

Clinical features and surgical outcomes of intracranial and spinal cord subependymomas

Jordina Rincon-Torroella, MD,¹ Maureen Rakovec, BA,¹ Adham M. Khalafallah, MD,¹ Ann Liu, MD,¹ Anya Bettegowda,¹ Carmen Kut, MD, PhD,² Fausto J. Rodriguez, MD,³ Jon Weingart, MD,¹ Mark Luciano, MD, PhD,¹ Alessandro Olivi, MD,¹ George I. Jallo, MD,⁴ Henry Brem, MD,¹ Debraj Mukherjee, MD, MPH,^{1,5} Michael Lim, MD, PhD,¹ and Chetan Bettegowda, MD, PhD¹

¹Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, Maryland; ²Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; ³Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland; ⁴Department of Neurosurgery, Johns Hopkins Medicine, Institute for Brain Protection Sciences, Johns Hopkins All Children's Hospital, St. Petersburg, Florida; and ⁵Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland

OBJECTIVE Subependymomas are low-grade ependymal tumors whose clinical characteristics, radiographic features, and postsurgical outcomes are incompletely characterized due to their rarity. The authors present an institutional case series and a systematic literature review to achieve a better understanding of subependymomas.

METHODS Adult patients with histologically confirmed subependymoma or mixed subependymoma-ependymoma surgically treated at a tertiary hospital between 1992 and 2020 were identified. A systematic literature review of the PubMed, Embase, Web of Science, and Google Scholar databases from inception until December 4, 2020, was conducted according to PRISMA guidelines. Data extracted from both groups included demographics, radiographic features, tumor characteristics, management, and follow-up variables.

RESULTS Forty-eight unique patients with subependymoma were identified by chart review; of these patients, 8 (16.7%) had mixed subependymoma-ependymoma tumors. The median age at diagnosis was 49 years (IQR 19.8 years), and 26 patients (54.2%) were male. Forty-two patients (87.5%) had intracranial subependymomas, and 6 (12.5%) had spinal tumors. The most common presentation was headache (n = 20, 41.7%), although a significant number of tumors were diagnosed incidentally (n = 16, 33.3%). Among the 42 patients with intracranial tumors, 15 (35.7%) had hydrocephalus, and the most common surgical strategy was a suboccipital approach with or without C1 laminectomy (n = 26, 61.9%). Gross-total resection (GTR) was achieved in 33 cases (68.7%), and 2 patients underwent adjuvant radiotherapy. Most patients had no major postsurgical complications (n = 34, 70.8%), and only 1 (2.1%) had recurrence after GTR. Of 2036 reports initially identified in the systematic review, 39 were eligible for inclusion, comprising 477 patients. Of 462 patients for whom tumor location was reported, 406 (87.9%) were intracranial, with the lateral ventricle as the most common location (n = 214, 46.3%). Spinal subependymomas occurred in 53 patients (11.5%), with 3 cases (0.6%) in multiple locations. Similar to the case series at the authors' institution, headache was the most common presenting symptom (n = 231, 54.0%) among the 428 patients whose presentation was reported. Twenty-seven patients (6.3%) were diagnosed incidentally, and 36 cases (8.4%) were found at autopsy. Extent of resection was reported for 350 patients, and GTR was achieved in 250 (71.4%). Fifteen of 337 patients (4.5%) had recurrence or progression.

CONCLUSIONS The authors' case series and literature review demonstrate that patients with subependymoma are well managed with resection and generally have a favorable prognosis.

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KEYWORDS subependymoma; ependymoma; ventricular tumor; spinal tumor; systematic review; PRISMA guidelines; oncology

ABBREVIATIONS EOR = extent of resection; ETV = endoscopic third ventriculostomy; EVD = external ventricular drain; GTR = gross-total resection; KPS = Karnofsky Performance Scale; STR = subtotal resection.

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Subependymomas are slow-growing WHO grade I primary central nervous system tumors.^{1,2} While the incidence of subependymomas is difficult to assess given that many patients may be asymptomatic, subependymomas are estimated to represent 0.2%–0.7% of all intracranial tumors.^{3–7}

Perhaps due to their rarity or relatively benign nature, there is a paucity of literature on subependymomas. This has resulted in an incomplete characterization of the features and outcomes of subependymomas. This study aims to better describe the characteristics, management, and outcomes of subependymoma patients treated over almost 30 years at a tertiary care academic center and via a systematic literature review.

Methods

Case Series

The hospital records of adult patients (≥ 18 years) diagnosed with histologically confirmed subependymoma or mixed subependymoma-ependymoma at The Johns Hopkins Hospital between 1992 and 2020 were reviewed. Pediatric patients, and patients without pathological confirmation at our institution, with recurrent or progressive subependymomas previously treated at an outside institution, or diagnosed histologically with a different tumor type were excluded. Expert neuropathologists make the diagnosis at our large-volume brain tumor referral center.

This study was approved by the institutional review board. The medical records, pathology reports, and imaging archives were reviewed for each patient. Patient demographics, clinical data, radiographic characteristics, surgical approach, extent of resection (EOR), adjuvant therapies, and postoperative outcomes were collected. Two authors (M.R. and C.K.) independently analyzed the available radiological data. A third independent reviewer (J.R.T.) resolved discrepancies. Complications included any postoperative findings that differed from an optimal course, including radiological findings without a clinical impact (e.g., subdural blood at the surgical site). As described in prior publications, complications were divided between major and minor.⁸ Major complications included hematoma, stroke, deep venous thrombosis, pulmonary embolism, CSF leak, prolonged mechanical ventilation or reintubation, seizures, and/or permanent neurological deficit. Pneumonia, urinary tract infection, or temporary neurological deficits (resolved by last follow-up or earlier) were classified as minor complications. When available, complications and follow-up, including death, were obtained from institutional records or shared clinical records.

Literature Review

This review was performed following the PRISMA guidelines (Fig. 1). To identify relevant studies, the PubMed, Embase, Web of Science, and Google Scholar databases were searched from their inception until December 4, 2020, by a medical informationist. The review was not registered.

The search queries for the different databases were the following. The PubMed database was searched using the query “Glioma, Subependymal”[MeSH] OR “subependymoma” OR “subependymal glioma” OR “subependymal tumor” OR “Subependymal Gliosis” OR subependymoma*[tiab]. Embase was searched for ‘subependymoma’/exp OR ‘subependymal astrocytoma’:ti,ab,kw OR ‘subependymal glioma’:ti,ab,kw OR ‘subependymal tumor’:ti,ab,kw OR ‘subependymal gliosis’:ti,ab,kw OR subependymoma*:ti,ab,kw. Web of Science was searched for the topic (“subependymal astrocytoma” OR “subependymal glioma” OR “subependymal tumor” OR “Subependymal Gliosis” OR subependymoma*). Finally, Google Scholar was searched using the keyword “subependymoma.”

