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Clinical Study

Spinal cord gangliogliomas: a review of 56 patients

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Summary

There have been only case reports concerning the management of intramedullary spinal cord gangliogliomas. We review our experience of 56 patients with respect to functional status, progression-free survival and long-term outcome. In this retrospective review, 56 patients, 35 males and 21 females ranging in age from 7 months to 25 years (mean, 7.0 y), underwent surgical treatment for intramedullary gangliogliomas located throughout the spinal cord. Forty-six patients had gross total resection as confirmed by postoperative imaging studies, and 10 had radical subtotal resection. Only five patients underwent postoperative irradiation or chemotherapy after surgery at our center and therefore outcome was attributed to surgery alone. There were no operative deaths, and the 5-year actuarial survival rate was 88%. The progression-free survival rate at 5 years was 67%. Neurological function in the surviving patients at recent follow-up evaluation was stable or improved in 72%. Patients have a long survival following radical surgery. These tumors have an indolent course, and radiotherapy appears to be unnecessary.

Gangliogliomas are central nervous system (CNS) neoplasms composed of a mixture of neuronal and glial elements. These tumors were first identified in 1928 by Ewing, but it was not until 1930 that Courville gave a thorough pathological description of gangliogliomas [1]. The glial elements are usually astrocytes and the neoplastic neurons are characteristically large and relatively mature. Characteristic features (hematoxylin and eosin stained sections) for gangliogliomas include: population of large cells which have larger but paler nuclei than astrocytes. These cells represent ganglion cells; neurons that are not typical for perineuronal satellitosis or arranged in normal architecture; the presence of fibrosis or desmoplasia in the background; and features of calcification and large cells [2]. The histopathological diagnosis is sometimes difficult because of sampling: biopsies may not contain the clusters of neurons, astrocytes may resemble neurons, and some neoplastic neurons may be confused as astrocytes. The neoplastic nature of neuronal cells is easily recognized when a large sample is available and when the neurons were grouped in clusters. In addition, an antibody marker for synatophysin (a synaptic vesicle membrane glycoprotein) is a sensitive and specific stain for neoplastic neurons and has allowed for the differentiation from normal neurons [2–4]. Since these original reports, gangliogliomas have been regarded as rare and benign tumors. Although, gangliogliomas have been associated with a benign clinical course, several authors have suggested that these tumors behave in an aggressive fashion [5,6]. The current understanding of the treatment for spinal cord gangliogliomas is derived from studies in which these tumors are located in the cerebral hemispheres [7–14].

Historically, gangliogliomas comprise 1.1% of intramedullary spinal neoplasms [15]. There has been only case reports of spinal cord gangliogliomas in the literature [2,5,9,16–19]. There has been no dedicated report concerning the prognosis and optimal management of these tumor, however there is a recent imaging study from our center [20]. This current study examines these two questions and in particular the effects of radical surgery and adjuvant therapy on the progression-free survival and outcome.

Patients and methods

Between the years 1980 and 1995, 59 patients (retrospectively identified from the files of the

Neuropathology Department) were pathologically diagnosed with spinal cord gangliogliomas at New York University (NYU) Medical Center. The diagnosis was confirmed for all tumor specimens [21]. Three patients were excluded because follow-up information was not available. The remaining 56 patients form the basis of this review. Thirty patients in this study have previously been published in a study concerning CNS gangliogliomas [7].

During the study period, no uniform policy was in place regarding preoperative diagnostic evaluation and postoperative treatment. Since the majority of patients were referred to our center, patients were followed by their primary care physician. All postoperative imaging studies were obtained and reviewed by our office. A detailed neurological history and examination was completed on each patient. The details of adjuvant therapy were obtained by a review of the office charts, and contact with the treating physician. Patient outcome was assessed by a review of the hospital and outpatient charts. If a patient had not been evaluated within the previous 9 months, a telephone interview was conducted with the family or primary physician.

Of the 56 patients, 35 were male and 21 were female (male : female 1.7 : 1). The median age at diagnosis was 6 years (range, 7 months–25 years). Seventy-five percent were younger than 16 years at the age of diagnosis. The age distribution is shown in Figure 1.

