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Prognostic factors for recurrence and complications in the surgical management of primary chordoid gliomas: a systematic review of literature

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Abstract

Introduction—Chordoid Gliomas (CG) are rare neoplasms which frequently arise within the third ventricle. Surgery remains the mainstay treatment for CG. The present study comprehensively reviews all reported cases of CG within the literature in order to identify risk factors for surgical complications and tumor recurrence.

Methods—A comprehensive search on MEDLINE (OVID and Pubmed), Scopus, Embase, and Web of Science was conducted following PRISMA guidelines to identify all reported cases of CG.

Results—A total of 81 patients met the study criteria, comprised of 33 males and 48 females. Median age at diagnosis was 48 years with a range from 5 to 72 years, and mean tumor size was 3.1 cm. Biopsy, subtotal resection (STR), and gross total resection (GTR) was achieved in 8, 34, and 33 patients, respectively, with 6 cases not reporting extent of eresection (EOR). Thirteen patients underwent adjuvant radiotherapy. Postoperative complications were noted in 30 cases (37%), with new onset diabetes insipidus being the most common. Postoperative morbidity was not associated with age, tumor size, or extent of resection. A trans-lamina terminalis approach demonstrated a strong trend towards decreased overall rates of postoperative morbidity compared to other approaches (p=0.051). GTR was associated with improved progression-free survival (PFS; p=0.028), while adjuvant radiotherapy, age, tumor size and MIB-I were not predictive of patient outcomes.

Conclusion—GTR should be the primary goal for the management of CG, as it is associated with improved rates of tumor control without an increased rate of postoperative complications. Surgical approach was a stronger predictor of complication rates than extent of resection.

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Disclosures

Morbidity remains high, and future studies to further elaborate on factors predictive of postoperative complications are critical.

Keywords

chordoid glioma; surgery; radiation therapy; hypothalamic dysfunction; diabetes insipidus

Introduction

Intraventricular neoplasms can be highly challenging to treat due to an elevated morbidity profile associated with surgical approach to resection. Tumors that originate in the anterior portion of the 3rd ventricle include ependymomas, central neurocytomas, craniopharyngiomas, and suprasellar meningiomas. Chordoid gliomas (CG) are rare intracranial tumors characterized by the histological presence of both glial and chordoid elements that also occur primarily in this location. Initially described by Brat et al[1], CG are classified as World Health Organization (WHO) grade II neuroepithelial tumors of uncertain histogenesis.[2] CG are typically found within the suprasellar region and the anterior third ventricle. These tumors present as solid, hyperdense lesions on computed tomography (CT), with uniform contrast enhancement on T1-weighted MRI, and mild hyperintensity on T2-weighted MRI. Cystic components have also been observed on rare occasions.[3] Histologically, CG are comprised of clusters and cords of epithelial cells in a mucinous matrix background with a strong presence of GFAP staining on immunohistochemistry.[4]

Their specific location of origin results in a unique symptom profile at presentation consisting of intracranial hypertension symptoms associated with obstructive hydrocephalus, hypothalamic dysfunction, and/or visual impairment. Their close association, and sometimes tight adherence, to the hypothalamus makes *en bloc* resection difficult due to the increased risk of post-operative diabetes insipidus (DI) and other neuroendocrine dysfunction. Their growth is indolent and patients may present with persistent symptoms that originated months, or even years, previously. Surgeons have attempted to balance maximal cytoreduction with complication avoidance, and radiotherapy is often used as an adjuvant therapy in patients that undergo subtotal resection. Factors that govern morbidity, mortality, and recurrence in this disease have not been clearly elucidated and there is a lack of large retrospective studies on these tumors due to their rare nature. Various case reports and case series have attempted to illustrate some of these important points. The current systematic review accrued data from 81 patients presented in various case reports and smaller case series in the literature in order to elucidate factors that influence recurrence, morbidity, and mortality, of patients with chordoid gliomas.

