

Surgical outcomes of pediatric spinal cord astrocytomas: systematic review and meta-analysis

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OBJECTIVE Pediatric spinal astrocytomas are rare spinal lesions that pose unique management challenges. Therapeutic options include gross-total resection (GTR), subtotal resection (STR), and adjuvant chemotherapy or radiation therapy. With no randomized controlled trials, the optimal management approach for children with spinal astrocytomas remains unclear. The aim of this study was to conduct a systematic review and meta-analysis on pediatric spinal astrocytomas.

METHODS The authors performed a systematic review of the PubMed/MEDLINE electronic database to investigate the impact of histological grade and extent of resection on overall survival among patients with spinal cord astrocytomas. They retained publications in which the majority of reported cases included astrocytoma histology.

RESULTS Twenty-nine previously published studies met the eligibility criteria, totaling 578 patients with spinal cord astrocytomas. The spinal level of intramedullary spinal cord tumors was predominantly cervical (53.8%), followed by thoracic (40.8%). Overall, resection was more common than biopsy, and GTR was slightly more commonly achieved than STR (39.7% vs 37.0%). The reported rates of GTR and STR rose markedly from 1984 to 2015. Patients with high-grade astrocytomas had markedly worse 5-year overall survival than patients with low-grade tumors. Patients receiving GTR may have better 5-year overall survival than those receiving STR.

CONCLUSIONS The authors describe trends in the management of pediatric spinal cord astrocytomas and suggest a benefit of GTR over STR for 5-year overall survival.

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KEYWORDS extent of resection; gross-total resection; intramedullary spinal cord tumor; astrocytoma; spine

INTRAMEDULLARY spinal cord tumors (IMSCTs) are rare lesions, with 100–200 new cases reported annually within the United States.¹⁷ The low incidence of these tumors has limited the development of evidence-based management strategies.^{5,19} Astrocytoma is the most common pediatric IMSCT and thus is the focus of this paper.^{1,15,16,23} Children with spinal cord astrocytoma often present several months after the onset of symptoms,⁸ with the degree of preoperative neurological function at diagnosis correlating with worse postoperative outcomes.^{6,7,21,}

^{27,35} At clinical presentation, the most commonly reported symptoms are pain, motor deficits, frequent falls, sensory symptoms, and sphincter dysfunction.^{1,8,27,28}

Surgical management of spinal cord astrocytomas can vary from biopsy to attempted gross-total resection (GTR). The extent of resection is influenced by age, tumor size and location, degree of dissemination, patient preference, and quality of life. In contrast to spinal ependymomas, astrocytomas often lack a clear surgical plane with which to attempt GTR. Use of adjuvant radio- or chemotherapy var-

ABBREVIATIONS GBM = glioblastoma; GTR = gross-total resection; IMSCT = intramedullary spinal cord tumor; OS = overall survival; SEER = Surveillance, Epidemiology, and End Results; STR = subtotal resection.

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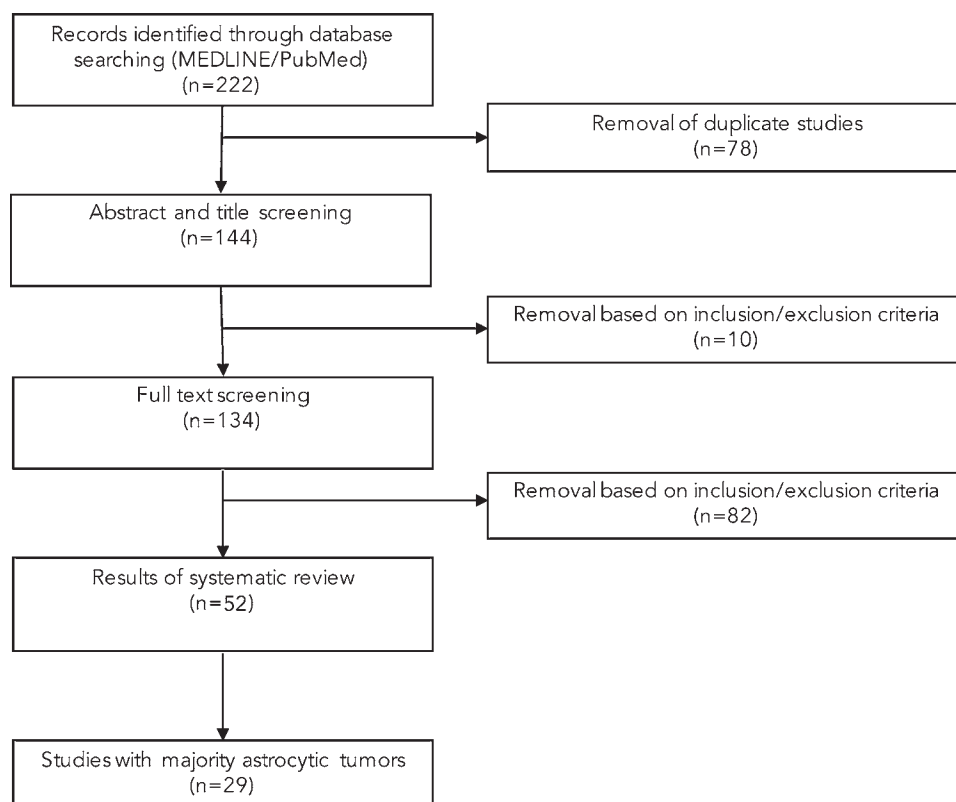


