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The prognostic value of neurologic function in astrocytic spinal cord glioma[1]

Hoon K. Lee, Eric L. Chang,[2] Gregory N. Fuller, Kenneth D. Aldape, George J. Atkinson, Lawrence B. Levy, Ian E. McCutcheon, and Moshe H. Maor

Departments of Radiation Oncology (H.K.L., E.L.C., G.J.A., M.H.M.), Pathology (G.N.F., K.D.A.), Biomathematics (L.B.L.), and Neurosurgery (I.E.M.), The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA

To assess the prognostic value of neurologic function (NF) in patients with astrocytic spinal cord glioma, we conducted a retrospective study of 25 patients who were treated at our institution between January 1970 and December 1999. The median age was 40 years, and the median follow-up was 54 months. Nineteen patients had a biopsy, 5 had a subtotal resection, and 1 had a gross total resection. Twenty-two patients received postoperative radiotherapy to a median dose of 45 Gy. NF ratings of 1 and 2 were considered favorable, and 3 and 4 were considered unfavorable, based on a scale of 1 to 4. Dual neuropathologic review confirmed the tumor to be low, intermediate, or high grade, based on the WHO grades I-II, III, or IV, respectively. Actuarial rates of local control (LC), progression-free survival (PFS), and overall survival (OS) were analyzed. Our study results revealed that an improved 5-year OS rate was associated with favorable NF at diagnosis (73% vs. 22% for patients with unfavorable NF; $P = 0.04$) and favorable NF before radiation therapy (89% vs. 28% for patients with unfavorable NF; $P = 0.049$). There was a significant difference in OS based on tumor grade ($P < 0.001$) and age (risk ratio, 1.04; $P = 0.027$). PFS and LC were significantly better for young patients and those with lower tumor grade ($P < 0.05$). A multivariate analysis of age, NF at diagnosis, and postoperative NF for all patients showed postoperative NF and age to be independent prognostic factors for OS. We conclude that favorable NF may be associated with improved outcome in patients with astrocytic spinal cord glioma. *Neuro-Oncology 5, 208–213, 2003 (Posted to Neuro-Oncology [serial online], Doc. 02-059, May 07, 2003. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/S1152 8517 02 00059 5)*

Primary spinal cord tumors are rare, their prevalence being only 10% to 19% of that for brain tumors (Connolly, 1982). Ependymoma is more common, generally has better outcome, and is often more amenable to complete resection than primary astrocytic spinal cord glioma (Constantini et al., 2000; McCormick et al., 1990; Rodrigues et al., 2000). In contrast, patients with astrocytic glioma of the spinal cord are usually unresectable and have poorer outcome, with the 5-year overall survival rates (OS)[3] ranging from 40% to 60% (Chun et al., 1990; Huddart et al., 1993; Linstadt et al., 1989; Reimer and Onofrio, 1985).

The tumor grade, duration of symptoms, and patient age have been previously suggested as prognostic factors for astrocytic spinal cord glioma (Linstadt et al., 1989; Rodrigues et al., 2000). Although neurologic function (NF) of these patients has been characterized in the literature (Cohen et al., 1989; Constantini et al., 2000; Cooper, 1989; Epstein et al., 1992; Garcia, 1985; Jyothirmayi et al., 1997; Kim et al., 2001; Kopelson et al., 1980; McCormick et al., 1990; Rodrigues et al., 2000; Shirato et al., 1995), it is unclear whether NF provides any prognostic value. The purpose of this retrospective study was to assess the significance of NF in patients with astrocytic spinal cord glioma.

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[2] Address correspondence to Eric L. Chang, Department of Radiation Oncology, Box 97, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4009, USA (echang@mdanderson.org).

[3] Abbreviations used are as follows: LC, local control; NF, neurologic function; OS, overall survival; PFS, progression-free survival.

Clinical Materials and Methods

Patient Population

Twenty-five patients (13 males and 12 females) with astrocytic spinal cord glioma were treated at The University of Texas M.D. Anderson Cancer Center between January 1970 and December 1999. The median age was 40 years (range, 1–58 years), and the median follow-up was 54 months (range, 10–313 months).