The symptoms at presentation varied by the level of the tumor in the spinal canal (Table 1). There were 8 tumors located in the cervicomedullary region, 7 cervical, 21 cervicothoracic, 16 thoracic and 4 conus. The most common preoperative symptom was paraparesis (50%) followed by segmental pain (46%). The medical histories, from onset of symptoms to diagnosis, were generally quite long, with a mean duration of 12.0 months (range, 2 weeks–84 months). The patients with cervical tumors had the shortest mean prodrome (3.4 months) whereas the cervicothoracic location was the longest (14.8 months). There was no correlation between the character or duration of symptoms and the age of the patients. Most of the tumors (53%) spanned 4–8 vertebral segments.

Thirty-two patients (57%) were treated at other institutions prior to referral to NYU Medical Center. The mean time between diagnosis and referral was 38 months. All these patients were referred because of recurrence or progression of symptoms. Of the 32 patients, 4 patients had tumors located in cervicomedullary region, 4 in the cervical region, 13 in cervicothoracic region, 8 in the thoracic region and 3 in the conus. The most frequent 'prior treatment' for these patients was laminectomy and biopsy (50%), and 40% of these patients received adjuvant radiation therapy. Fourteen patients had partial resection, and 43% of

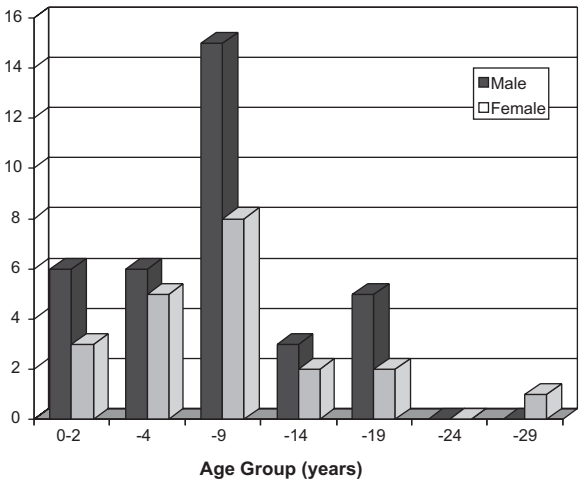

Figure 1. Bar graph showing distribution of age at diagnosis in 56 spinal ganglioglioma patients by sex.

Table 1. Frequency of tumors and preoperative symptoms by spinal level

Spinal level	Cases	Pain	Dermatomal sensory deficit	Radicular motor weakness	Paraparesis/ unable to walk	Bladder dysfunction	Torticollis
Cervicomedullary	8	2	0	4	2	0	2
Cervical	7	6	2	4	2	1	2
Cervicothoracic	21	9	1	10	13	0	2
Thoracic	16	7	1	8	5	2	1
Conus	4	2	1	2	2	1	0

these patients received adjuvant therapy. The radiation parameters and the chemotherapy agents used prior to our treatment was not able to be assessed in the retrospective chart review. Only two patients had gross total resection prior to referral.

Treatment

At our center, all 56 patients underwent surgery by the senior author (FJE). Intraoperative neurophysiological monitoring, both sensory and motor evoked potentials, were used for the procedures. We have previously published our surgical technique [22]. Gross total resection was achieved in 46 patients. The remaining patients underwent radical subtotal resection, defined as removal of at least 75% of the tumor. The extent of tumor removal, defined at time surgery with ultrasound or visually was confirmed by postoperative imaging studies, either CT myelography or magnetic resonance images (MRI). CT myelography was used for only very few early patients. The majority of patients (99%) had MRI as the initial postoperative study. All patients now undergo MRI studies for radiographic assessment.

Adjuvant radiation or chemotherapy was given to eight patients after initial surgery at our institution; one patient had a subtotal resection and seven patients had a gross total resection. Three patients received radiation therapy, 3 chemotherapy and 2 combined therapy. Three of these patients had received radiotherapy prior to referral to our center. These patients received adjuvant therapy because initial diagnosis was intramedullary astrocytoma prior to retrospective review of the histological slides. The choice of adjuvant therapy was based on treatment protocols available at time of initial surgery.