FIG. 1. PRISMA diagram for systematic review.

ies by institution.⁵ While there has been no definitive study demonstrating improved survival outcomes with more aggressive extent of resection in the management of pediatric spinal cord astrocytomas, a recent population-level study of the Surveillance, Epidemiology, and End Results (SEER) database reported a survival benefit for both subtotal resection (STR) and GTR in pediatric patients with spinal cord astrocytomas.²⁴

In the current study, we systematically reviewed the literature on pediatric spinal cord astrocytomas. We describe management trends and synthesize data on the impact of histological grade and extent of resection on overall survival (OS).

Methods

Search Strategy and Study Selection

The present study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Fig. 1). The PubMed/MEDLINE electronic database and bibliographies of relevant articles were systematically searched for English-language articles with no timeframe restrictions through June 2016. The following terms in various combinations were used: spine, spinal, intramedullary, tumor, astrocytoma, glioma, glioblastoma, child, children, and pediatric. Three authors independently performed the literature searches. Discrepancies among reviewers were resolved through discussion.

Studies were included if the majority of patients in the

study had a confirmed diagnosis of pediatric spinal cord astrocytomas, received operative management, and belonged to the pediatric population. Exclusion criteria included review articles, case reports, fewer than 3 patients meeting inclusion criteria, studies in which pediatric and adult natural history and outcome variables could not be distinguished, and studies in which intramedullary location of the tumor could not be confirmed in the report.

Data Extraction

From the 29 published studies, we extracted the study type, sample size, patient demographics, extent of resection, adjuvant therapy, and outcome measures. We collected data on the following outcomes: OS and recurrence rate. These data were either directly taken from the studies when reported or calculated from raw data published in the paper.

Data Synthesis

Using data from studies that enabled extraction of data on astrocytomas only, we evaluated survival outcomes.^{1,2,5,7,9–15,17,18,21,22,25–27,29–34,36,37,39–41} We extracted individual patient data to calculate the 5-year OS stratified by histological grade and extent of resection using the Kaplan-Meier estimator. OS and the 95% CI were plotted for each study using forest plots. Heterogeneity among studies was assessed using the Q-test. The I^2 statistic, which is the percentage total variation, was reported, with $I^2 > 50\%$ used

