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Neurologic impairments from pediatric low-grade glioma by tumor location and timing of diagnosis

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Abstract

Background—The neurologic outcomes of low-grade gliomas (LGGs) according to tumor location and duration of presenting symptoms remain poorly characterized in children.

Procedure—We retrospectively reviewed neurologic impairments in 246 pediatric patients with LGGs (88 with optic pathway and midline tumors, 56 with posterior fossa tumors, 52 with cerebral hemisphere tumors, 35 with brainstem tumors and 15 with spinal cord tumors) who were treated at St. Jude Children's Research Hospital between 1995 and 2005. We compared neurologic impairments (defined by Common Terminology Criteria for Adverse Events, version 4.03) by tumor location and prediagnosis symptom interval (PSI) (≥ 3 months or < 3 months) at first and last patient visits.

Results—The median age of diagnosis was 7.1 years; median PSI was 2.1 months; and median time to last follow-up was 11.6 years. LGGs in the cerebral hemispheres resulted in significantly fewer neurologic impairments, compared with that of other locations at baseline ($P < 0.001$) and at last follow-up ($P < 0.001$). In all patients, PSIs greater than 3 months resulted in a significantly higher incidence of ataxia and dysmetria at last follow-up (41.6%, $P = 0.003$). Greater PSI was also significantly associated with worsening lower extremity motor weakness from cerebral hemisphere tumors; dysmetria from optic pathway and midline tumors; eye and visual dysfunction from posterior fossa tumors; and ear and vestibular disturbances from brainstem tumors ($P = 0.05$).

Conclusion—Neurologic impairment in pediatric LGGs varies by tumor location, and PSIs greater than 3 months affect some functionally important neurologic outcomes.

Keywords

low-grade glioma; neurologic outcomes; pediatric brain tumors; prediagnosis symptom interval

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

INTRODUCTION

Brain tumors are the most common solid tumors of childhood and are the leading cause of disease-related pediatric mortality.¹ Low-grade gliomas (LGGs) comprise a large and heterogeneous group of brain tumors that vary in location, treatment, histology, and outcome. These tumors have higher survival rates than do other brain tumors,^{2,3} but recurrence may occur in 50% of cases with incomplete surgical resection, thus resulting in long-term neurologic morbidity.⁴ LGGs in the cerebellum account for 15% to 25% of central nervous system (CNS) tumors. Hemispheric, midline structure, optic pathway, spinal cord, and brainstem LGGs also account for a considerable number of CNS tumors.^{5–7} Children with LGG may experience long-term neurologic impairments, including ataxia, visual impairment, eye movement disorders, hemiplegia, seizures, hearing loss, cranial nerve deficits, and cognitive dysfunction.^{8–11} Such long-term neurologic deficits vary by LGG location, with 30% occurring in the infratentorial region of the brain and 73% occurring in the supratentorial region.⁹ Diagnosis of childhood brain tumors is delayed when compared with that of other childhood cancers.^{12–15} Delayed diagnosis, measured by prediagnosis symptom interval (PSI), is associated with lower tumor grade, older age, and progressive disease.¹⁶ Here, we characterized neurologic impairments in pediatric patients with LGG according to tumor site and timing of diagnosis.

METHODS

Participants

All patients with LGG who were treated at St. Jude Children's Research Hospital (St. Jude) between January 20, 1995, and December 28, 2005, were eligible for this retrospective study and included if baseline and long-term neurologic assessments were available. Diagnosis of LGG was confirmed by pathology reports. If tumor biopsy information was unavailable, diagnosis was confirmed by imaging and clinical reports. The 2007 World Health Organization Classification of Tumors of the Central Nervous System criteria for LGG was used.¹⁷ Patients with neurofibromatosis type I were excluded. Symptom duration was based on reports in the initial history and abstracted via chart review. If a patient did not provide a specific date of symptom onset, the most conservative date was used. For example, if only the month was given, the last day of the month was used. If the patient used seasonal terms (i.e., summer, winter, fall, or spring), the last day of the month for each season (i.e., August, February, November, or April) was used. If a patient provided only a year, then December 31 of that year was used. The date of diagnosis was defined as the date of the first computed tomography or magnetic resonance imaging report after initial presentation. Therefore, the PSI was defined as the period from symptom onset to the first imaging report. In the case of multiple symptoms, the patient's longest PSI was used.¹⁶

Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional review board at St. Jude as a retrospective chart review under the classification of exempt research and waived the requirement for informed consent for this study.