The functional status was assessed in accordance to the previously published scale of McCormick et al. [23]. Grade I, neurologically normal, with a mild focal deficit not significantly affecting the function of the involved limb, mild spasticity or reflex abnormality and normal gait; Grade II, the presence of a sensorimotor deficit affecting the function of the involved limb, mild to moderate gait difficulty, and severe pain or dysesthetic syndrome impairing the patient's quality of life, but with independent function and ambulation; Grade III, more severe neurological deficit, the requirement of a cane or brace for ambulation, or significant bilateral upper extremity impairment, with or without independent function; and Grade IV, a severe neurological deficit, the requirement of a wheelchair or cane or brace due to bilateral upper extremity impairment, and usually without independence of function.

Statistical analysis

For each patient in the study group, a series of clinical and treatment related parameters was recorded. The parameters included the following: (1) age at operation; (2) gender; (3) duration of symptoms prior to diagnosis; (4) tumor location; (5) extent of resection; (6) preoperative functional status; (7) prior treatment at an outside institution and (8) whether chemotherapy or radiation therapy was employed.

Actuarial survival curves were generated using the Kaplan–Meier method with tumor progression and death as the two endpoints [24]. The relationship between each of the aforementioned parameters and overall survival and progression-free survival was examined in a series of univariate analysis performed using Mantel–Cox log-rank to assess the strength of association between the parameters and outcome [25]. All statistical analysis and calculations were performed using JMP software (SAS Institute Inc., Cary, NC).

Results

Long-term outcome

There was no operative mortality (death within 1 month of operation) after radical resection, regardless of the tumor site. Overall, 46 (82%) of the 56 patients were alive at the most recent follow-up evaluation. The mean follow-up period was 7.1 years (range, 1.7–17.3 years). The actuarial survival rate at 5 years was 88% and at 10 years 77% (Figure 2). The mean overall survival for the study group was 85 months. Of the 10 deaths, 9 patients had undergone surgery prior to referral to NYU Medical Center. Previous surgery at an outside institution was the only significant prognostic factor for death in this series ($P < 0.01$). No other parameter tested was significant.

Progression-free survival

Tumors recurred in 17 (30%) of the 56 patients after surgery: three (37%) of 8 in the cervicomedullary

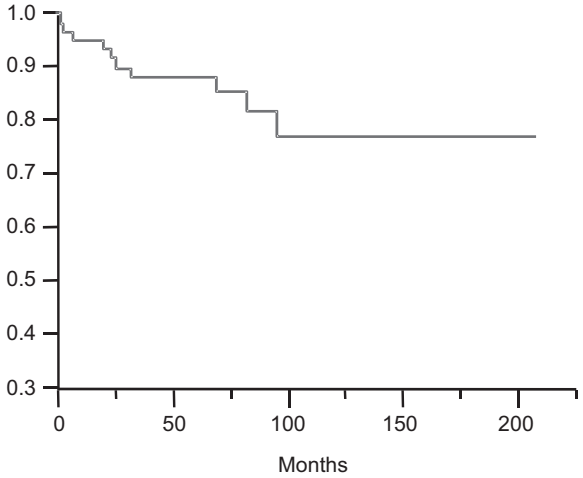

Figure 2. Kaplan–Meier curve demonstrating survival from surgical diagnosis for all 56 patients with spinal cord gangliogliomas. The 5- and 10-year survival rates are 88% and 77%, respectively.

location; one (14%) of 7 in the cervical, five (24%) of 21 in the cervicothoracic, 6 (38%) of 16 in the thoracic and 2 (50%) of 4 in the conus. Of these 17 patients, 13 had a gross total resection and 4 had a subtotal resection. Ten patients (59%) had previous treatment at an outside institution, and four patients received adjuvant radiotherapy. All patients with recurrent tumors presented with progression of symptoms following a period of stable function. The overall actuarial progression-free survival was 67% at 5 years and 58% at 10 years. There was no statistically significant difference in the progression-free survival rate for tumor location or any other parameter.