Only indexed, English-language studies published in peer-reviewed journals were included. Conference abstracts and letters to the editor were excluded. Full-text articles were excluded if the study population was obtained via a national registry database or presented in another published article. Our previous limited institutional case series was excluded to prevent duplication of cases and minimize selective reporting bias.⁹ Articles with fewer than 3 patients with subependymoma were excluded to omit atypical presentations. Publications based on pathological, molecular signature, or genetic analysis with no or incomplete clinical data were excluded. Publications that reported aggregated subependymoma outcomes with other pathologies were excluded. No exclusions were made based on patient age, management, outcome, or length of follow-up in the systematic review.

Two independent authors (J.R.T. and M.R.) conducted this review. Initial search results were loaded into Covidence systematic review software (Veritas Health Innovation), and the software’s standard review protocol was followed. Preliminary screening was performed by title and abstract. Articles that one or both reviewers designated as relevant then underwent full-text review by the same two researchers. After applying the exclusion criteria, the remaining articles were scrutinized for quality assessment, data extraction, and analysis. Any discrepancies between reviewers were discussed until agreement was achieved.

Collected variables from the selected articles included number of patients, clinical information (demographics and symptoms), tumor characteristics (location and pathology), radiographic imaging (size and features), surgical characteristics (approach, EOR, and outcome), adjuvant therapies, and postoperative outcomes. Given the variability with reported tumor size, the maximum dimension was extracted. Heterogeneity in reporting and data aggregation of complications and follow-up time precluded any meaningful analysis of these variables. Therefore, a meta-analysis was not performed, and intra- and interstudy bias was not investigated.

Results

Institutional Case Series

Forty-eight unique patients with pathologically confirmed subependymoma, treated between 1992 and 2020, were identified through institutional chart review. Of these, 8 patients (16.7%) had mixed subependymoma-ependymoma tumors. The median age at diagnosis was 49 years (IQR 19.8 years), and 26 patients (54.2%) were

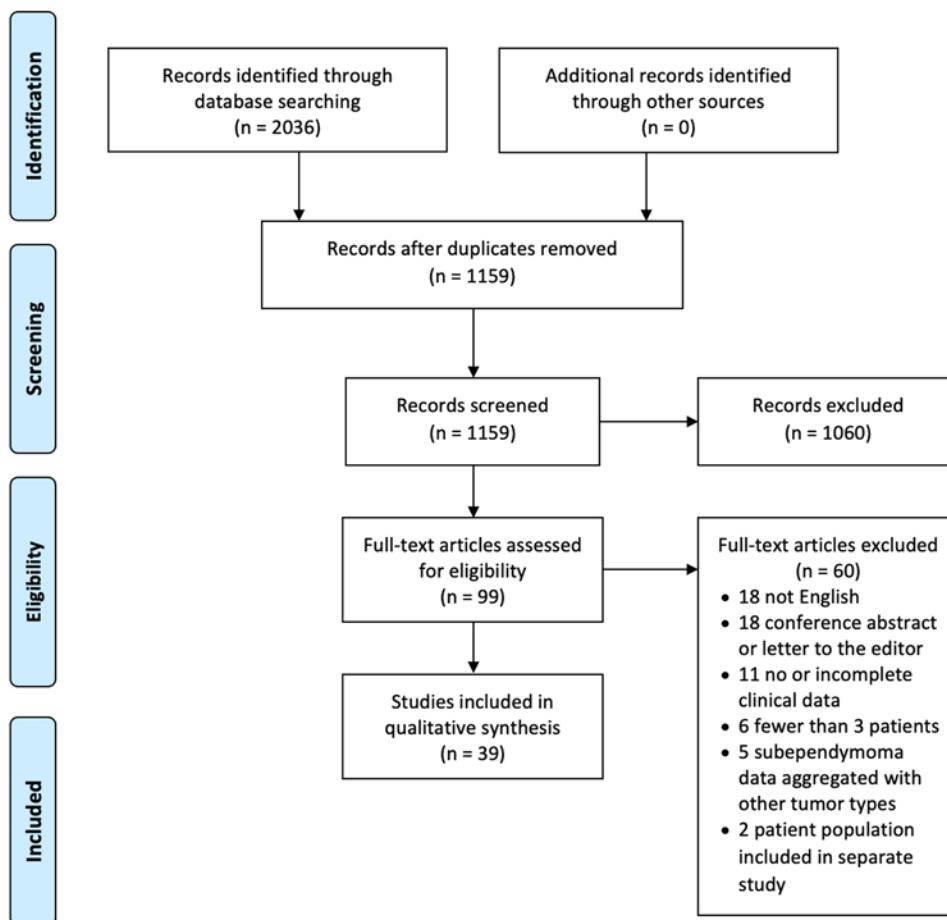


FIG. 1. PRISMA flowchart representing the flow of information and number of articles through the different phases of the systematic review. After removing duplicates, the remaining 1159 unique articles were screened by title and abstract, excluding 1060 irrelevant articles. A total of 99 records underwent independent full-text review, of which 60 were excluded based on the eligibility criteria described in Methods. Data added to the PRISMA template [from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 6(7):e1000097] under the terms of the Creative Commons Attribution License. Figure is available in color online only.

male (Table 1). Forty-three patients (89.6%) were Caucasian, 2 (4.2%) were African American, and 3 (6.2%) were Hispanic. The median Karnofsky Performance Scale (KPS) score at presentation was 90 (IQR 10). A majority of patients (n = 26, 54.2%) had one or more comorbidities, including hypertension (n = 18, 37.5%), other oncological history (n = 8, 16.7%), and/or type 2 diabetes (n = 4, 8.3%).

Forty-two patients (87.5%) had an intracranial subependymoma: 26 (54.2%) in the fourth ventricle, 13 (27.1%) in the lateral ventricle, and 2 (4.2%) in the third ventricle (Table 2). An additional patient had multiple subependymomas in both lateral ventricles. Six patients (12.5%) had spinal tumors, including 2 cervical, 2 thoracic, and 2 cervicothoracic subependymomas. The median tumor volume for all tumors was 5.1 cm³ (IQR 6.2 cm³).