Data collection

Scale scores and adverse event grades were determined from reports collected during the first and last patient visits at St. Jude. Relevant clinical information included birth date, sex, race, age at diagnosis, histologic diagnosis, description of symptoms, duration of symptoms, and treatment history. Neurologic impairment was assessed with the Modified Rankin Scale (MRS), which assigns scores from 0 (no symptoms) to 6 (death), and the Karnofsky Performance Status scale (KPS), which assigns scores from 0 (death) to 100 (normal activity), at first and last visits.^{18,19} Neurologic severity was scored with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.03), which assigns scores from 1 (absent) to 5 (death), by a board-certified pediatric neurologist (ZS). Neurologic impairments determined with CTCAE criteria included facial sensory and motor disorders, lower cranial nerve palsies, eye and visual dysfunction, disorders of the ear and vestibular apparatus, motor weakness, movement disorders, ataxia and dysmetria, speech disorders, sensory disorders, apraxia, headache, cognitive dysfunction, sleep disturbances, urinary disturbances, gastrointestinal disturbances, and autonomic dysfunction. Indicators for the presence of neurologic impairments at first and last visits were obtained for seizure, endocrine dysfunction, history of posterior fossa (PF) syndrome, stroke, and hydrocephalus (Supplementary Table S1). The incidence of each neurologic outcome by time point (first and last visit) and tumor site group was classified as positive for toxicity, if the CTCAE grade was 1 or higher or if the indicator was yes for yes or no outcomes. Tumor location information was obtained from radiology reports. Tumor site groups included spinal cord, PF, brainstem, optic pathway and midline, and the cerebral hemispheres. If the tumor involved multiple locations or was metastatic, the tumor's origin (per imaging report) was used.

Statistical analyses

Continuous variables were compared among the three tumor site groups with Kruskal–Wallis tests. We used χ^2 tests to compare the proportions of patients with worsening MRS and KPS scores by tumor site group. Continuous variables were compared among PSI groups (< 3 months versus ≥ 3 months) by Wilcoxon rank-sum tests. Incidence of neurologic impairment was calculated for all patients and by tumor site group, in which neurologic dysfunction was present in patients with a CTCAE grade 1 or greater. Fisher exact tests were used to compare the incidence of neurologic impairments for each PSI group. Proportions of patients who experienced worsening neurologic impairments from the first to last visits were calculated and compared among PSI groups with Fisher exact tests. We compared the incidence of neurologic impairments at last follow up among prior treatment regimens such as radiation therapy, chemotherapy, radiation therapy and chemotherapy, or neither chemotherapy or radiation therapy (i.e., surgery only) with χ^2 tests. Data were considered statistically significant when $P < 0.05$. All tests were two-sided, and no adjustments were made for multiple comparisons.

RESULTS

Patient characteristics

We included 246 patients in this analysis (88 with optic pathway and midline, 56 with PF, 52 with cerebral hemisphere, 35 with brainstem, and 15 with spinal cord tumors) (Table 1). The median age at cancer diagnosis was 7.1 years (range, 0.1–20.7 years), and the median time to last follow-up was 11.6 years (range, 0.1–21.4 years). The time between the first and last visits did not differ among the tumor site groups ($P = 0.68$). The median times to last follow-up by tumor site group were 12.0, 11.8, 11.2, 11.4, and 10.6 years for cerebral hemisphere, optic pathway and midline, PF, brainstem, and spinal cord LGGs, respectively.