Tumor Characteristics

Two neuropathologists (G.N.F. and K.D.A.) reviewed 19 available pathologic specimens in order to confirm the accuracy of tumor grade. For the other 6 cases, pathologic diagnosis had been made previously at our institution, but the tissue specimens were not available from the archive. Based on the WHO classification, 15 pathologic specimens were classified as low grade (WHO I or II), 4 specimens as intermediate grade (WHO III), and 6 specimens as high grade (WHO IV) (Table 1).

Treatment

Nineteen of 25 patients underwent biopsy as the only surgical management. Five patients had a subtotal resection, and 1 had a gross total resection (Table 2). The cavitron ultrasound aspirator has been available at our institution for the last 20 years; however, it has not been widely used in this series. Twenty-two patients received postoperative radiotherapy to a median dose of 45 Gy (range, 22–60 Gy, in fractions of 1.5–3.0 Gy). Generally, the tumor bed with a 2 vertebral body margin superiorly and inferiorly was used as the target volume. A 2-year-old boy who had a biopsy, a 1-year-old boy with a subtotal resection, and a 16-year-old male with a gross total resection did not receive postoperative radiotherapy. Radiation therapy was delivered locally to the primary tumor bed in 18 cases and to the entire spine in 2 cases with either cobalt 60 or megavoltage photons or electrons. Information on the radiotherapy technique that was used was not available in 2 cases. Chemotherapy was administered to 13 patients. The chemotherapy agents and the sequence of delivery varied considerably among patients (Table 2); therefore, chemotherapeutic effects were not analyzed in this study.

Pretreatment Assessment

Neurologic function was assessed at diagnosis, postoperatively, before radiation therapy, and at subsequent follow-ups. The NF classification was based on a previous clinical-functional scheme graded from 1 to 4 devised by

Table 1. Patient characteristics

Patient No.	Age	Sex	Location	Histology	WHO Grade
1	45 years	M	C2	A	II
2	7 years	M	T10 – L1	AA	III
3	6 months	F	C2 – T3	PA	I
4	58 years	F	T9 – 12	AA	III
5	51 years	F	C4 – 6	A	II
6	9 years	F	L1-2, Medulla to C4, CM	A	II
7	53 years	M	C1 – 3	GBM	IV
8	33 years	M	C3	A	II
9	30 years	F	T12 – L2	AA	III
10	15 years	F	T9 – CM	GBM	IV
11	33 years	F	C3 – 5	GBM	IV
12	34 years	M	T12 – L1	A	II
13	5 years	M	C4 – T8	PA	I
14	32 years	F	T7 – 9, T12 – L1, CM	GBM	IV
15	54 years	M	T12 – L2	GBM	IV
16	47 years	M	C5 – T2	GBM	IV
17	16 years	M	C2 – T3	PA	I
18	2 years	M	T9 – L2	A	II
19	24 years	F	C5 – T1	PA	I
20	47 years	F	T12 – L1	A	II
21	23 years	F	C3 – C6	PA	I
22	24 years	M	T11 – Caudal Sac	PA	I
23	16 years	M	C2 – 4	PA	I
24	11 months	M	C2 – T2	PA	I
25	40 years	M	T12 – L1	AA	III

Abbreviations: A = astrocytoma, AA = anaplastic astrocytoma, CM = conus medullaris, GBM = glioblastoma multiforme, PA = pilocytic astrocytoma