Thirty-two patients (66.7%) had a symptomatic presentation, with the most common symptom being headache (n = 20, 41.7%), followed by dizziness/loss of balance (n = 18, 37.5%) (Table 2). Of note, 4 of 6 patients (66.7%) with spinal tumors had a sensorimotor deficit, 1 had a sensory deficit, and 1 had a motor deficit only. Pain was a prevalent

symptom among the spinal subependymoma group, with 5 of 6 patients (83.3%) with neck, extremity, or thoracic pain.

Sixteen patients (33.3%) of the total cohort had intracranial tumors that were incidentally found. Those tumors were encountered on independent imaging (e.g., after trauma) or during workup for unrelated circumstances such as tinnitus or depression. The median time from tumor discovery to surgery in patients with incidental tumors was 36.5 days (IQR 269 days), and the median tumor volume at the time of resection was 3.49 cm³ (IQR 3.23 cm³). Surgery was recommended to 6 patients after discovery due to unusual tumor location (i.e., temporal or brainstem), hydrocephalus, large size, or concern for impending neurological deficits. Another 6 tumors were resected after growth. One small subependymoma was unexpectedly encountered during a Chiari decompression. An additional patient was observed for years until their tumor migrated from the lateral ventricle to the third ventricle, causing acute hydrocephalus. After follow-up and appropriate counseling of likely benign pathology and unlikely related

TABLE 1. Demographic information for patients with subependymoma

Variable	Case Series (n = 48)	Systematic Review (n = 477)*
Age at diagnosis in years		
Mean (SD)	47.9 (14.0)	46.1
Median (Q1, Q3)	49.0 (37.5, 57.3)	47.0 (33.0, 55.0)
Sex, n (%)		463
Male	26 (54.2)	295 (63.7)
Female	22 (45.8)	168 (36.3)
Race, n (%)		
Caucasian	43 (89.6)	—
African American	2 (4.2)	—
Other	3 (6.2)	—
Hispanic, n (%)		
No	45 (93.8)	—
Yes	3 (6.2)	—
Comorbidities, n (%)		
0	22 (45.8)	—
1	21 (43.8)	—
2	3 (6.2)	—
≥3	2 (4.2)	—
Comorbidity type, n (%)		
Hypertension	18 (37.5)	—
Other oncological history	8 (16.7)	—
Type 2 diabetes	4 (8.3)	—
CAD/MI	3 (6.2)	—
Initial KPS score, median (Q1, Q3)	90 (80, 90)	—

CAD = coronary artery disease; MI = myocardial infarction; — = information not available or underreported.

* Missing 8 patients for mean age and 185 patients for median age. SD could not be calculated for the mean due to lack of reported individual ages.

symptoms, 2 patients underwent surgery given the tumor size and the need for final pathological diagnoses.

Of the 42 patients with intracranial subependymomas, 15 (35.7%) had hydrocephalus (Table 2). Of those 15 patients with hydrocephalus, 9 patients (60%) were treated with tumor resection only, and 4 patients (26.7%) required an intraoperative external ventricular drain (EVD) during surgery for tumor resection. One patient underwent an endoscopic third ventriculostomy (ETV) separately before tumor resection. One underwent preoperative EVD placement and surgery for ETV with endoscopic tumor resection. Conservatively, 3 of 42 patients (7.1%) had an EVD placed intraoperatively despite no significant evidence of preoperative hydrocephalus.

Preoperative MRI was available for review in 31 patients (64.6%) (Table 3). Generally, subependymomas were isointense on T1 sequences (n = 22, 71%), hyperintense on T2 sequences (n = 25, 80.6%), and contrast enhancing (n = 21, 67.7%). Although calcifications were not common (n = 7, 22.6%), most tumors had well-defined borders (n = 20, 64.5%) and cystic changes (17, 54.8%).

Given the need for pathological confirmation for inclusion, all patients in this cohort underwent surgery at our institution (Table 4). Time to surgery was variable, with a median of 25.5 days (IQR 137 days). Among the 42 patients with intracranial tumors, suboccipital craniotomy with or without C1 laminectomy was the most common surgical approach (n = 26, 61.9%). All spinal patients underwent laminectomies for microsurgical resection with or without laminoplasties. Gross-total resection (GTR) was achieved in 33 cases (68.7%). Only 2 patients (4.2%) in our cohort underwent radiation therapy. Both had mixed subependymoma-ependymomas that recurred after subtotal resection (STR). One received adjuvant radiation therapy after repeat resection and the other as definitive treatment for recurrence.

Postoperative outcomes are summarized in Table 5. Most patients (n = 34, 70.8%) had no major postsurgical complications. The most common major complications were permanent motor deficit (n = 5, 10.4%) and hematoma/hemorrhage (n = 5, 10.4%). Of the 5 patients with postoperative hematoma/hemorrhage at the surgical site, 2 were asymptomatic, 1 required a temporary postoperative EVD for hydrocephalus, and 2 were associated with major neurological deficits. In one of those cases, the patient underwent intraventricular hematoma evacuation and delayed shunt placement. Nineteen patients (39.6%) had no complications, and minor postoperative complications are listed in Table 5. The median length of stay was 5 days (IQR 5 days) with a median follow-up time of 28 months (IQR 85.8 months). Reasons for readmission within 90 days included CSF leak, hydrocephalus management, altered mental status in the context of urinary tract infection, a low-grade temperature, and pneumonia management. Additionally, 1 patient with a partially resected cervicothoracic spinal cord tumor had a postoperative pulmonary embolism and a watershed infarct of the spinal cord with a CSF leak. The median reported KPS score at the time of the last follow-up was 90 (IQR 20). At the time of data collection, no deaths were reported in the institutional medical records.

Only 1 patient (2.1%) had a recurrence 31 months after GTR. However, the initial pathology was mixed subependymoma-ependymoma with distinct ependymoma features. Five patients (10.4%) had progression after STR. Time to progression ranged from 4 to 186 months with a median of 16 months (IQR 48.5 months). Of note, none of the spinal patients had recurrence or progression, with a median follow-up time of 32.5 months (IQR 59.7 months).