The most prevalent histology was pilocytic astrocytoma (59.8%). One hundred twenty-six (51.2%) patients were male, and 191 (77.6%) were white. Seventy-four patients (30.1%) received gross total resections of their tumors. Twenty-one patients (8.5%) received chemotherapy, and 59 (24.0%) also received radiation therapy. Fifty-one (20.7%) patients received only radiation therapy, and 115 (46.7%) received neither chemotherapy nor radiation therapy following surgery. The median PSI was 2.1 months (range, < 1–131.1 months) for all patients. The distribution of PSI as a continuous variable did not differ among tumor site groups ($P = 0.22$). The median PSI for LGGs in the cerebral hemispheres was 1.3 months (range, 0–107.7 months), and 35 (67.3%) had “short PSIs” (i.e., < 3 months), whereas 17 (32.7%) had “long PSIs” (i.e., ≥ 3 months). The median PSI for optic pathway and midline LGGs was 1.8 months (range, 0–99.4 months), and 52 (59.1%) had short PSIs, whereas 36 (40.9%) had long PSIs. The median PSI for brainstem tumors was 2.7 months (range, 0–58.7 months), and 19 (54.3%) had short PSIs. The median PSI for PF tumors was 3.5 months (range, 0–128.6 months), and 27 (48.2%) had short PSIs. The median PSI for spinal cord tumors was 4.2 months (range, 0.1–131.1 months), and six (40.0%) had short PSIs (Table 1).

Presenting symptoms at diagnosis

The most commonly reported symptoms before diagnosis in all patients were headache (38.2%), nausea and vomiting (31.3%), motor weakness (22.8%), and eye and visual dysfunction (25.2%) (Supplementary Table S2). Before diagnosis the most commonly reported symptoms by site group were the following: (1) seizures (57.7%), headache (34.6%), and nausea and vomiting (21.2%) in the cerebral hemisphere; (2) eye and visual dysfunction (44.3%), headache (36.4%), and nausea and vomiting (33.0%) in the optic pathway or midline; (3) motor weakness (40.0%) in the spinal cord; (4) nausea and vomiting (45.7%), motor weakness (45.7%), and headache (31.4%) in the brainstem; and (5) headache (58.9%), nausea and vomiting (35.7%) and motor weakness (26.8%) in the PF.

Incidence of baseline and long-term neurologic impairments by location

Significant differences in the number of neurologic impairments at the first and last visits were present by tumor site group (Supplementary Table S3). Patients with cerebral hemisphere LGG had the lowest median number of neurologic impairments (two impairments) at baseline, compared with those of the PF (three impairments), optic pathway and midline (four impairments), spinal cord (four impairments), and brainstem (six

impairments) ($P < 0.001$). The number of impairments for cerebral hemisphere and PF tumors was also lower at last follow-up (three impairments), compared with that of the other site groups (five impairments for optic pathway/midline and spinal cord and eight impairments for brainstem tumors) ($P < 0.001$). In all patients, the most common neurologic impairments at the first visit were eye and visual dysfunction (41.6%), motor weakness (40.6%), ataxia and dysmetria (28.3%), and headache (26.4%). The most common neurologic deficits at the last visit were eye and visual dysfunction (46.3%), motor weakness (42.3%), cognitive dysfunction (37.3%), ataxia and dysmetria (30.8%), endocrine dysfunction (28.3%), and headache (26.0%).

The median MRS score was 1 (range, 0–5) for all patients at first visit and 2 (range, 0–5) at last follow-up (Supplementary Table S3). Baseline and last follow-up MRS scores were significantly different among tumor site groups ($P < 0.001$ for both time points). Patients with spinal cord, PF, and brainstem LGGs had the lowest median baseline MRS scores. The proportion of patients whose MRS scores worsened over time were not different among tumor site groups ($P = 0.16$). The proportion of patients whose MRS scores worsened over time did not differ by PSI among the site groups ($P = 0.67$) except for PF tumors, in which short PSIs were marginally associated with worsening MRS ($P = 0.053$). The median KPS score for all patients was 90 (range, 40–100) at baseline and 80 (range, 20–100) at last follow-up (Supplementary Table S3). Baseline and last follow-up KPS scores were significantly different for tumor site groups ($P = 0.003$ and $P < 0.001$, respectively). Patients with brainstem and cerebral hemisphere LGG had the highest baseline KPS scores.