Table 2. Treatment summary

Patient No.	Surgery	Chemotherapy	Dose (Gy)
1	Bx	None	60
2	Bx	Vincristine	48
3	Bx	MOPP, cisplatin	40
4	Bx	None	30
5	Bx	None	45
6	Bx	None	36
7	Bx	None	22
8	Bx	None	50
9	Bx	None	45
10	Bx	VP-16, dexamethasone, temozolomide	45
11	Bx	VP-16, temozolomide, cis-retinoic acid	45
12	STR	None	45
13	Bx	None	48
14	STR	Cisplatin	46
15	Bx	Carboplatin, VP-16, thioguanine, procarbazine, hydroxyurea, CCNU	50
16	STR	Procarbazine, CCNU, vincristine, cis-retinoic acid	45
17	Bx	None	45
18	Bx	Carboplatin, vincristine	None
19	STR	VP-16, carboplatin, BCNU, cis-retinoic acid	45
20	Bx	CCNU, vincristine, procarbazine	50
21	Bx	BCNU, AZQ	52
22	Bx	None	50
23	GTR	None	None
24	STR	Vincristine, carboplatin	None
25	Bx	BCNU	NA

Abbreviations: AZQ = 2,5-diazisidinyl-3,6-bis(carbethoxyamino)-1-4-benzoquinone; Bx = biopsy; GTR = gross total resection; MOPP = mechlorethamine, oncovin, prednisone, procarbazine; NA = not available; STR = subtotal resection.

McCormick and colleagues (Table 3; McCormick et al., 1990). The extent of disease was approximated by the number of vertebral segments that spanned the diseased area and was determined from the preoperative radiographic studies, intraoperative findings, or from both sources. The use of MRI for initial staging and follow-up has been widely used since it became available at our institution in the late 1980s. Patients treated before its availability underwent a myelography that showed abnormal enlargement of the spinal cord.

Statistical Analysis

Local control (LC) was defined as the absence of tumor recurrence at the initial site of disease, even if distant metastases were present. Progression-free survival (PFS) was defined as the time from diagnosis until first relapse at any site. Overall survival was defined as the interval from diagnosis until time of death or last follow-up. Kaplan-Meier curves were generated for LC, PFS, and OS from the date of pathologic diagnosis (Kaplan and Meier, 1958). Comparisons between the actuarial curves were made by using the log-rank test (Mantel, 1966). The Jonckheere-Terpstra test was used to determine the relationship between tumor grade and NF. The multivariate analysis was performed by using the Cox proportional hazards model, incorporating patient age, NF at diagnosis, and postoperative NF. For this model, the time interval for OS was measured from the date of the postoperative NF observation so that the analysis could be done when all 3 variables were known for the 25 patients. The maximum likelihood estimates could not be computed when additional variables were included in the multivariate model because of the small number of cases.

Results

Preoperative Clinical Findings

The most common clinical presentations were pain, paresthesia, and extremity weakness. Neurologic function at diagnosis was independent of the tumor grade (Jonckheere-Terpstra test; $P = 0.69$). The actuarial OS rate at 5 years for favorable NF at diagnosis was 73%, compared to 22% for patients with unfavorable preoperative NF (Fig. 1; $P = 0.04$). No significant improvement in LC ($P = 0.088$) or PFS ($P = 0.09$) was observed based on NF at diagnosis. Older age adversely affected LC (risk ratio, 1.07; $P = 0.004$), PFS (risk ratio, 1.06; $P = 0.002$), and OS (risk ratio, 1.04; $P = 0.027$). There was no significant difference in LC ($P = 0.12$), PFS ($P = 0.07$), or OS ($P = 0.38$) by sex.

Extent of Disease

The locations of the tumors are described in Table 1. The extent of disease, approximated by the number of vertebral bodies in the diseased area, did not significantly correlate with LC ($P = 0.30$), PFS ($P = 0.22$), or OS ($P = 0.52$).

Primary and Adjuvant Therapy

There was no significant difference in LC ($P = 0.64$), PFS ($P = 0.32$), or OS ($P = 0.13$) with respect to the type of surgery performed. In univariate analysis, there was no

Table 3. Neurologic function classification*

Neurologic Function	Clinical Definition
1	Normal to mild focal deficit
2	Moderate deficit; significant motor or sensory loss but able to function independently
3	Moderate to severe deficit; requires assistance to ambulate
4	Severe deficit; unable to function independently or to ambulate

*Based on the scheme of McCormick et al. (1990).