Systematic Literature Review

A total of 2036 articles were retrieved via electronic database searching, with 39 studies analyzed in the systematic review (Fig. 1).^{3,5,7,10–45}

A total of 477 patients were included in the literature review (Table 1). The median age at diagnosis was 47 years (IQR 22 years). Of the 463 patients for whom patient sex was reported, 295 (63.7%) were males. Of the 462 patients for whom tumor location was reported, 406 (87.9%) were intracranial, 53 (11.5%) were spinal, and 3 (0.6%) had multiple locations. The lateral ventricle was the most common location (n = 214, 46.3%). Of the 428

TABLE 2. Tumor and presentation for patients with subependymoma

Variable	Case Series (n = 48)	Systematic Review (n = 477)
Tumor location, n (%)		462
Intracranial	42 (87.5)	406 (87.9)
4th ventricle	26 (54.2)	161 (34.8)
Lateral ventricle	13 (27.1)	214 (46.3)
3rd ventricle	2 (4.2)	10 (2.2)
Intraparenchymal	—	18 (3.9)
Brainstem	—	9 (50.0)
Occipital lobe	—	3 (16.7)
Temporal lobe	—	2 (11.1)
Parietal lobe	—	2 (11.1)
Parietooccipital lobe	—	1 (5.6)
Frontal lobe	—	1 (5.6)
Cerebellopontine angle	—	3 (0.6)
Spinal	6 (12.5)	53 (11.5)
Cervicothoracic	2 (33.3)	20 (37.7)
Cervical	2 (33.3)	19 (35.8)
Thoracic	2 (33.3)	11 (20.8)
Thoracolumbar	0	3 (5.7)
Multiple tumors	1 (2.1) multiple intracranial	3 (0.6)
Max tumor size, range in cm	0.7–7.1*	0.2–10.0
Symptomatic presentation, n (%)	32 (66.7)	365/428 (85.3)
Headache	20 (41.7)	231 (54)
Dizziness/loss of balance	18 (37.5)	115 (26.9)
Hydrocephalus	15 (31.2)	167 (39)
Sensory deficit	13 (27.1)	37 (8.6)
Ataxia/tremor	12 (25)	53 (12.4)
Motor deficit	11 (22.9)	60 (14)
Visual changes	9 (18.8)	42 (9.8)
Nausea/vomiting	8 (16.7)	74 (17.3)
Extremity/thoracic pain	5 (10.4)	30 (7)
Memory loss	5 (10.4)	23 (5.4)
Dysarthria	2 (4.2)	2 (0.5)
Hearing changes	1 (2.1)	12 (2.8)
Mental status changes	5 (10.4)	44 (10.3)
Altered mentation	3 (60)	4 (9.1)
Loss of consciousness	2 (40)	4 (9.1)
Seizures	0	17 (38.6)
Change in personality	0	8 (18.2)
Not specified	0	11 (25.0)
Incidentally found, n (%)	16 (33.3)	27/428 (6.3)
Found at autopsy, n (%)	0 (0)	36/428 (8.4)
Variable	Case Series (n = 42)	Systematic Review (n = 428)†
Hydrocephalus, n (%)	15 (35.7)	167 (39)
Hydrocephalus treatment, n (%)		—
Tumor resection only	9 (60)	
EVD	4 (26.7)	
ETV	2 (13.3)	
Before tumor resection	1 (6.7)	
During tumor resection‡	1 (6.7)	

CONTINUED ON PAGE 936 »

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TABLE 2. Tumor and presentation for patients with subependymoma

Variable	Case Series (n = 42)	Systematic Review (n = 428)†
Required shunting, n (%)	1 (2.4)	—

* Preoperative imaging not available for 12 tumors.

† May include both intracranial and spinal tumors.

‡ This patient had an EVD placed before surgery for ETV with tumor resection.

patients with reported presenting symptoms, 365 (85.3%) were symptomatic. Headache was the most common presentation (n = 231, 54%), followed by hydrocephalus (n = 167, 39%), and 63 patients (14.7%) were diagnosed incidentally or at autopsy (Table 2). MRI tumor characteristics were discussed in 232 of the literature review patients. Although not all sequences were reported for each patient, most of the tumors were T1 hypointense (n = 130, 62.5%), T2 hyperintense (n = 212, 93.4%), contrast enhancing (n = 140, 76.9%), and had well-defined borders (n = 126, 82.4%) (Table 3).

The surgical procedure was specified in 152 cases; 118 patients (77.6%) underwent a craniotomy/craniectomy, 4 (2.6%) underwent an endoscopic approach, and 30 (19.7%) had a laminectomy (Table 4). Of the 118 patients undergoing a craniotomy/craniectomy, 63 (53.4%) underwent a

supratentorial approach, with the transcallosal route being the most common (n = 27, 22.9%); 55 patients (46.6%) underwent a posterior fossa approach, with the suboccipital approach without C1 laminectomy being the most common (n = 42, 35.6%). Of the 457 patients with histological diagnosis, 412 cases (90.2%) were subependymomas, and 41 (9%) were mixed subependymoma-ependymoma tumors (Table 4). EOR was reported for 350 patients; GTR was achieved in 250 patients (71.4%), and 15 of 337 patients (4.5%) had recurrence or progression (Table 5). Of the 399 patients for whom adjuvant therapies were reported, only 29 (7.3%) underwent radiotherapy. Complications and follow-up time could not be meaningfully analyzed due to the heterogeneity of reporting among the articles.

Discussion

The first description of subependymoma as a distinct entity is attributed to I. Mark Scheinker in 1945 when he compiled 7 tumors derived from “subependymal neuroglial elements.”^{1,2} Within the Surveillance, Epidemiology, and End Results (SEER)-18 Program, the overall incidence of subependymomas is 0.055 per 100,000 person-years in the United States.⁴⁶ With this low incidence, the current literature on subependymomas is still limited to case series. The two most extensive series presented in this systematic review include the clinicopathological evaluation of 83 subependymomas (27 autopsies and complete follow-up data for 34 patients) from the Armed Forces Institute of Pathology by Rushing et al.³ and 43 cases from the Beijing Tiantan Hospital by Bi et al.¹⁰ This article analyzes 48 institutional subependymoma cases with follow-up data and aggregated data from 477 patients in the literature to summarize the presentation, characteristics, treatment, and outcomes of subependymomas.

Demographics

Historically, subependymomas have been associated with the older male population and rarely reported in children.^{13,22,38} However, in our extensive literature review, the mean age was 46 years. Based on our updated results, these low-grade ependymal tumors most frequently present in middle-aged men, likely with some comorbidities but with a good KPS score at presentation.