Combining all tumor locations, we compared the incidence of neurologic impairments at last evaluation by prior treatment regimen (Supplementary Table S4). The incidence of facial sensory and motor disorder, lower cranial nerve palsies, eye and visual dysfunction, motor weakness, ataxia and dysmetria, endocrine dysfunction, stroke, hydrocephalus, sleep disturbances, and urinary dysfunction were significantly different in each treatment group ($P = 0.001, < 0.001, < 0.001, < 0.001, 0.047, < 0.001, 0.025, 0.026, 0.019, \text{ and } < 0.001$, respectively). Patients who were treated with chemotherapy and radiation had higher incidences of facial motor and sensory disorder (27.1%), lower cranial nerve palsies (28.8%), eye and visual dysfunction (62.7%), motor weakness (67.8%), sleep disturbances (33.9%), and urinary dysfunction (20.3%), when compared with the other treatment groups. The radiation only group had higher incidences of ataxia and dysmetria (41.2%) and endocrine dysfunction (52.9%), when compared with the other treatment groups. Those who received chemotherapy only had higher incidences of stroke (9.5%) and hydrocephalus (14.3%).

Incidence of baseline and long-term neurologic impairments by location and PSI

The distribution of total neurologic impairments by time point, PSI, and tumor site were overall not significantly different (Table 2). In all tumor sites combined, the incidence of ataxia and dysmetria was significantly higher at last follow-up in patients with long PSIs (22.8% short PSI versus 41.6% long PSI; $P = 0.003$). Long PSIs of brainstem LGG were associated with increased ear and vestibular dysfunction at last follow-up (25.0% long PSI versus 0.0% short PSI; $P = 0.039$). The incidence of motor weakness for cerebral

hemisphere tumors was significantly different by PSI at the first visit (34.3% short PSI versus 5.9% long PSI; $P = 0.039$), but not at the last follow-up.

The only neurologic impairment that significantly worsened for all tumor sites combined with long PSIs was dysmetria ($P < 0.001$) (Table 3). For cerebral hemispheric tumors, motor weakness (lower extremity) significantly worsened over time in patients with long PSIs ($P = 0.031$). Optic pathway and midline tumors with long PSIs had significantly worsened dysmetria over time ($P = 0.007$). In brainstem tumors with long PSIs, ear and vestibular apparatus disturbances ($P = 0.039$) significantly worsened over time. In PF tumors with long PSIs, eye and visual dysfunction significantly worsened over time ($P = 0.021$). Patients with short PSIs and brainstem tumors experienced significantly worsened vagal nerve deficits over time ($P = 0.049$) (Table 3).

DISCUSSION

We conducted the first and largest known study of long-term neurologic impairments in pediatric patients with LGG with respect to tumor location and timing of diagnosis. A previous study of delayed diagnosis of pediatric LGG by Arnautovic et al., demonstrated that increased PSIs are associated with lower tumor grade, older age, and disease progression, yet did not address neurological outcomes.¹⁶ We found that the incidence of neurologic impairments varied by tumor location and that long PSIs particularly affected the long-term incidence of ataxia and dysmetria.

Our findings are in agreement with reports that children with LGG commonly exhibit signs of increased intracranial pressure before diagnosis and that localized symptoms, such as focal neurologic deficits, seizures, and endocrinopathies, are dictated by tumor location.^{20,21} The frequencies of neurologic impairments at first and last visits (i.e., three and four, respectively) were similar to those reported in another study, with at least one long-term impairment occurring in 85% of patients and a minimum of three occurring in 28%.²² Of the five tumor site groups, cerebral hemisphere LGGs resulted in the fewest number of neurologic impairments at first and last visits, and brainstem tumors resulted in the highest numbers. We found no differences among tumor sites for worsening functional outcome, as measured by MRS. We observed higher incidences of worsening KPS scores over time in brainstem (57.1%), cerebral hemisphere (46.2%), and optic pathway and midline tumors (53.4%), as compared with those in PF (30.4%) and spinal cord (26.7%).

