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Molecular and clinical prognostic factors for favorable outcome following surgical resection of adult intramedullary spinal cord astrocytomas

Roy Xiao[a,b], Kalil G. Abdullah[c], Jacob A. Miller[a,b], Daniel Lubelski[a,b,d], Michael P. Steinmetz[f], John H. Shin[g], Ajit A. Krishnaney[a,b,e], Thomas E. Mroz[a,b,e], Edward C. Benzel[a,b,e,*]

[a] Cleveland Clinic Center for Spine Health, Cleveland Clinic, Cleveland, OH, USA
[b] Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA
[c] Department of Neurosurgery, Hospital of the University of Pennsylvania, Philadelphia, PA, USA
[d] Department of Neurosurgery, Johns Hopkins University, Baltimore, MD, USA
[e] Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA
[f] Department of Neurosurgery, Case Western Reserve University School of Medicine, MetroHealth Medical Center, Cleveland, OH, USA
[g] Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Objective: Intramedullary spinal cord astrocytomas are uncommon but important entities. Aggressive surgical resection is believed to be critical to prevent subsequent neurological deterioration; however, the prognostic significance of numerous patient and molecular variables remains unclear. We sought to investigate the clinical and molecular factors associated with outcomes following surgical resection of adult spinal cord astrocytomas.

Methods: A consecutive retrospective chart review of all patients who underwent intramedullary spinal cord astrocytoma resection at a single tertiary-care institution between January 1996 and December 2011 was conducted. Molecular data collected included p53 mutation status, proliferative activity (Ki-67), 1p/19q chromosome loss, and EGFR amplification. Multivariable logistic and Cox proportional hazards regression were used to identify variable associated with postoperative outcomes.

Results: Among 13 patients undergoing surgical resection followed for a median of 54 months, 54% experienced improvement in neurological status, while 15% remained unchanged and 31% deteriorated. Following resection, the 5-year local control (LC), progression-free survival (PFS), and overall survival (OS) rates were 83%, 63%, and 83%. Median PFS time was found to be 5.6 years. Multivariable regression revealed limited characteristics associated with postoperative outcomes, though no molecular characteristics were found to be prognostic. Older age at surgery predicted decreased probability of PFS (HR 0.91, 95% CI 0.81–0.99, $p = 0.03$) and trended towards predicting lack of neurological improvement (OR 0.94, 95% CI 0.83–1.02, $p = 0.21$) and decreased OS (HR 0.93, 95% CI 0.81, 1.03, $p = 0.15$). Preoperative motor symptoms (OR 0.12, 95% CI <0.01–1.91, $p = 0.14$) and adjuvant chemotherapy (OR 0.07, 95% CI <0.01–1.82, $p = 0.12$) also trended towards predicting lack of neurological improvement.

Conclusion: Age was the only patient variable found to have a statistically significant association with profession-free survival and no other factors were significantly associated with postoperative outcomes. These findings were limited by a relatively small sample size; thus, future studies with increased power investigating the prognostic effects of molecular characteristics could provide further clarity in identifying patients most likely to benefit from surgical resection.

1. Introduction

Intramedullary spinal cord tumors (IMSCT) account for 2–4% of central nervous system neoplasms and 20–25% of spinal cord tumors [1–3]. Among these, spinal cord astrocytomas are the second most common IMSCT in adults, comprising 30–35% of

* Corresponding author at: Neurological Institute, Cleveland Clinic Center for Spine Health, Departments of Neurological Surgery, The Cleveland Clinic, 9500 Euclid Avenue, S-40 Cleveland, OH 44195, USA.
E-mail addresses: xiaor@ccf.org (R. Xiao), benzele@ccf.org (E.C. Benzel).

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such tumors [4,5]. While aggressive tumor resection is believed to be critical to prevent permanent neurological deficits [6–8], numerous studies have observed neurological deterioration following surgery, as well as significant long-term morbidity [9–14]. Since greater extent of resection and gross total resection (GTR) have been associated with superior progression-free survival (PFS) for subtypes like ependymomas and hemangioblastomas, maximal safe tumor resection in conjunction with radiotherapy and chemotherapy remain the mainstays of optimal management [8]. However, no such correlation between GTR and PFS has been established for astrocytomas [14,15]. At present, the only established factor affecting prognosis is tumor grade [8].

Several genetic and molecular variables have been associated with the development of astrocytomas. In particular, p53 mutation, proliferative activity (Ki-67), 1p/19q chromosome loss, and EGFR amplification have all been implicated in astrocytoma development [5,16]. While none of these factors have been associated with clinical outcomes following tumor resection, similar molecular information such as tumor histology has been shown to predict neurological outcomes and PFS following the resection of several other IMSCT subtypes [10,16–20]. Thus, we sought to examine the role of molecular and clinical characteristics in predicting the postoperative outcomes of astrocytoma resection. Herein, we present an analysis of 16 years of institutional experience with adult patients who underwent surgical resection of intramedullary spinal cord astrocytomas.