Symptoms and Location

Subependymomas can arise in either the brain or spinal cord. When intracranial, they are typically intraventricular, particularly within the lateral and fourth ventricles.^{3,9,14,36,46} In our institutional case series, subependymomas of the fourth ventricle were more prevalent (Fig. 2). Interest-

TABLE 3. Preoperative MRI characteristics of patients with subependymoma

Variable	Case Series (n = 31)	Systematic Review (n = 232)
T1 intensity, n (%)	208	
Hypointense	7 (22.6)	130 (62.5)
Isointense	22 (71.0)	76 (36.5)
Hyperintense	2 (6.4)	2 (1.0)
T2 intensity, n (%)	227	
Hypointense	0	8 (3.5)
Isointense	6 (19.4)	7 (3.1)
Hyperintense	25 (80.6)	212 (93.4)
Contrast enhancement, n (%)	182	
Yes	21 (67.7)	140 (76.9)
Heterogeneous	19 (90.5)	—
Homogeneous	2 (9.5)	—
Minimal	—	37 (26.4)
No	10 (32.3)	42 (23.1)
Calcification, n (%)	116*	
Yes	7 (22.6)	44 (37.9)
No	24 (77.4)	72 (62.1)
Cystic, n (%)	160	
Yes	17 (54.8)	94 (58.8)
No	14 (45.2)	66 (41.2)
Well-defined border, n (%)	153	
Yes	20 (64.5)	126 (82.4)
No	11 (35.5)	27 (17.6)

* In the literature, this was based on CT imaging.

TABLE 4. Treatment information for patients with subependymoma

Variable	Case Series (n = 48)	Systematic Review (n = 477)
Pathology, n (%)		457
Subependymoma	40 (83.3)	412 (90.2)
Mixed w/ ependymoma	8 (16.7)	41 (9.0)
Mixed w/ astrocytoma	0	3 (0.6)
Mixed w/ craniopharyngioma	0	1 (0.2)
Time to op in days, median (Q1, Q3)	25.5 (10, 147)	—
Surgical approach, n (%)		152
Craniotomy/craniectomy	41 (85.4)	118 (77.6)
Posterior fossa approach	26 (63.4)	55 (46.6)
Suboccipital w/o C1 laminectomy	18 (43.9)	42 (35.6)
Suboccipital w/ C1 laminectomy	8 (19.5)	3 (2.5)
Telovelar	—	10 (8.5)
Supratentorial approach	15 (36.6)	63 (53.4)
Transcortical	7 (17.1)	14 (11.9)
Transcallosal	4 (9.7)	27 (22.9)
Transsulcal	2 (4.9)	0
Temporoparietal	2 (4.9)	0
Frontal	—	7 (5.9)
Frontal keyhole	—	10 (8.5)
Middle temporal gyrus	—	2 (1.7)
Parietal	—	2 (1.7)
Anterior temporal lobectomy	—	1 (0.8)
Endoscopic	1 (2.1)	4 (2.6)
Laminectomy	6 (12.5)	30 (19.7)
w/ laminoplasty	3 (50.0)	11 (36.7)
w/o laminoplasty	3 (50.0)	19 (63.3)
EOR, n (%)		350
GTR	33 (68.7)	250 (71.4)
STR/partial	14 (29.2)	97 (27.7)
Biopsy	1 (2.1)	3 (0.9)
Adjuvant radiotherapy, n (%)	2 (4.2)	29/399 (7.3)

ingly, all mixed subependymoma-ependymoma tumors were located in the fourth ventricle. While the lateral ventricle is the most reported location in the systematic review, many individual studies also encountered the fourth ventricle as the most common location for subependymomas.^{3–5,7,37,41,42,44} Spinal subependymomas are uncommon and accounted for 12.5% and 11.5% of cases in our series and literature review (Fig. 3). In addition, encountering multiple subependymomas in the same patient is rare: only 1 and 3 patients presented with multiple subependymomas in the case series and literature review, respectively.

Although earlier cases were often encountered in autopsies,^{18,47} subependymomas can commonly present with

TABLE 5. Postoperative outcomes of patients with subependymoma

Variable	Case Series (n = 48)	Systematic Review (n = 441)*
Postop complications, n (% of total cases)		—
Major complications	14 (29.2)	
Hematoma/hemorrhage	5 (10.4)	
Stroke	3 (6.2)	
DVT/PE	3 (6.2)	
CSF leak	3 (6.2)	
Meningitis	3 (6.2)	
Prolonged mechanical ventilation/reintubation	3 (6.2)	
Seizure	1 (2.1)	
Permanent deficits		
Motor	5 (10.4)	
Cognitive	2 (4.2)	
Sensory	2 (4.2)	
Nystagmus	2 (4.2)	
Diplopia	2 (4.2)	
Dysphagia	1 (2.1)	
Dysarthria	1 (2.1)	
Language	1 (2.1)	
CN VI palsy	1 (2.1)	
Minor complications	15 (31.2)	
Pneumonia	3 (6.2)	
Urinary tract infection	2 (4.2)	
Temporary deficits		
Dysphagia	8 (16.7)	
Motor	4 (8.3)	
Language	3 (6.2)	
CN VI palsy	3 (6.2)	
Cognitive	2 (4.2)	
Nystagmus	2 (4.2)	
Dysarthria	1 (2.1)	
Diplopia	1 (2.1)	
No complications, n (%)	19 (39.6)	
LOS in days, median (Q1, Q3)	5 (4, 9)	—
Readmission w/in 90 days, n (%)	9 (18.8)	
w/in 30 days	7 (14.6)	—
31–90 days	2 (4.2)	—
Follow-up in mos		337
Mean	Not calculated	74†
Median (Q1, Q3)	28 (3.0, 88.8)	—
Deaths, n (%)	0	31/356 (8.7)
Recurrence after GTR, n (%)	1 (2.1)	5/337 (1.5)
Progression after STR, n (%)	5 (10.4)	10/337 (3.0)
Final KPS score, median (Q1, Q3)	90 (80, 100)	—

CN = cranial nerve; DVT = deep vein thrombosis; PE = pulmonary embolism.

* Subependymomas encountered in autopsies were excluded from this analysis.

† Unable to calculate SD of the mean follow-up time due to lack of individually reported follow-up times.