The most common long-term neurologic deficits observed in our study were similar to those reported in other studies, such as visual and motor deficits.^{22–24} For all patients, we found that long PSIs were associated with a higher incidence of long-term ataxia and dysmetria, and long PSIs were associated with ear and vestibular dysfunction specifically in patients with brainstem LGG. The only specific neurologic impairment that worsened over time for all patients with long PSIs was dysmetria. We found that long PSIs were associated with worsened ear and vestibular dysfunction in brainstem tumors; lower extremity motor weakness in cerebral hemisphere tumors; eye and visual dysfunction in PF tumors; and dysmetria in optic pathway and midline tumors. Long PSIs were reported for pediatric patients with spinal cord LGGs, of whom 83% experienced morbidity and 35% required

orthopedic interventions for severe kyphoscoliosis at long-term follow-up.²⁵ Of the 15 patients with spinal cord tumors in our study, 13 (86.7%) had scoliosis and seven (46.7%) required rod placement, but their neurologic deficits did not significantly worsen over time, regardless of PSI length. This could be due to functional compensation by neural plasticity in children with spinal cord LGGs.²⁶

The strengths of our study include the presence of similar demographic data in our study as those in other large population-based studies. We also used increments of 3 months for PSI intervals, which were similarly reported by others.^{24,27} Our study included a higher proportion of patients with supratentorial LGG, which was similarly reported by other population-based studies of LGG. A relatively low incidence of spinal cord LGGs has been reported in other studies as well.^{28,29} We found that receiving both chemotherapy and radiation therapy was a risk factor for higher rates of long-term facial motor and sensory disorder, lower cranial nerve palsies, eye and visual dysfunction, motor weakness, sleep disturbances, and urinary dysfunction. Patients who received radiation had higher rates of long-term ataxia and dysmetria and endocrine disturbances, whereas higher rates of long-term stroke and hydrocephalus occurred in those treated with chemotherapy. This is consistent with other reports of radiation as an independent risk factor for endocrine dysfunction, but our findings highlight other neurologic deficits arising from radiation, chemotherapy, or both treatments, which have not been extensively described before.²³

We report that stroke and hydrocephalus were more prevalent at long-term follow-up in the chemotherapy only group. However, the chemotherapy group consisted of only 21 patients, of which two (9.5%) had strokes. These two patients had optic pathway/midline LGG. Three (14.2%) of the 21 patients treated with chemotherapy only also had hydrocephalus. These three patients had optic pathway/midline LGG. The higher prevalence of stroke and hydrocephalus in patients treated with chemotherapy only is most likely attributed to the small number of patients in this group. Although the Childhood Cancer Survivor Study reported a cumulative incidence of late-occurring strokes in brain tumor survivors to be higher in those treated with radiation therapy, strokes occurred in survivors who did not receive radiation as well (2.69% radiation vs. 1.04% non-radiation).³⁰ Risk factors for stroke typically include younger age at tumor diagnosis, radiation therapy, and neurofibromatosis type I.^{31,32} However, optic pathway/midline tumor location may also associate with risk of stroke.³³

We were unable to compare specific chemotherapy regimens or radiation doses because of variability in the patient population and tumor locations. The retrospective nature of our study constitutes another weakness, in which data were collected from charts containing examinations and reports by various physicians. However, these data were reviewed by a board-certified neurologist who independently scored the neurologic impairments in a PSI interval-blinded manner. St. Jude is a referral center; therefore, referral bias may have also been introduced in our study cohort.

Although pediatric patients with LGG have high rates of survival, long-term neurologic morbidity persists and varies by tumor location. Prevention of delayed diagnosis is encouraged to prevent disease progression. Because neurologic deficits negatively affect