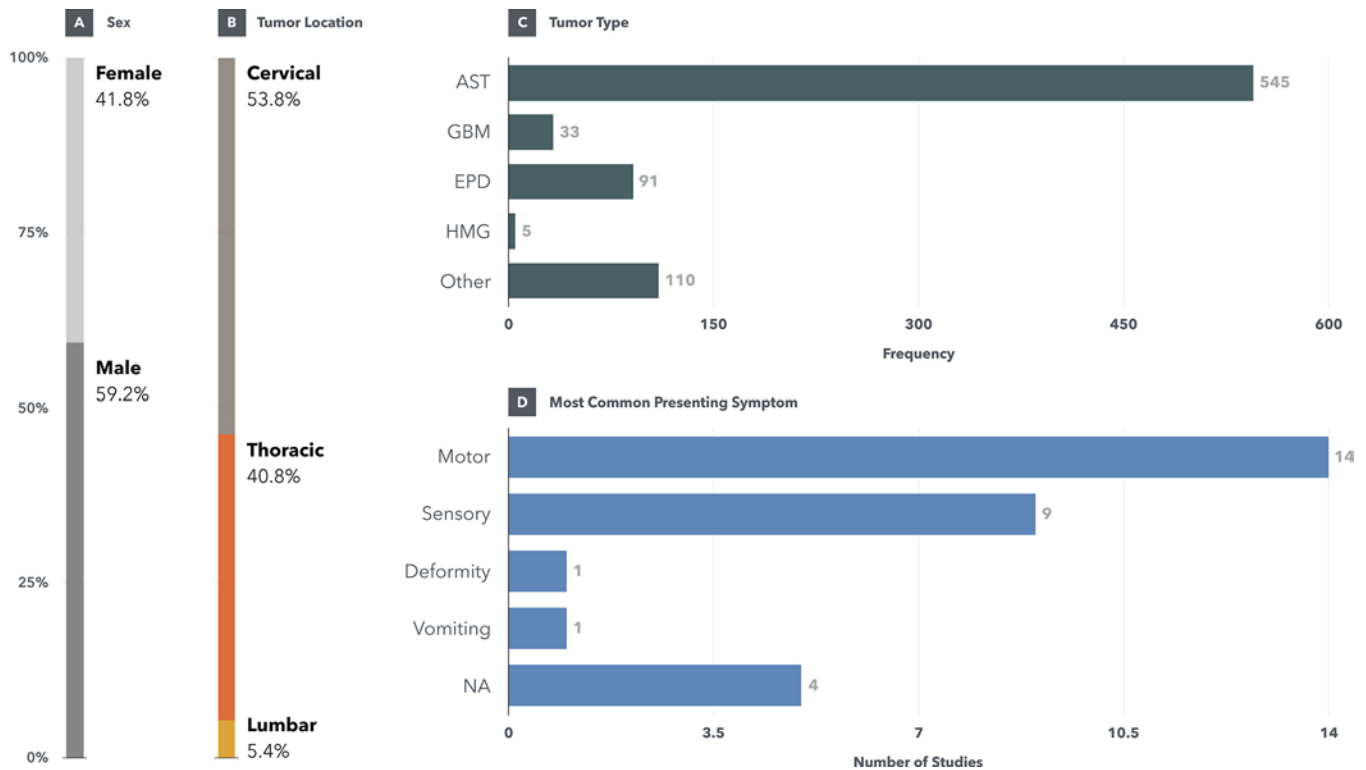


FIG. 2. Pediatric spinal astrocytoma demographics with regard to sex (A), tumor location (B), tumor histology (C), and presenting symptoms (D). Astrocytoma (AST) includes grade I–III astrocytomas. GBMs are reported separately, as many studies reported findings for spinal GBM distinct from other spinal astrocytomas. EPD = ependymoma; HMG = hemangioma; NA = not available. Figure is available in color online only.

as the threshold for significant study heterogeneity. As hazard ratios were not computed, bias was not assessed.

Statistical Analysis

Descriptive statistics are presented as mean and standard deviation or median and interquartile range. All statistical analyses were performed using the *R* statistical computing language.

Results

Results of Systematic Review

Eligibility criteria were met by 29 previously published studies (Fig. 1), totaling 578 patients with spinal astrocytomas. The median cohort size of the studies was 20 (IQR 10–29), with the smallest and largest studies enrolling 3 and 164 patients, respectively. The overall quality of eligible studies was found to be either low (36%) or very low (64%), utilizing the GRADE (Grade of Recommendations Assessment, Development and Evaluation) criteria.³

Demographics of Patients With Pediatric Spinal Cord Astrocytomas

The mean age at diagnosis in our study was 8.6 years (SD 2.2), while the mean age at surgery was 10.1 years (SD 2.6). Males were represented more than females, with a male-to-female ratio of 1.45:1 (Fig. 2A). The spinal level

of IMSCtS was predominantly cervical (53.8%), followed by thoracic (40.8%; Fig. 2B). While this report focused on spinal astrocytomas, several of the studies in the systematic review also included other pediatric IMSCtS. Non-glioblastoma (GBM) astrocytomas (545 patients, 69.5% of all tumors) represented most tumors, followed by other tumors (e.g., ganglioglioma) (110, 14.0%), ependymoma (91, 11.6%), GBM (33, 4.2%), and hemangioblastoma (5, 0.6%; Fig. 2C). The most common presenting symptoms were motor (14, 56% of studies) and sensory (9, 36% of studies) deficits. Other presenting symptoms included deformity (1, 4%) and vomiting (1, 4%; Fig. 2D). Four studies (16%) did not report presenting symptoms.