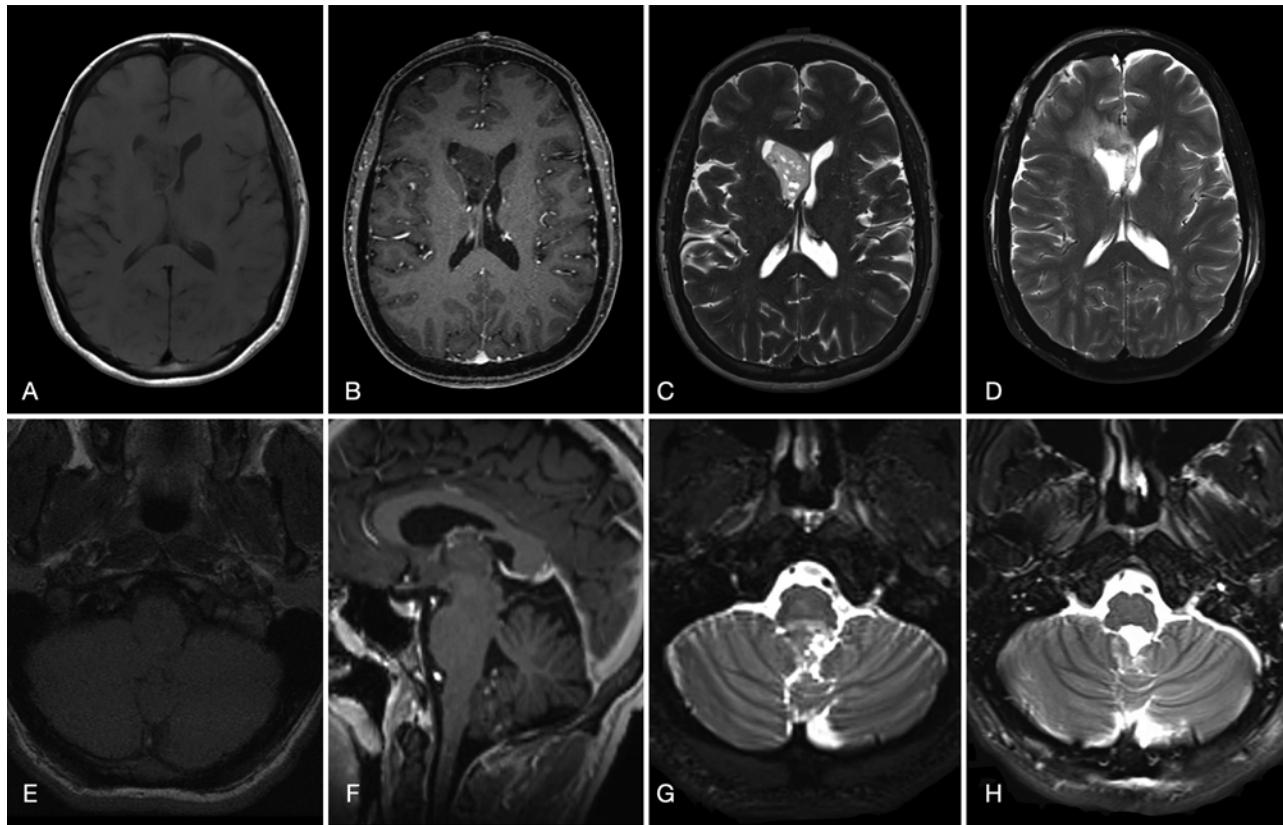


FIG. 2. Examples of intracranial subependymomas included in the present case series. **A–D:** A 57-year-old woman presented with dizziness and one syncopal episode. On MRI, the tumor is T1 hypointense (**A**) with minimal areas of contrast enhancement (**B**), T2 hyperintense (**C**) with well-defined margins, and cystic. There is no hydrocephalus. The patient underwent GTR of the mass (**D**) through a right frontal craniotomy with a transsulcal approach to the lateral ventricle, and the final pathology confirmed the diagnosis as subependymoma. **E–H:** A 45-year-old man presented with neck pain, bilateral hand numbness, nausea, and vomiting. Preoperative MRI shows a 2.5-cm fourth ventricular mass that is T1 isointense (**E**) with scattered contrast enhancement (**F**), T2 hypointense (**G**), cystic, and with poorly defined borders. The patient underwent a suboccipital craniectomy for GTR (**H**), and pathology confirmed mixed subependymoma-ependymoma.

symptomatic CSF obstruction or be diagnosed incidentally.^{9,11,23,42,43} Other presenting symptoms are location specific. Spinal subependymomas are most often intramedullary within the cervical and/or thoracic cord, are eccentric, and often present with motor changes, sensory changes, or pain in the upper limbs or neck.^{9,17,39} This was consistent with our findings.

Hydrocephalus Management

More than one-third of patients with intracranial subependymomas presented with hydrocephalus. Bi et al. reported hydrocephalus in 7 of 9 posterior fossa subependymomas, for which ventriculoperitoneal shunting was recommended.¹⁰ In the present series, preoperative hydrocephalus was managed with tumor resection only, temporary EVD placement, or an ETV before or during tumor resection. Of note, the only patient who needed a preoperative EVD had a subependymoma that migrated from the frontal horn of the left lateral ventricle into the third ventricle, causing acute hydrocephalus.⁴⁸

Only 1 patient in our series required long-term shunting. Varma et al.⁴² report a 23% rate of postoperative hy-

drocephalus as the most common complication in their cases. In the present series, 7 patients had an EVD placed intraoperatively to prevent further hydrocephalus. Most patients were able to be weaned from their EVD, and the drain was removed in the immediate postoperative period with no major complications. However, in 1 case with an intraoperative EVD, the patient experienced a postoperative intraventricular hemorrhage that required hematoma evacuation. Despite being able to be weaned from the EVD and have it removed, the patient presented 1 month after surgery with progressive hydrocephalus requiring shunt placement. Additionally, only 1 patient required postoperative EVD placement after developing hydrocephalus shortly after surgery. The EVD was removed following a steroid course, and the patient was discharged in good condition without requiring CSF diversion.

Imaging

In these results, subependymomas were commonly T1 iso- or hypointense, T2 hyperintense, contrast enhancing, and with well-defined borders. Similar imaging features are consistently reported in the literature, and perhaps the

presence of contrast enhancement has been the most controversial characteristic.^{3,5,21,24–26,29,35,37,42} In our results, contrast enhancement was present in most tumors but often scattered and heterogeneous. Despite their well-defined borders on imaging, in surgery, subependymomas may have an ependymal wall attachment where the mass may be difficult to distinguish from normal parenchyma.