physical function, academic performance, and quality of life^{34–37} and some long-term deficits are associated with long PSIs, we propose that earlier diagnoses of pediatric LGGs will prevent development of some neurologic deficits and improve the quality of life of survivors. This is specifically evidenced by the success of a quality-improvement campaign, known as HeadSmart: Be Brain Tumour Aware, that was initiated in 2011 in the United Kingdom.³⁸ After its launch, the campaign facilitated a remarkable reduction in the PSIs associated with pediatric brain tumors in the United Kingdom.³⁸ It augmented professional and public awareness of the presenting symptoms of brain tumors in children and created guidelines for seeking medical attention, with improved referral times for diagnostic neuroimaging.³⁹ Although it is unclear whether such a methodology would be successful in the United States health care system, it is worthy of future investigation with prospective studies on survival and neurologic outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CNS	central nervous system
CTCAF	Common Terminology Criteria for Adverse Events
KPS	Karnofsky Performance Status
LGG	low-grade glioma
MRS	Modified Rankin Scale
PF	posterior fossa
PSI	prediagnosis symptom interval
St. Jude	St. Jude Children's Research Hospital

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TABLE 1

Patient characteristics (n = 246)

	Site Group											
	Brainstem (n = 35)		Cerebral (n = 52)		Optic pathway/ midline (n = 88)		Posterior fossa (n = 56)		Spinal cord (n = 15)		All Patients (n = 246)	
	n	%	n	%	n	%	n	%	n	%	n	%
Sex												
Female	13	37.1	24	46.2	46	52.3	29	51.8	8	53.3	120	48.8
Male	22	62.9	28	53.8	42	47.7	27	48.2	7	46.7	126	51.2
Race												
White	25	71.4	40	76.9	67	76.1	44	78.6	15	100.0	191	77.6
Black	5	14.3	12	23.1	13	14.8	10	17.9	0	0.0	40	16.3
Other	4	11.4	0	0.0	6	6.8	2	3.6	0	0.0	12	4.9
Unknown	1	2.9	0	0.0	2	2.3	0	0.0	0	0.0	3	1.2
Age at diagnosis (years)												
Median	6.4	–	9.0	–	6.6	–	7.2	–	8.8	–	7.1	–
Minimum	0.1	–	0.4	–	0.3	–	0.6	–	2.1	–	0.1	–
Maximum	16.0	–	20.7	–	17.8	–	17.5	–	17.0	–	20.7	–
Histology												
Pilocytic astrocytoma	23	65.7	10	19.2	55	62.5	50	89.3	9	60.0	147	59.8
Ganglioglioma	1	2.9	7	13.5	6	6.8	4	7.1	2	13.3	20	8.1
Fibrillary astrocytoma	2	5.7	6	11.5	6	6.8	0	0.0	0	0.0	14	5.7
Oligodendroglioma	0	0.0	13	25.0	0	0.0	0	0.0	1	6.7	14	5.7
Astrocytoma, NOS	4	11.4	4	7.7	4	4.5	0	0.0	0	0.0	12	4.9
Pleomorphic xanthoastrocytoma	0	0.0	10	19.2	1	1.1	0	0.0	0	0.0	11	4.5
Glioma, optic	0	0.0	0	0.0	8	9.1	0	0.0	0	0.0	8	3.3
Glioma, NOS	4	11.4	0	0.0	3	3.4	0	0.0	0	0.0	7	2.8
Piloxyoid astrocytoma	1	2.9	0	0.0	4	4.5	2	3.6	0	0.0	7	2.8
Other	0	0.0	2	3.8	1	1.1	0	0.0	3	20.0	6	2.4
Grade												

	Site Group											
	Brainstem (n = 35)			Cerebral (n = 52)			Optic pathway/ midline (n = 88)			Posterior fossa (n = 56)		
	n	%		n	%		n	%		n	%	
I	28	80.0		20	38.5		73	83.0		53	94.6	
II	7	20.0		32	61.5		15	17.0		3	5.4	
Therapy												
Chemotherapy only	1	2.9		2	3.8		14	15.9		2	3.6	
Chemotherapy and RT	11	31.4		6	11.5		32	36.4		4	7.1	
RT only	16	45.7		4	7.7		25	28.4		3	5.4	
No chemotherapy or RT	7	20.0		40	76.9		17	19.3		47	83.9	
GTR	0	0.0		25	48.1		8	9.1		38	67.9	
Duration of symptoms/PSI (months)												
Median	2.7	–		1.3	–		1.8	–		3.5	–	
Minimum	0.0	–		0.0	–		0.0	–		0.0	–	
Maximum	58.7	–		107.7	–		99.4	–		128.6	–	
< 3 months	19	54.3		35	67.3		52	59.1		27	48.2	
3 months	16	45.7		17	32.7		36	40.9		29	51.8	