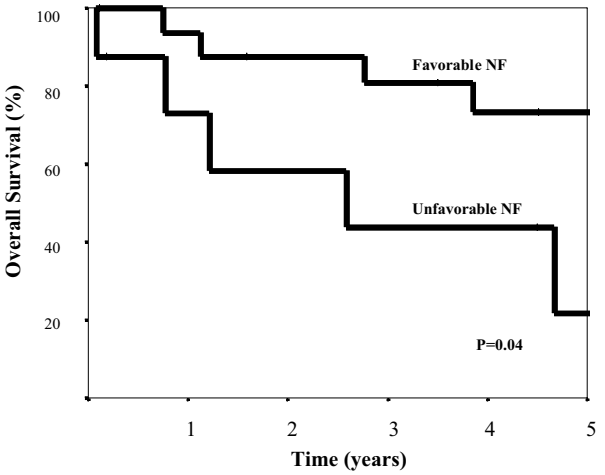

Fig. 1. Overall survival based on neurologic function at diagnosis

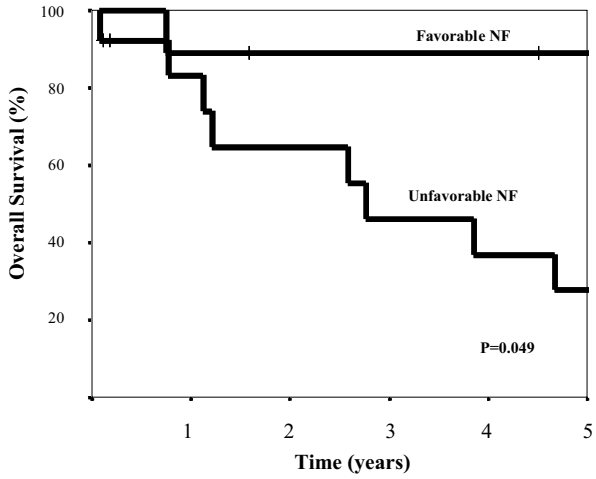

Fig. 2. Overall survival based on neurologic function before radiation therapy for 22 patients

difference in LC ($P = 0.12$), PFS ($P = 0.11$), or OS ($P = 0.079$) based on favorable or unfavorable postoperative NF of the 25 patients.

Twenty-two patients underwent postoperative radiotherapy. Nine patients had favorable NF at the time of radiation therapy, and 13 patients had unfavorable NF. For those 22 patients, the estimated actuarial OS rates at 5 years were, respectively, 89% and 28% with favorable and unfavorable NF at the time of radiation therapy ($P = 0.049$, Fig. 2). There was no significant improvement in LC ($P = 0.14$) or PFS ($P = 0.12$) based on NF at the time of radiation therapy. The interval change in NF for all patients is shown in Table 4. After postoperative radiotherapy, 3 patients had improvement of NF, 10 had stable NF, and 9 had NF deterioration.

A multivariate analysis of patient age, NF at diagnosis, and postoperative NF showed that age (hazard ratio 1.035; 95% confidence interval 1.0007–1.07; $P = 0.045$) and postoperative NF (hazard ratio 4.74; 95% confidence interval 1.015–22.1; $P = 0.048$) were associated with OS. Additional variables, such as tumor grade, could not be incorporated into the multivariate model because of the small number of statistical events and cases.

Pathologic Findings

The estimated actuarial LC rates at 5 years were 48%, 0%, and 0% for low-, intermediate-, and high-grade tumors, respectively ($P = 0.001$). The estimated actuarial PFS rates at 5 years were 43%, 0%, and 0% ($P < 0.001$), and OS rates were 78%, 67%, and 17% ($P < 0.001$) for low-, intermediate-, and high-grade tumors, respectively (Fig. 3).

Patterns of Failure

Eighteen of 25 patients had known disease progression at the time of analysis. In 1 patient, the location of disease progression was unavailable. Local recurrence accounted for 78% of all relapses and was the predominant pattern of treatment failure. Ten patients had local recurrence; 3 had distant metastasis; and in 4 the disease recurred at local and distant sites. Distant metastasis was limited to the craniospinal axis, and no patient had systemic disseminated disease. No patient with stable or improved NF at last follow-up had distant metastasis. Of the 7 patients who had distant metastasis, 3 had WHO grade I tumors, 1 had a WHO grade II tumor, and 3 had WHO grade IV tumors.