Management Trends of Patients With Pediatric Spinal Cord Astrocytomas

Overall, resection was more often performed than biopsy alone (76.7% vs 23.3%), and more patients received GTR than STR (39.7% vs 37.0%). To better understand current trends in management of spinal astrocytomas, we evaluated the rates of different treatment modalities (GTR, STR, adjuvant radiotherapy, and adjuvant chemotherapy) from 1984 to 2015 (Fig. 3). Over this time, the average rate of reported GTR rose from less than 25% (prior to 1990) to roughly 50% (in 2016), with rates of STR rising in parallel. We further observed a marked increase in rates of adjuvant chemotherapy and a decrease in the percentage of patients receiving adjuvant radiotherapy. We further ob-

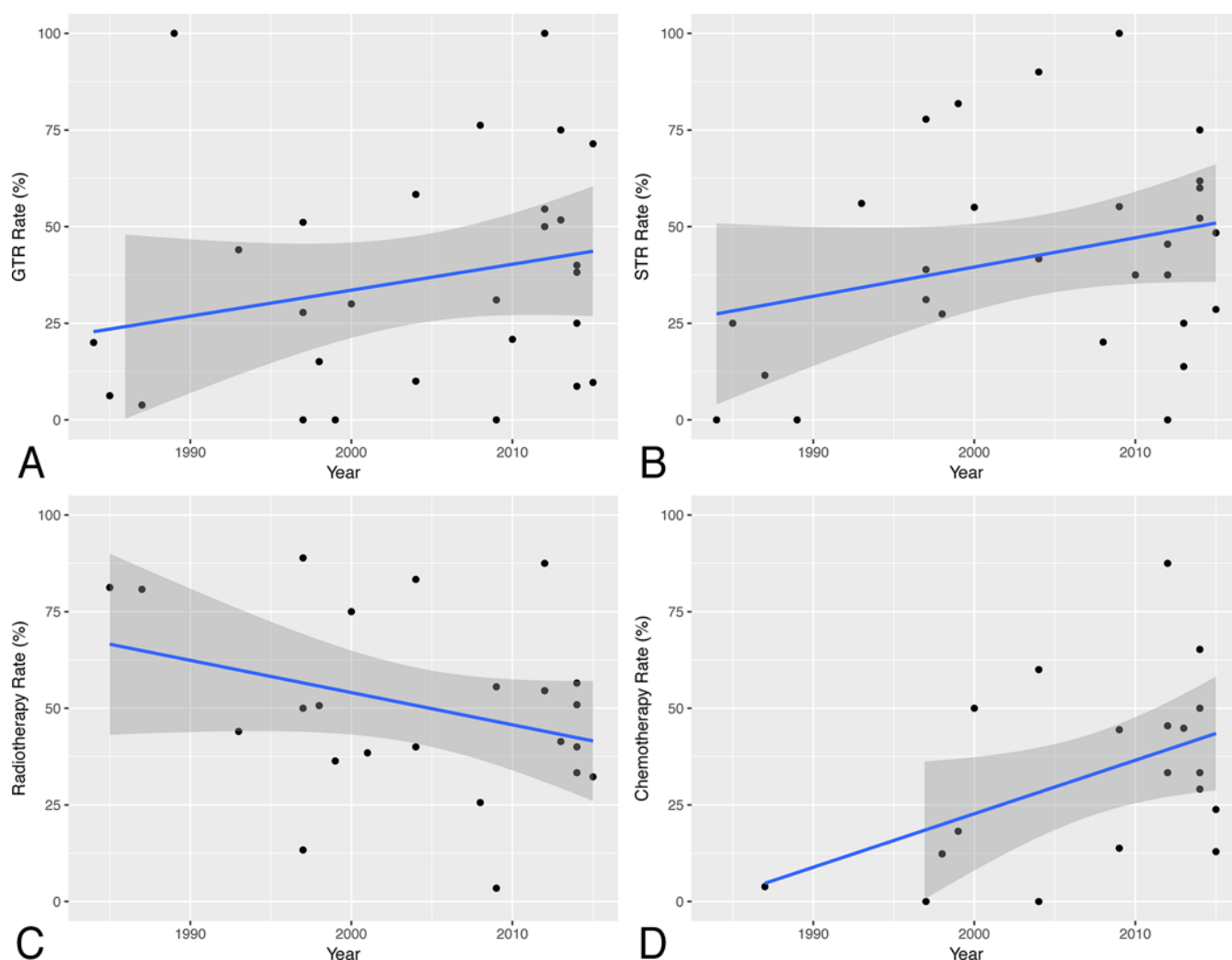


FIG. 3. Trends in the management of patients with pediatric spinal astrocytomas, 1984–2015, for GTR (A), STR (B), radiotherapy (C), and chemotherapy (D). Figure is available in color online only.

served an overall decrease in reported rates of recurrence over time (Fig. 4).

Influence of Extent of Resection and Histological Grade on 5-Year OS

To investigate the influence of histological grade and extent of resection on survival among patients with pediatric spinal astrocytoma, we selected studies that reported either individual patient data or composite outcomes in series that included astrocytomas only. Four studies reported survival outcomes for patients receiving GTR, with 