GTR, gross total resection; NOS, not otherwise specified; PSI, prediagnosis symptom interval; RT, radiation therapy

TABLE 2

Incidence of neurologic impairments by site group, time point, and PSI^a (< 3 months versus 3 months)

	Brainstem			Cerebral hemisphere			Optic pathway/midline			Posterior Fossa			Spinal cord			All patients		
	Baseline (%)			LFU (%)			Baseline (%)			Baseline (%)			Baseline (%)			Baseline (%)		
	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo	<3 mo
PSI																		
	52.6	43.8	52.6	25.0	0.0	5.9	9.6	8.3	15.4	19.4	11.1	10.3	7.4	10.3	0.0	0.0	0.0	12.9
Facial sensory and motor disorder	52.6	43.8	52.6	25.0	0.0	5.9	9.6	8.3	15.4	19.4	11.1	10.3	7.4	10.3	0.0	0.0	0.0	12.9
Lower cranial nerve palsies (IX–XII)	21.1	43.8	42.1	31.3	0.0	11.8	2.9	0.0	9.6	2.8	9.6	13.9	7.4	6.9	3.7	13.8	0.0	8.0
Eye and visual dysfunction	47.4	56.3	63.2	50.0	14.3	29.4	34.3	29.4	61.5	69.4	71.2	72.2	18.5	41.4	14.8	34.5	0.0	36.7
Ear and vestibular dysfunction	5.3	12.5	0.0*	25.0*	0.0	11.8	11.4	11.8	5.8	0.0	7.7	11.1	7.4	3.4	14.8	20.7	0.0	11.1
Motor weakness	57.9	56.3	73.7	62.5	34.3*	5.9*	34.3	35.3	36.5	28.6	34.6	38.9	29.6	55.2	29.6	34.5	100.0	77.8
Movement disorders	5.3	18.8	5.3	18.8	2.9	0.0	0.0	5.9	1.9	8.3	3.8	13.9	3.7	3.4	11.1	3.4	0.0	11.1
Ataxia and dysmetria	36.8	43.8	52.6	68.8	8.6	0.0	11.4	11.8	15.4	11.1	17.3	33.3	63.0	69.0	29.6	55.2	0.0	11.1
Sensory disorder	5.3	0.0	5.3	6.3	2.9	11.8	8.6	11.8	2.0	0.0	3.8	8.3	3.7	6.9	0.0	6.9	66.7	44.4
Headache	10.5	37.5	15.8	25.0	22.9	17.6	22.9	35.3	30.8	33.3	21.2	30.6	29.6	31.0	40.7	27.6	0.0	11.1
Cognitive dysfunction	21.1	18.8	42.1	43.8	20.0	17.6	37.1	35.3	17.3	25.0	38.5	33.3	7.4	27.6	40.7	37.9	0.0	11.1
Seizure	10.5	6.3	10.5	12.5	74.3	88.2	31.4	35.3	3.8	8.3	11.5	19.4	3.7	6.9	3.7	3.4	0.0	11.1
Endocrine dysfunction	0.0	6.3	47.4	43.8	2.9	0.0	14.3	0.0	7.7	11.1	36.5	41.7	0.0	0.0	14.8	10.3	0.0	66.7
Hydrocephalus	5.3	25.0	5.3	0.0	0.0	0.0	0.0	0.0	50.0	50.0	15.4	16.7	3.7	3.4	0.0	0.0	0.0	0.0
Sleep	0.0	6.3	15.8	18.8	0.0	0.0	31.4	23.5	7.7	0.0	23.1	33.3	0.0	3.4	0.0	10.3	0.0	11.1
Urinary	0.0	6.3	5.3	12.5	0.0	0.0	0.0	5.9	1.9	2.8	9.6	11.1	3.7	3.4	0.0	0.0	11.1	0.0
Autonomic	21.1	18.8	10.5	18.8	25.7	25.0	34.3	18.8	25.5	22.2	41.2	30.6	3.7	10.3	11.1	10.3	0.0	11.1

LFU, last follow-up; mo, months; PSI, prediagnosis symptom interval

^aImpairments < 10% for all site/PSI groups were excluded.