Complications

None of the patients who received radiation therapy developed radiation myelopathy. One patient had Lhermitte's sign that spontaneously resolved. One patient had bilateral external otitis after receiving radiotherapy to the cervical spine. Scoliosis developed in 3 children who had undergone radiotherapy at the ages of 5, 9, and 11; of these, 2 were alive without evidence of disease at the time of analysis. One child experienced delayed molar development after receiving radiotherapy. Another child had a surgical correction for scoliosis, but died of disease progression 162 months after her diagnosis.

Discussion

Previous studies have described various neurologic deficits that commonly occur in patients with spinal cord tumors (Cohen et al., 1989; Constantini et al., 2000; Cooper, 1989; Epstein et al., 1992; Garcia, 1985; Jyothirmayi et al., 1997; Kim et al., 2001; Kopelson et al., 1980; McCormick et al., 1990; Rodrigues et al., 2000; Shirato et al., 1995). A scheme devised by McCormick and colleagues (1990) was used in this study to classify neurologic deficits. Although NF has been characterized preoperatively as part of staging, its prognostic value for patients with astrocytic spinal cord glioma is unclear. Kim and colleagues (2001) suggested that preoperative NF was associated with survival; however, the relationship was not shown to be significant in a multivariate

Table 4. Changes in neurologic function classification by interval

Patient No.	Diagnosis*	Postoperative/ Preradio-therapy	Postradio-therapy	Last follow-up	Ultimate Change**
1	2	2	2	4	2
2	1	3	2	3	2
3	2	3	3	4	2
4	4	4	4	4	0
5	2	3	3	3	1
6	2	3	2	4	2
7	4	4	4	4	0
8	1	1	1	1	0
9	3	3	3	3	0
10	3	4	3	4	1
11	1	2	2	1	0
12	2	3	3	4	2
13	2	2	2	1	–1
14	1	1	3	4	3
15	3	3	3	4	1
16	2	3	3	4	2
17	2	2	2	3	1
18	3	3	NA	4	1
19	2	4	3	4	2
20	1	1	2	2	1
21	3	3	2	4	1
22	2	2	1	3	1
23	1	2	NA	1	0
24	3	3	NA	2	–1
25	2	2	1	1	–1

* See Table 3.

** Ultimate change was defined as the difference in neurologic function from diagnosis to last follow-up.

NA = not applicable for patients that did not receive radiotherapy.

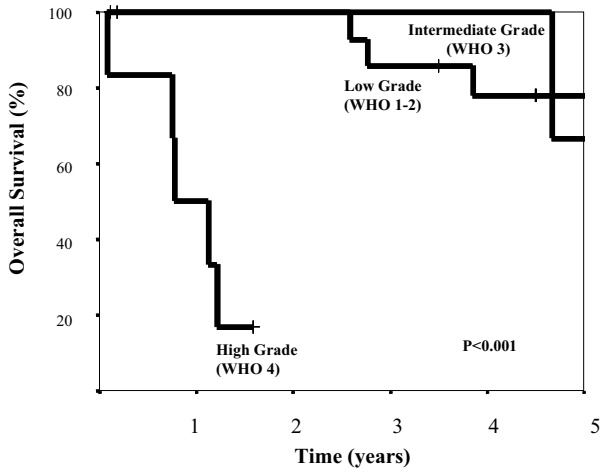

Fig. 3. Overall survival based on the WHO tumor grade

analysis. In that study, patients with low-grade tumors had a significantly higher proportion of favorable NF at diagnosis. In our series, there was no such association between NF at diagnosis and tumor grade. Nevertheless, favorable NF at diagnosis appeared to be associated with improved OS in univariate analysis. In multivariate analysis, postoperative NF appeared to be better correlated with OS than NF at diagnosis, independent of the patient age.