5-year OS ranging from 0.9 to 1.0 (Fig. 5A). Among the 5 studies that provided data for patients receiving STR, 5-year OS ranged from 0.5 to 1.0 (Fig. 5B). The study with the largest sample size, Bouffet et al. ($n = 53$), reported a 5-year OS of 0.9.⁷

Seven studies reported outcomes for patients with low-grade astrocytomas, with 5-year OS ranging from 0.8 to 1.0 (Fig. 5C). Among the 5 studies reporting outcomes for high-grade astrocytomas, 5-year OS ranged from 0.0 to

0.71 (Fig. 5D), with the largest series reporting a 5-year OS of 0.33.

Discussion

In this study, we conducted a systematic review of the literature to better understand the demographics and management trends of patients with spinal cord astrocytoma. We collected data on 578 patients with pediatric spinal astrocytomas from a total of 29 published reports and sought to evaluate the impact of histological grade and extent of resection on overall survival, efficacy of adjuvant treatments and resection on recurrence, and mortality within the pediatric age group. Analysis of all studies meeting inclusion criteria demonstrated a preponderance of retrospective single-institution studies and an absence of prospective studies or randomized trials. These findings are consistent with prior literature reviews and reflect the rarity of spinal astrocytomas and the difficulty in designing neurosurgical randomized trials.⁴ In an effort to overcome these challenges, several authors have called for