* *P* 0.05.

TABLE 3

Worsening of neurologic impairments by PSI group and location^a

PSI	Brainstem		Cerebral hemisphere		Optic pathway/midline		Posterior fossa		Spinal cord		All patients	
	< 3 mo	3 mo	< 3 mo	3 mo	< 3 mo	3 mo	< 3 mo	3 mo	< 3 mo	3 mo	< 3 mo	3 mo
Facial sensory and motor	36.8	12.5	0.0	5.9	9.6	19.4	7.4	6.9	0.0	0.0	10.1	11.2
CN IX–XII	42.1	31.3	2.9	0.0	9.6	13.9	3.7	13.8	0.0	0.0	10.8	13.1
CN IX	31.6	6.3	0.0	0.0	1.9	2.8	0.0	0.0	0.0	0.0	5.0	1.9
CN X	26.3 *	0.0 *	0.0	0.0	1.9	5.6	0.0	0.0	0.0	0.0	4.3	1.9
Eye and visual dysfunction	57.9	43.8	28.6	17.6	59.6	50.0	7.4 *	34.5 *	0.0	0.0	38.8	35.5
Ear and vestibular dysfunction	0.0 *	25.0 *	11.4	5.9	7.7	11.1	7.4	20.7	0.0	11.1	7.2	15.0
Motor weakness (overall)	68.4	50.0	25.7	35.3	26.9	36.1	29.6	24.1	66.7	22.2	34.5	33.6
Motor weakness (LE)	26.3	43.8	5.7 *	29.4 *	13.5	16.7	11.1	13.8	16.7	22.2	12.9	22.4
Movement disorder	5.3	18.8	0.0	5.9	3.8	13.9	11.1	3.4	0.0	0.0	4.3	9.3
Ataxia	36.8	25.0	11.4	5.9	9.6	13.9	11.1	17.2	0.0	11.1	13.7	15.0
Dysmetria	10.5	37.5	2.9	11.8	1.9 *	19.4 *	3.7	17.2	0.0	0.0	3.6 *	18.7 *
Speech disorder	5.3	0.0	0.0	0.0	1.9	0.0	0.0	0.0	0.0	0.0	1.4	0.0
Sensory disorder	5.3	6.3	8.6	11.8	1.9	8.3	0.0	6.9	33.3	11.1	5.0	8.4
Seizures	0.0	12.5	5.7	0.0	9.6	16.7	0.0	0.0	0.0	0.0	5.0	7.5
Cognitive dysfunction	31.6	37.5	34.3	29.4	34.6	30.6	37.0	31.0	16.7	11.1	33.8	29.9
Stroke	0.0	0.0	0.0	0.0	1.9	5.6	0.0	3.4	0.0	0.0	0.7	2.8
Hydrocephalus	5.3	0.0	0.0	0.0	5.8	2.8	0.0	0.0	0.0	0.0	2.9	0.9
Sleep disturbances	15.8	18.8	31.4	23.5	21.2	33.3	0.0	6.9	0.0	11.1	18.0	20.6
Urinary	5.3	12.5	0.0	5.9	9.6	11.1	0.0	0.0	0.0	33.3	4.3	9.3
Gastrointestinal	5.3	0.0	0.0	5.9	0.0	2.8	0.0	0.0	0.0	11.1	0.7	2.8
Autonomic	10.5	18.8	20.0	11.8	26.9	25.0	11.1	10.3	0.0	11.1	18.7	16.8

CN, cranial nerve; LE, lower extremity; mo, months; PSI, prediagnosis symptom interval

^aThe percentage of patients who had worsening neurologic impairments from first to last visit for each PSI and tumor site group are indicated in each cell.* *P* 0.05.