the long periods over which most studies are conducted introduce bias based on changing treatment technology and evaluation methods. Randomized trials comparing different treatments or tactics are unlikely for such a small number of patients.

Radiation therapy is the modality with which other therapies are compared in terms of disease control and visual outcome. Through the use of conformal treatment methods, we may be able to reduce or eliminate the cognitive, audiometric or endocrine effects of radiation for some patients. The visual outcome after radiation therapy should not depend on the technique provided that the targeted volume is adequate and the prescribed fractionation and total dose is conventional. With the advent of newer treatment methods and mounting evidence that delays in the administration of irradiation may reduce disease control and lead to inferior outcomes, the role of radiation therapy in all patients with optic pathway tumors should be reappraised, and a systematic evaluation of patients should be conducted regardless of treatment approach to gather more evidence to support one or more treatment approaches.

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Fig. 1.

Visual acuity (logarithm of the minimal angle of resolution [logMAR]) after conformal radiation therapy (CRT) as a function of time for patients who had or had not received chemotherapy before CRT. Changes in visual acuity are plotted separately for the best and worse eye. Visual acuity was measured up to 6 months before patients received CRT, at the start of CRT (time 0), and at 3- to 6-month intervals after CRT.

Fig. 2.

Visual acuity (logarithm of the minimal angle of resolution [logMAR]) after conformal radiation therapy (CRT) as a function of time for patients who had or had not undergone surgical resection of the tumor before CRT. Changes in visual acuity are plotted separately for the best and worse eye. Visual acuity was measured up to 6 months before patients received CRT, at the start of CRT (time 0), and at 3- to 6-month intervals after CRT.

Fig. 3.

Visual acuity (logarithm of the minimal angle of resolution [logMAR]) after conformal radiation therapy (CRT) as a function of time for patients who had or had not experienced symptomatic progression before CRT. Changes in visual acuity are plotted separately for the best and worse eye. Visual acuity was measured up to 6 months before patients received CRT, at the start of CRT (time 0), and at 3- to 6-month intervals after CRT.

Table

Clinical and treatment information and visual outcomes at last follow-up (range, 2–5 years after irradiation) for the patients in this series

Case	Pre-CRT chemotherapy	Sex	Age (y)	DX-RT interval (mo)	Pre-CRT progression	Surgery extent	Steroids	Best eye	Worst eye	Time after CRT (y)
1	None	F	6.6	64.1	Yes	Biopsy	None	Stable	Worse	2.5
2	None	M	14.1	0.8	No	Biopsy	None	Stable	Worse	2.5
3	None	F	14.2	0.7	Yes	Biopsy	Postop	Stable	Stable	5.1
4	None	M	5.7	0.8	Yes	Biopsy	Postop	Better	Better	4.5
5	None	M	14.6	5.1	No	Biopsy	Postop	Better	Better	2.2
6	None	M	9.7	53.4	Yes	None	Postop	Worse	Worse	4.1
7	None	F	7.8	1.0	Yes	Subtotal	On treatment	Better	Worse	3.2
8	None	M	9.4	1.8	Yes	Subtotal	Postop	Better	Stable	4.8
9	None	M	9.2	2.9	No	Subtotal	Postop	Better	Better	2.1
10	None	F	12.1	2.6	Yes	Subtotal	Postop	Better	Better	1.3
11	None	M	6.7	35.0	Yes	Subtotal	Pre/postop	Worse	Stable	3.3
12	None	F	13.3	1.6	No	Subtotal	Pre/postop	Better	Worse	0.5
13	Yes	F	4.1	24.1	Yes	Biopsy	None	Better	Better	3.0
14	Yes	F	5.5	63.4	Yes	Biopsy	None	Worse	Worse	2.3
15	Yes	F	10.8	26.5	Yes	Biopsy	On treatment	Stable	Worse	3.6
16	Yes	F	9.4	83.6	Yes	None	None	Worse	Worse	0.7
17	Yes	M	10.8	94.3	Yes	None	On treatment	Worse	Worse	3.0
18	Yes	M	6.5	58.5	Yes	Subtotal	Pre/postop	Better	Worse	0.8
19	Yes	M	8.2	65.4	Yes	Subtotal (<i>n</i> =2)	Postop	Better	Better	2.0
20	Yes	M	3.2	27.7	Yes	Subtotal (<i>n</i> =2)	Postop	Stable	Stable	2.0

Abbreviations: CRT = conformal radiation therapy; DX-RT = diagnosis to radiation therapy; F = female; M = male; postop = postoperative; pre = preoperative.