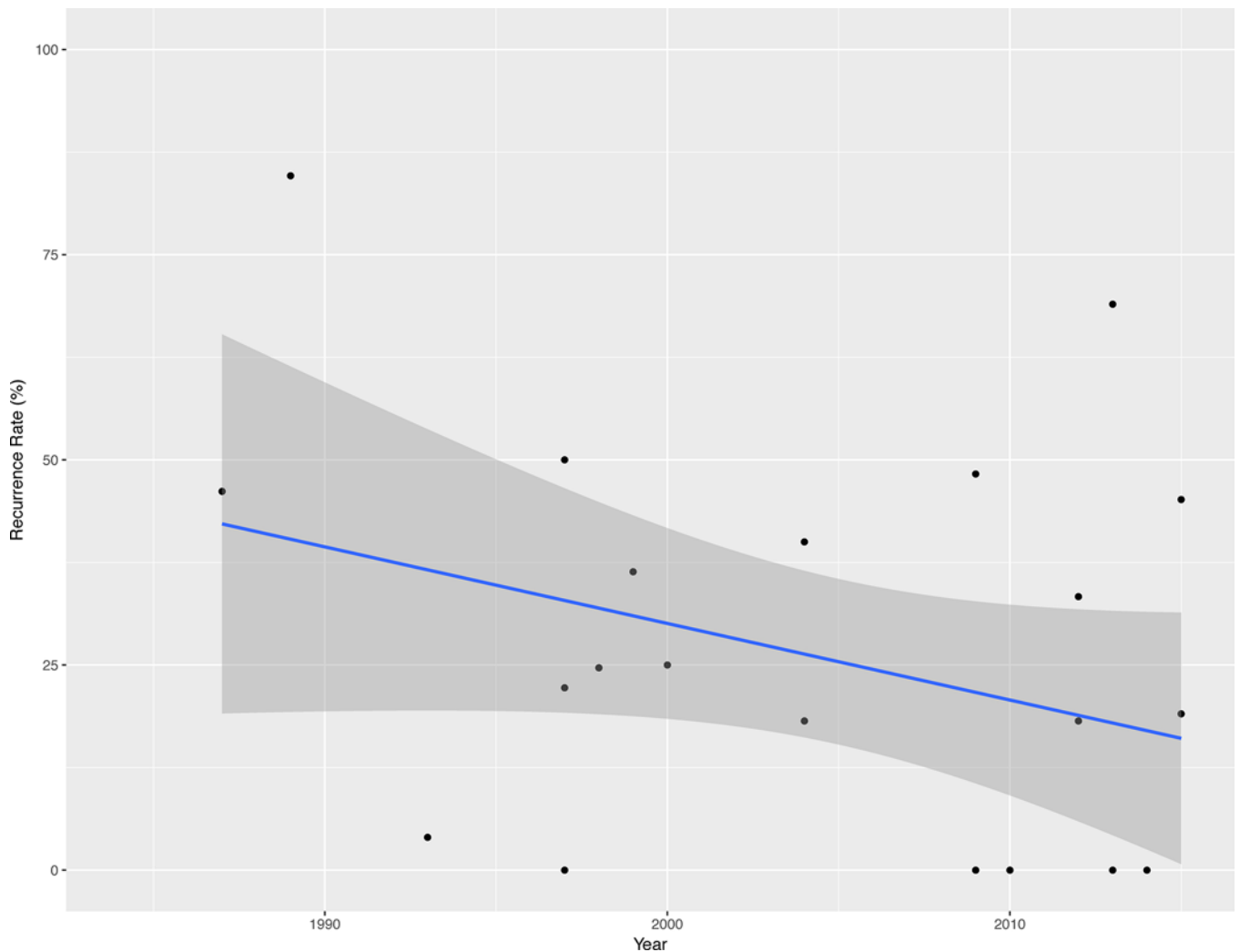


FIG. 4. Decrease in overall recurrence rates, 1984–2016. Figure is available in color online only.

multiinstitutional studies.^{20,42} However, with an incidence rate of 100–200 new cases per year in the United States, we agree with Scheinmann et al. that an international registry of patient data may be the best means to evaluate, refine, and expand on existing treatment approaches in the literature.³⁶

We found a male preponderance among the patients in this review, which appears to be consistent with previous reports.^{15,38} We also found that among individuals studied, patients first presented to care near the middle of childhood (mean 8.6 years) and underwent surgery only slightly later (mean 10.1 years old). The vast majority of tumors were located in the cervical or thoracic spine, and the most common presenting symptoms were motor. Consistent with previous reports^{5,7} and a recent population-level study,²⁴ we found a marked impact of histological grade on survival outcomes. We also observed that patients receiving GTR might have improved survival outcomes, compared with patients receiving STR. However, this finding must be interpreted with caution, as we were unable to control for tumor grade in this analysis. Low-grade astrocytomas, which have definitively better survival outcomes,

may be more amenable to GTR. An important companion finding to our results is that both GTR and STR appear to be protective for survival when histological grade was accounted for in a recent SEER study of pediatric spinal astrocytomas.²⁴

This study is not without limitations. All studies we identified were retrospective and thus may be biased with regard to patient selection and recall. Moreover, hazard ratios for OS and progression-free survival were largely unavailable for synthesis. Thus, we were limited in our ability to explicitly assess bias. At the review level, a potential limitation is incomplete retrieval of studies, a limitation of all systematic reviews. In this review of spinal astrocytomas, a particular concern is the overall low quality of the constituent studies. The rare nature of these lesions has, to date, precluded studies that are prospective and/or randomized, directly limiting the GRADE scores of these studies.