In the 17 patients with recurrent tumors a second operation was performed. The median time for the second surgery was 27 months. Gross total resection was performed in 13 patients. There was no deaths following the second surgery during the peri-operative period. The functional status of patients undergoing a second surgery did not deteriorate from the preoperative grade. The mean preoperative grade prior to second surgery was 2.5 compared to 2.8 following reoperation. One patient at the time of recurrence had a ganglioglioma whereas at initial surgery the diagnosis was a ganglioneurocytoma. All other patients had the same histology at reoperation as the initial surgery. Only 2 patients received adjuvant therapy following reoperation. The mean follow-up time following the second surgery was 6.5 years.

Table 2. Clinical outcome of patients at last follow-up evaluation. The functional grading is in accordance to the scale McCormick et al. [23]

Spinal level	I	II	III	IV	Dead
Cervicomedullary	1	4	1	1	1
Cervical	2	1	0	1	3
Cervicothoracic	3	5	3	5	5
Thoracic	1	5	6	3	1
Conus	0	2	2	0	0

Follow-up functional status

The pre- and postoperative functional grade as well as the grade at follow-up of all the patients alive was recorded. The postoperative grade was assessed 7–10 days after the operation, and the one at follow-up is the most recent clinical examination. The mean preoperative grade for the study was 2.39. Of the 46 patients alive, 25 (55%) were unchanged, 8 (17%) were improved and 13 (28%) were worse when the preoperative clinical condition was compared to the condition at recent follow-up evaluation. The deterioration in 85% of the patients was by only 1°. The mean postoperative grade at recent follow-up was 2.54. When the functional grade was compared to extent of resection, patients who underwent gross total removal did not have a significantly lower grade. The mean postoperative grade in the gross total resections was 2.5, as compared to 2.6 for the subtotal resections. The outcome of the patients in relation to the tumor location is summarized in Table 2.

Discussion

This review provides new information regarding patient characteristics, prognostic factors and treatment results for patients with gangliogliomas of the spinal cord. In our series, which represents a referral center, such tumors most commonly occurred in children, had a 1.7 : 1 male sex predilection, occurred predominantly in the cervical and thoracic spinal cord, usually involved 4–8 vertebral segments, and most often produced signs and symptoms consisting of pain, radiculopathy and sensory or motor deficits.

Long-term outcome

There have been only anecdotal reports which suggest that patients with spinal cord gangliogliomas

experience long-term survival [9,17–19,26]. There is no study which investigates intramedullary spinal cord gangliogliomas. Henry et al. [27], reported a mean survival of 7 years for 50 patients with gangliogliomas distributed throughout the neuraxis. Recently, Lang et al. [7] reported a 10-year actuarial survival rate of 84% for these CNS tumors, with a 89% 5-year actuarial survival for the spinal cord location [7]. Park et al. [26] reported on a large series of five cases of intramedullary tumors. In this series there was no evidence of tumor recurrence in a relatively short follow-up period of 4.1 years. Our study supports the indolent course as the 5 year survival rate was 88%. These results confirm that patients with gangliogliomas tend to survive for long periods after radical surgery. The survival of these patients is better than that reported for intramedullary astrocytomas [28–30]. The only parameter found to be significant for survival was previous surgery. Patients who had their initial surgery at NYU survived longer than those that had previous surgery elsewhere. Since our institution serves as a tertiary referral center, spinal gangliogliomas which have not recurred are not seen. Although tumor location was not statistically significant, the cervical or thoracic region accounted for 9 of 10 deaths. The cause of death in 70% of patients was repeated pulmonary infections (aspiration or bacterial pneumonia) which progressed to sepsis.