2. Materials and methods

2.1. Study sample

A consecutive retrospective chart review of all patients who underwent intramedullary spinal cord astrocytoma resection at a single tertiary-care institution between January 1996 and December 2011 was conducted. Patients were excluded if they presented after prior resection at another institution, were under the age of 18 at time of surgery, had metastatic disease or von Hippel-Lindau disease, or underwent biopsy alone.

2.1.1. Data collection

Clinical, operative, pathologic, and radiologic reports were reviewed for each patient. To ascertain neurological status, the Modified McCormick Scale (MMS), a simplified ordinal scale of functional status, was applied both preoperatively and over follow-up [12,21]. This scale ranges from intact neurologic status (I) to paraplegia or quadriplegia (V). Preoperative status was further characterized by the presence or absence of motor, sensory, and bladder or bowel dysfunction, previous radiation therapy or chemotherapy, and tumor location.

Perioperative data collected from the electronic medical record included number of operative spinal levels, presence or absence of a plane of dissection (POD), and achievement of GTR. Tumors were evaluated using the WHO grading system, and numerous molecular statuses were ascertained, such as p53 immunohistochemistry status, Ki-67 index, 1p/19q chromosomal status, and epidermal growth factor receptor (EGFR) status. Postoperative data collected included complications such as surgical site infection (SSI) and cerebrospinal fluid (CSF) leak, length of hospital stay, discharge disposition, change in neurological status, local control (LC), progression-free survival (PFS), overall survival (OS). Adjuvant therapies such as radiation or chemotherapy were recorded as well.

2.1.2. Statistical analyses

All collected data were analyzed using the JMP Pro 10 statistical software package (SAS Institute Inc., Carey, North Carolina 2012) [22]. Continuous data were expressed as a median with interquartile range, and categorical data were presented as counts with corresponding percentages. Kaplan-Meier curves were produced to present LC, PFS, and OS following resection. Multivariable logistic and Cox proportional hazards regression were used to investigate the association between patient and operative characteristics, such as patient age and GTR, and postoperative outcomes, such as change in neurological status and PFS; $p < 0.05$ was considered statistically significant.

Table 1
Patient demographics and disease characteristics.

Characteristic	Statistic
N	13
Age (years)	41 [30–57]
Male	8 (62)
Tumor Location	
Cervical	5 (38)
Cervicothoracic	1 (8)
Thoracic	6 (46)
Conus	1 (8)
Previous Radiation Therapy	1 (8)
Previous Chemotherapy	0 (0)
Presenting Symptoms	
Sensory Change	11 (85)
Motor Weakness	6 (46)
Bladder or Bowel Dysfunction	4 (31)
Duration of Symptoms (months)	36 [8–49]
Presenting Modified McCormick Scale	2 [1–3]
Incidentally Discovered	1 (8)

Values are presented as median [interquartile range] or number (%). Subtotals may exceed 100% if patient had multiple presenting symptoms, etc. N, Number.

3. Results

3.1. Clinical and molecular characteristics

Over the 16-year enrollment period, 13 patients with intramedullary astrocytoma were included. Median age was 41 years, and 62% of patients were male (Table 1). Cervical (38%) and thoracic (46%) tumor locations were most common, though the cervicothoracic and conus locations were each involved as well. One patient (8%) underwent prior radiation therapy, while no patients received preoperative chemotherapy. Sensory change was the most common presenting symptom (85%), while motor weakness (46%) and bladder/bowel dysfunction (31%) were common as well, with frequent overlapping of symptoms. The median duration of these symptoms prior to surgery was 36 months. The median preoperative MMS value was 2, while only one astrocytoma (8%) was incidentally discovered.

The median number of vertebral levels operated upon was two (Table 2). POD was possible in 31% of patients, while GTR was achieved in 23% of patients. Postoperative SSI was the most common complication (23%), followed by clinical deterioration (15%) and CSF leak (15%). The median length of hospital stay was 5 days, with most patients discharged home (62%) over rehabilitation (38%).

When using the WHO grading system, 1 patient (8%) was grade I, 9 patients (69%) were grade II, 2 patients (15%) were grade III, and 1 (8%) was grade IV. p53 IHC status was determined to be less than 5% in 46% of patients, 50% in 8% of patients, and 90% in 8% of patients; however, this was not performed in 38% of cases. Ki-67 index was less than 2% in 46% of patients and 10–25% in 23% of patients; again, this was not ascertained in 31% of cases. 1p/19q chromosomal status was intact/intact in 62% of patients and intact/loss in 8% of patients; similarly, 31% of cases did not determine this status. Finally, EGFR status was found to not be amplified in all cases