Conclusions

Overall, our results appear to be consistent with literature advocating that more aggressive resection may be

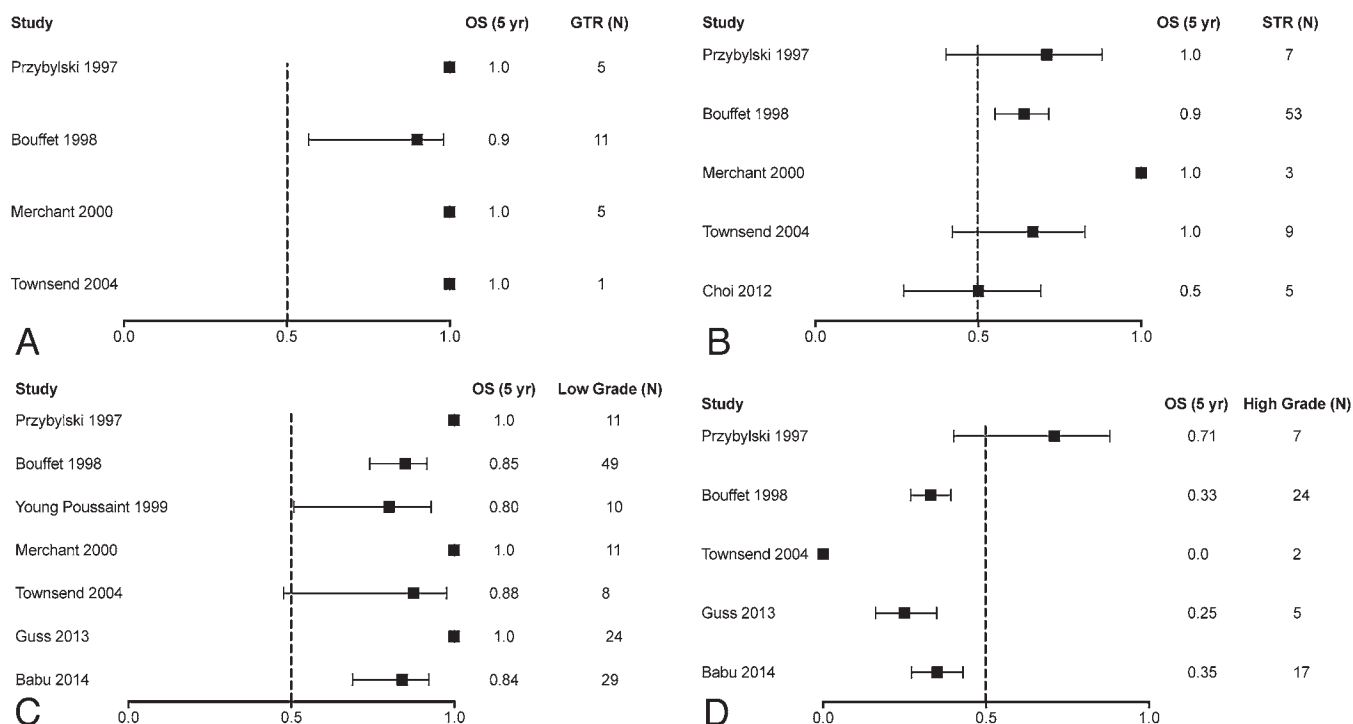


FIG. 5. Forest plots of 5-year OS stratified by GTR (A), STR (B), low-grade histology (C), and high-grade histology (D).

beneficial in the management of pediatric spinal astrocytoma. Given the rare nature of these lesions, synthesis across studies enables analysis of a larger cohort, an advantage of our study. Further studies, possibly through collaborative patient registries, are required to elucidate the optimal treatment strategy for children with spinal astrocytoma.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Grant, Azad, Pendharkar, Veeravagu, Cheshier. Acquisition of data: Azad, Pan, Huang, Li, Esparza, Mehta, Connolly, Campen, Cheshier, Edwards, Fisher. Analysis and interpretation of data: Grant, Azad, Pendharkar, Pan, Huang, Li, Esparza, Mehta, Connolly, Campen, Cheshier, Edwards, Fisher. Drafting the article: Grant, Azad, Pendharkar, Pan, Huang, Li, Esparza, Mehta, Connolly, Veeravagu, Campen, Fisher. Critically revising the article: Azad, Pendharkar, Veeravagu, Campen, Cheshier, Edwards, Fisher. Reviewed submitted version of manuscript: Grant, Azad, Veeravagu, Campen, Edwards. Approved the final version of the manuscript on behalf of all authors: Azad. Statistical analysis: Azad, Huang. Administrative/technical/material support: Grant.

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