Histopathological and Molecular Characteristics

Histologically, subependymomas have been characterized as clusters of cells embedded in a hypocellular fibrillary matrix of glial cell processes with a lobular growth pattern and, in some cases, microcysts.^{3,11,19,32,47,49} Subependymomas have rare or absent mitotic activity, although they can also contain areas of classic ependymoma morphology.^{3,44} We found that most subependymomas have pure histology. However, approximately 17% and 10% of the cases showed mixed pathology in the present case series and systematic review, respectively.

Changes in chromosomal copy number variation such as chromosome 6 loss or deletions and TERT promoter mutation have been described.^{28,39,50,51} The latest WHO 2021 brain tumor classification highlighted that subependymomas can be identified with methylome studies. However, the molecular classification of subependymomas does not provide added clinicopathological utility, and their diagnosis remains a histological one.⁵² Given their low incidence, a multiinstitutional study is necessary to elucidate new molecular markers that can further the subependymoma classification. But, as the analysis of molecular markers advances, we hope that these mixed tumors can one day be classified in either category.

Surgical Management

No formal guidelines on the management of subependymoma have been published. Treatment may consist of observation if asymptomatic or surgery with the goal of GTR if the tumor is symptomatic.^{3,5,9,12,15,16,42} Open resections (suboccipital, transcallosal, or transcortical/transsulcal approaches) are common for intracranial subependymoma. Endoscopic approaches are reserved for rare occasions.^{20,45} Interestingly, a transcallosal approach was most commonly chosen in our earlier cases, with transcortical or transsulcal approaches favored in more recent years.

Incidental Tumors

A significant proportion of intracranial subependymomas are found incidentally. Incidental, asymptomatic subependymomas can be managed conservatively with serial imaging.^{23,42} However, surgery may be considered in selected cases. As highlighted in our results and the literature, surgical indications include the need to rule out ependymoma, the presence of hydrocephalus, tumor location where growth can cause severe neurological deficits, and evidence of tumor growth or development of symptoms after a period of observation.^{19,42} Some authors have reported that subependymomas less than 2 cm are likely asymptomatic, while others have reported that they are symptomatic when they reach 3–5 cm in size.^{12,18,21} Thus, appropriate patient counseling is paramount in incidental

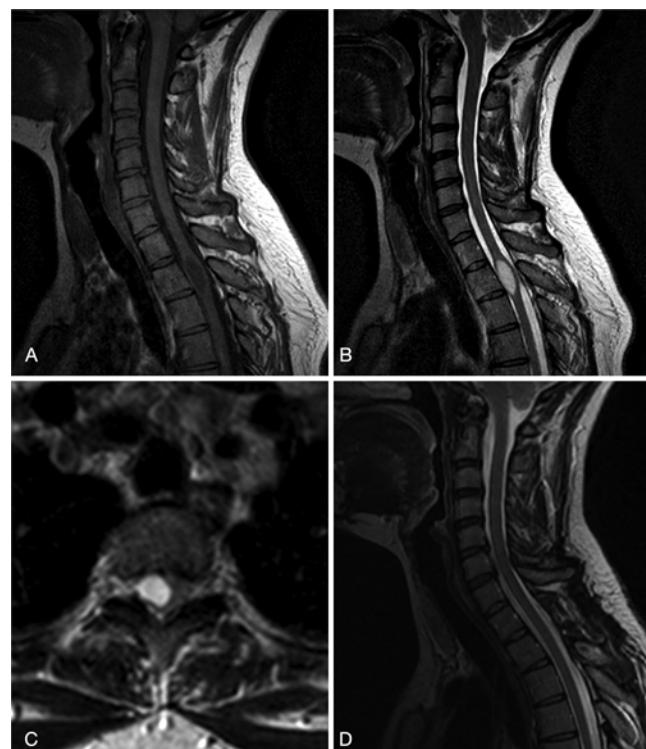


FIG. 3. Example of a spinal subependymoma. A 35-year-old woman presented with right arm pain, numbness, tingling, and difficulty opening jars/bottles with her right hand. Preoperative MRI shows a 2.2-cm thoracic intramedullary mass at the level of the T2 vertebrae. The mass is well defined, T1 hypointense (**A**), T2 hyperintense (**B**), and eccentric to the right with cord displacement (**C**). There was no contrast enhancement in postcontrast imaging. The patient underwent a T1–T2 laminoplasty for GTR as seen on sagittal T2-weighted MRI 8 months after the surgery (**D**). Pathology was consistent with subependymoma.

cases, especially balancing the rate of complications presented in the literature and this article.

Complications

Despite their benign histological nature, subependymomas carry considerable surgical risks. Major postoperative complication rates in the few modern subependymoma series that provide outcome details range from approximately 20% to 31%.^{5,10,21,27,33,42} Postoperative neurological deficits, hematomas, hydrocephalus, CSF leak, wound infection, venous thrombosis, and cardiac arrest have been reported at variable rates in the literature.^{5,10,17,23,27,42} In their 2020 article on intraventricular neuroepithelial tumors, including ependymomas, subependymomas, and central neurocytomas, Aftahy et al. also reported a 26.6% rate of new postoperative neurological deficits, a 20% decline in KPS score, and a 20% rate of postoperative adverse events.²⁷

Most patients in our series had no major postsurgical complications (70.8%). However, 14 patients (29.2%) had a major complication by literature standards.⁸ There was no clear association between approach or EOR and postoperative complications. The most common complications were postoperative hematoma (10.4%) and a permanent

motor deficit (10.4%). In one of the most recent series, Bi et al. encountered limb weakness or paralysis in 14% of intracranial subependymoma cases, with neurological worsening in 23% of cases.¹⁰ Intraventricular hematoma/hemorrhage is a dreaded complication that may require EVD placement or surgery for evacuation. Therefore, meticulous hemostasis is crucial. Similarly, watertight closure is essential to decrease the rate of postoperative CSF leaks.

Historical articles have cited high rates of devastating perioperative complications in subependymomas, many of them related to their fourth ventricular location.^{3,4,30,40,43} Scheithauer described mortality rates of 30% (7 of 23) and 70% (7 of 10) in the postoperative period of patients with pure and mixed subependymomas, respectively.⁴ Even in a more recent series, Rushing et al. described an 18% death rate during the immediate postoperative period that was thought to be related to surgical complications.³ In the present study, mortality rates were 0% and 8.7% in our case series and literature review, respectively. Subependymoma surgery still has complications, but surgical, imaging, and neuromonitoring advances facilitate drastic differences in morbidity and mortality.