While preoperative NF may provide a general clinical estimate of the extent of disease, NF may change postoperatively, particularly if aggressive complete resection is attempted. Since no study has reported improved outcome based on increasing degree of surgery with postoperative radiotherapy, a biopsy may be the optimal surgical intervention to preserve NF. In our series, 19 patients underwent a biopsy only, and 13 (68%) of those patients had no change in their NF after their surgery. In contrast, only 2 of 7 (29%) patients who underwent a subtotal or gross total resection had stable NF postoperatively. Although the number of patients to compare the NF changes based on the type of surgical resection is small, these data suggest that patients frequently have stable postoperative NF with only a biopsy.

The extent of resection did not have a significant impact on OS or LC in our analysis. This finding is consistent with other studies that revealed no significant association between improvement in survival and extent of surgical resection (Cooper, 1989; Houten and Cooper, 2000; Jyothirmayi et al., 1997; Kim et al., 2001; Minehan et al., 1995; O'Sullivan et al., 1994; Rodrigues et al., 2000). It is recognized that, unlike ependymoma, astrocytic spinal cord glioma is often difficult to resect completely (Bouffet et al., 1998; Guidetti et al., 1981; O'Sullivan et al., 1994). For this reason, patients with astrocytic spinal cord glioma are routinely given postoperative radiotherapy. Minehan et al. (1995) found that the highest survival rate in their series was among patients who underwent a biopsy followed by radiotherapy. In that study of 79 cases, there was a trend toward worse survival for patients who had more aggressive surgery compared to those who had a biopsy. These data suggest that aggressive resection, which may worsen NF, may not be warranted.

The prognostic value of tumor grade and patient age has been reported in other studies and is reaffirmed by our data (Cohen et al., 1989; Constantini et al., 2000; Jyothirmayi et al., 1997; Kim et al., 2001; Kopelson and Linggood, 1982; Minehan et al., 1995; Rodrigues et al., 2000; Shirato et al., 1995). Patients with low-grade tumors tended to infrequently have distant metastasis in the craniospinal axis. Of the 3 distant-only relapses in the craniospinal axis, 2 patients had WHO grade IV tumor, and 1 had WHO grade II tumor. Three patients with WHO grade I tumors had both local recurrence and distant metastasis in the craniospinal axis. The observed low incidence of distant failures in low-grade tumors, outside of synchronous local failure, has been reported previously (Cohen et al., 1989; Jyothirmayi et al., 1997; Kim et al., 2001).

No patient developed radiation-induced spinal cord myelopathy or any other life-threatening treatment-related complication in this series. Pediatric patients are more susceptible to the late effects of radiation, as demonstrated in the cases of the 3 children in whom scoliosis

developed and the child who had delayed molar development. However, the development of kyphoscoliosis may not be secondary to radiation therapy alone. Constantini and colleagues (2000) observed kyphoscoliosis in 71.6% of children and young adults, of whom 73.5% underwent surgery as their only treatment. In a study of 31 children, O'Sullivan and colleagues (1994) reported the actuarial incidence of second malignancies to be 13% at 20 years. No second malignancy was observed in our series.

Convincing data on dose response for this disease is lacking for obvious reasons, such as the rarity of cases and the inability to escalate dose above the spinal cord tolerance. Garcia (1985) suggested inferior tumor control at doses less than 40 Gy, and a case of myelopathy has been reported at 50.4 Gy by Linstadt and colleagues (1989). Other potential radiotherapy techniques have been described, such as high-dose radiocordectomy (Cohen et al., 1989; Shirato et al., 1995) and hyperfractionation (Linstadt et al., 1989), but further investigations on its effectiveness are needed.

Conclusions

Favorable NF was associated with improved survival in patients with astrocytic spinal cord glioma. Patients who underwent limited surgery with favorable postoperative NF had promising outcome. Our current treatment policy consists of limited surgery to obtain pathologic diagnosis followed by radiation therapy. Young age, low tumor grade, and favorable NF were found to be associated with improved survival outcome in this retrospective series.

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