Progression-free survival

There are fewer reports on the frequency of recurrence for intramedullary gangliogliomas. Lang et al. [7] found a clinical recurrence rate of 33% in their series of CNS gangliogliomas. This was confirmed at time of reoperation. Of interest, linear regression analysis demonstrated the spinal cord location to have a 3.5-fold increase relative risk of recurrence as compared to gangliogliomas in the cerebral hemispheres [7]. In their series recurrence occurred in 14 (47%) of 30 spinal cord gangliogliomas [7]. In our series, 30% of patients had a clinical recurrence. No parameter examined could be correlated with regrowth. In these 17 patients, 13 had a presumed gross total resection. Lang et al. [7] stated the cerebral recurrences occurred in the subtotally resected supratentorial tumors. The progression-free survival in our study (65%) was higher than the event-free survival when compared to the previous study (33%) [7]. Improved postoperative imaging studies and initial surgery at our institution may explain the better survival in this study. In addition, Lang et al. [7] investigated the event-free survival rather than progression-free survival. We concur with their observations that microscopic tumor probably persists after gross total resection of intramedullary gangliogliomas and provides the source for regrowth. Early in the study population, the extent of tumor resection was determined at time of surgery and with postoperative CT myelography. These methods were not as sensitive as MRI to determine extent of tumor resection. However, all patients were followed with routine semi-annual or annual MRI scans.

Functional outcome

A comparison of the pre- and postoperative function status at recent follow-up evaluation shows that 55% were unchanged, 17% were improved, and 28% were worse, 85% of those by 1 grade. The functional outcome of these patients does not differ from other intramedullary tumors as reported in previous studies [28,31]. The functional status between gross total resection *versus* subtotal resection was not statistically significant. In addition, the functional outcome grade was not much higher in the patients who had recurrent tumors and second surgery as compared to patients without recurrence.

Patients with a worse preoperative functional grade are at risk of developing a complete loss of function and the preoperative grade of those who improved was less than 3. Thus, we too recommend early surgical intervention for these intramedullary tumors [31,32].

The extent of tumor resection, gross total or subtotal, did not influence the functional prognosis. Whether the distinction between extent of tumor removal attains prognostic significance will be seen after a more extended follow-up of a larger number of patients. In addition radical resections were performed, subtotal $>75\%$ and gross total $>99\%$ resection; no biopsies were performed. Thus, an analysis would need to include the three categories of resection (biopsy, subtotal and gross total) to address this further.

Management of spinal cord gangliogliomas

Surgical resection has been advocated as the treatment for patients with gangliogliomas. These beliefs are based on retrospective analysis of gangliogliomas in the cerebral hemisphere. One such report by Silver et al. [12], described 16 patients with cerebral gangliogliomas, of whom 8 underwent gross total resection,

and 8 subtotal resection with adjuvant therapy. All 8 who underwent gross total resection are alive as compared to 4 of the subtotal resection group. They concluded complete resection led to better survival. Lang et al. [7], described 58 patients with gangliogliomas resected throughout the neuraxis. Their recommendations were the maximum feasible surgery should be performed followed by a period of close observation without adjuvant irradiation. For recurrent tumor, a second operation should be considered but radiation therapy may also be an option. Recently, Rumana et al. [33], reported malignant degeneration in 4 of 14 patients who received adjuvant radiotherapy following resection for benign supratentorial gangliogliomas.

There are few studies concerning the management of spinal cord gangliogliomas. Garrido et al. [17] treated three patients with spinal tumors. One patient underwent gross total resection was alive at 2 year follow-up; one patient had subtotal resection and radiation therapy was alive at 5 year follow-up, and 1 patient underwent biopsy and radiation therapy was quadriplegic but alive at 3 years. The authors concluded that surgical resection was more effective than biopsy and irradiation. Radiotherapy did not prolong the time to recurrence or increase the length of survival. Park et al. [26] also recommend gross total removal. In contrast, certain authors believe that radiotherapy results in a modest increase in survival for astrocytomas [28,29].

In our study, radical resection was achieved in 56 patients, and five received postoperative radiotherapy. Therefore, the overall survival, low recurrence rate and good functional outcome seen is best attributed to the radical surgical extirpation of these tumors. Patients with recurrent tumor had a second surgical procedure without increased morbidity.

Conclusion

Our experience demonstrates that intramedullary gangliogliomas are biologically indolent neoplasms. Radical extirpation is associated with minimal morbidity and an excellent long-term prognosis. After radical resection is achieved, we recommend that patients be followed closely. We follow these patients every 6 months for the first 2 years and then annually thereafter. Only patients who demonstrate a clinical deterioration undergo an urgent MRI scan. If a recurrence occurs a second surgical procedure can be performed and adjuvant therapy should be considered at that time.

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