Follow-Up

In the literature review, the average follow-up was 74 months. Recurrence and progression were 1.5% and 3%, respectively. Only 1 patient (2.1%) in our series had a recurrence, and 5 patients (10.4%) had progression after STR. All tumors with progression were intracranial: 3 in the fourth ventricle, 1 in the third ventricle, and 1 patient with multiple lobulated masses in both lateral ventricles. The initial pathology was subependymoma in 3 cases (60%) and mixed subependymoma-ependymoma in 2 cases (40%). Management for progression varied depending on the initial pathology and nature of progression. The patient with multiple lobulated masses had an initial right-sided craniotomy with STR, followed by a left-sided craniotomy almost 5 years later for progression of the intraventricular tumors on that side. Pathology was consistent with subependymoma in both instances. One patient with a subependymoma underwent repeat surgery 17 years later, with the second pathology showing progression to mixed subependymoma-ependymoma. For 2 patients with mixed pathology at initial resection, 1 underwent repeat surgery followed by postoperative adjuvant radiation therapy, and the other underwent radiation at the time of recurrence.

Adjuvant Therapies

The role of adjuvant radiation therapy in treating these tumors is still debated.^{5,15,41} Adjuvant radiation therapy is not commonly recommended for pure subependymomas but may be used in cases with mixed pathology.^{9,40,42,44} Within the SEER-18 database, only 15 of 466 (3.4%) intracranial subependymomas received radiation therapy, which was not significantly associated with prognosis.⁴⁶ Bi et al. treated 12 patients with STR or mixed pathology with postoperative radiotherapy, but radiotherapy was not associated with longer survival.¹⁰ As supported by this and prior reports, surgery is the only curative treatment for subependymomas, and radiation therapy has shown little benefit. We do not recommend follow-up radiation therapy

after STR for pure subependymomas because of the lack of high-quality evidence. However, radiation therapy can be considered in mixed pathology, especially with progression after STR. At our institution, 2 of 48 patients underwent radiation treatment (5040 cGy in 28 fractions using intensity-modulated radiation therapy). These 2 patients had elevated risk factors given mixed pathology and disease recurrence after initial resection. With the advances in molecular markers for ependymomas,^{53,54} true ependymomas may be easier to distinguish among patients with mixed pathology, thus streamlining the decision for adjuvant radiation therapy. Given the lack of standardized consensus, multidisciplinary tumor board discussion is recommended for those cases with mixed pathology, symptomatic residual tumors, or lesions that exhibit clinical or radiological signs of progression or recurrence after initial surgery.

Management of Spinal Cord Subependymomas

Reports on spinal cord subependymomas are scarce, with differing recommendations.^{15,17,31,34,39} Spinal subependymomas are frequently symptomatic with associated sensorimotor deficits but typically have an indolent course after resection. In one of the most extensive series of spinal subependymomas, Wu et al. achieved GTR in 69.2% of cases (9 of 13).¹⁵ In their multiinstitutional experience on spinal cord subependymomas, Yuh and colleagues³³ concluded that GTR is not always feasible, showing GTR in 5 of 10 patients (50%), similar to our series. Jallo et al. achieved GTR in all 6 of their patients, and there was no evidence of recurrence during a mean follow-up time of 39 months.¹⁷ Likewise, none of our spinal subependymoma patients had recurrence or progression of their tumor with a median follow-up of 32.5 months (IQR 59.7 months). Although longer follow-up and more cases are warranted to draw strong arguments, these data suggest that in cases in which GTR cannot be achieved due to concern for postoperative neurological deficits, patients with STR may still have an excellent overall prognosis without progression or recurrence.

Limitations

This study has the limitations inherent to a retrospective analysis, including selection and misclassification bias. To limit this, predictor and outcome variables were clearly defined before data collection, and several authors performed quality assessments of data extraction and analysis. Pathological confirmation at our institution was necessary for the inclusion; therefore, the present data do not reflect the natural history of subependymomas that are followed conservatively by our institution or never diagnosed.

Our systematic review included small clinical series, given the limited information on subependymomas. A systematic review does not overcome the intrinsic biases of these types of studies, such as selective publication and short follow-up time. Likewise, cases of subependymomas that were clinically followed may not be reported in the literature due to the lack of confirmatory pathology. Also, publications that did not meet the inclusion criteria were excluded from the analysis. To reduce methodological limitations, the authors systematically followed the recommended PRISMA guidelines.

Conclusions

Our case series and literature review demonstrate that patients with subependymomas are well managed with resection and generally have a favorable prognosis. Pre-operative hydrocephalus can often be treated with a temporary EVD, tumor resection, and/or ETV without requiring long-term shunting. After evaluating the present data, surgery would be recommended in patients with severe symptoms, hydrocephalus, growing lesions, or fourth ventricular tumors, given the need to rule out ependymoma. Close follow-up, conservative resection, or CSF diversion may also be adequate for milder symptoms, especially in older patients with comorbidities. Likewise, a period of close observation is advocated for asymptomatic lesions without the concerns above. As in some of the presented cases, a period of close observation is unlikely to be problematic, and surgery can be reassessed if the patient becomes symptomatic or develops hydrocephalus. Most importantly, the indolent course of these tumors and the relatively high rate of reported complications must be considered when approaching patients and families.

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Disclosures

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Author Contributions

Conception and design: C Bettegowda, Rincon-Torroella, Liu, Brem, Lim. Acquisition of data: Rincon-Torroella, Rakovec, Khalafallah, Liu, A Bettegowda, Kut. Analysis and interpretation of data: Rincon-Torroella, Rakovec, Khalafallah, Liu, A Bettegowda, Kut, Rodriguez. Drafting the article: Rincon-Torroella, Rakovec, Khalafallah, Liu. Critically revising the article: C Bettegowda, Rincon-Torroella, Khalafallah, Liu, Rodriguez, Weingart, Luciano, Olivi, Jallo, Brem, Mukherjee, Lim. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: C Bettegowda. Statistical analysis: Rincon-Torroella, Rakovec, Khalafallah. Administrative/technical/material support: C Bettegowda, Rodriguez, Weingart, Luciano, Olivi, Jallo, Brem, Mukherjee, Lim. Study supervision: C Bettegowda, Weingart, Luciano, Lim.

Supplemental Information

Current Affiliations

Dr. Olivi: Institute of Neurosurgery, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Catholic University, Rome, Italy.

Dr. Lim: Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA.

Correspondence

Chetan Bettegowda: Johns Hopkins University School of Medicine, Baltimore, MD. cbetteg1@jhmi.edu.