Methods

Literature search

Two researchers (LA, WC) each performed independent literature searches on MEDLINE (OVID and Pubmed), Embase, Scopus, and Web of Science with the keywords "chordoid" AND "glioma" to identify all published reports on CGs. Each database was searched on

3/9/2015 and no publication date restriction was placed on the study. The search was further refined by limiting to manuscripts published in English. Each reviewer constructed a data sheet for each searched database, which were utilized to compare and remove duplicate studies. Data sheets were also compared between researchers in order to agree and confirm the eligible studies included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was applied to this review. The protocol was not registered. (Figure 1) Our inclusion criteria were simplified by including all pathologically confirmed cases of intracranial CGs with disaggregated data available for each patient reported. Cases were excluded for studies that did not provide adequate treatment or clinical parameters for each individual patient.

Data collection

The following variables were collected from each study: age, gender, tumor location, size, duration of symptoms, surgical approach, extent of resection, Ki-67/MIB-1 proliferation index, post-operative complications, adjuvant radiotherapy, progression-free survival, recurrence status, follow-up time, patient clinical status on last follow-up, and overall survival. All components were not documented in each retrospective study and case report included in the review.

Statistical analysis

SPSS version 20.0 (Armonk, NY, IBM Corp) was utilized for all statistical analysis. Evaluation of rates of recurrence and overall survival were performed through Kaplan Meier analysis and log rank tests. Further subgroup analysis was also performed based on possible prognostic factors through univariate Kaplan Meier analysis. Fisher's exact test was utilized to evaluate categorical data, and student's t-test for comparing differences in means between subgroups. Tests were two tailed, and P < 0.05 was considered statistically significant.

Results

A total of 81 patients met study criteria and were included in our analysis. (Table 1 and Table 2) There were 33 males and 48 females. Median age at diagnosis was 48 years (range 5–72 years). Tumor diameter was reported in 42 patients, with a mean diameter of 3.1 cm (range 1.5 to 7.0 cm). Tumor diameter at presentation was neither correlated with MIB-1 labeling (p = 0.52) or time from symptom onset to clinical diagnosis (p = 0.35).

Clinical presentation

Due to the characteristic location within the third ventricle, nearly all patients presented symptomatically, with common symptoms of headache, nausea, vomiting, and ataxia, presumably from obstructive hydrocephalus. (Table 3). Only 3 of 81 (3.7%) patients reviewed presented incidentally.[10–12] Among the remaining 78 patients, the most common presenting symptoms, in order, were headache, visual symptoms, mental status changes and memory deficits (likely from forniceal involvement), nausea/vomiting, and lethargy/somnolence. Less frequently reported symptoms included ataxia/gait instability [8, 9, 13–16], seizures [6, 17], syncopal episodes [12, 15], and speech difficulties. [7] History of endocrine dysfunction was noted in a number of patients, including amenorrhea in 4 [8, 18–

20], diabetes insipidus in 4 [8, 21–23], and hypothyroidism in 2 patients.[8] Psychotic features were noted in 2 patients.[7, 8] In one series, presenting symptoms for 3 patients was not reported.[24]

Mean time from onset of symptoms to surgical management was 22.1 months (Range 0 to 20 years). There were 2 outliers with notably longer duration of symptoms. One patient was a 53 year old woman presenting visual deficits for 20 years, and a 50 kg weight gain over the past 10 years. [7] On evaluation, the only neurological symptom was bitemporal hemianopsia, with a 2.5 cm suprasellar tumor on MRI. [7] The other patient was a 55 year old male presenting with a 10 year history of memory deficits, seizures, and urinary incontinence who was noted to have a large mass occupying the anterior third ventricle. [6]

Imaging

Reporting of CT and MR findings in the literature was inconsistent. On CT, CG typically appear as well circumscribed, hyperdense lesions that homogenously enhance following contrast administration. Of the 41 cases with CT performed, 22 reports commented on signal intensity. Of these, 50% of the lesions appeared hyperdense, 18% appeared hypodense and 23% appeared isodense. The remaining 2 CTs demonstrated mixed density.[6, 25] Atypical CT features reported included calcification, intratumoral hemorrhage, and heterogeneous contrast enhancement. Presence of calcification was reported in 7 cases, of which 2 (28.6%) had calcification.[23, 26] Intratumoral hemorrhage was noted in 3 patients.[5, 15, 27] Heterogenous enhancement was noted in 3 patients [6, 28], and includes the present case.

On MRI, lesions are characteristically either isointense or hypointense, and homogenously contrast-enhancing on T1 weighted imaging. Iso- to hyperintense features were noted in 2 cases.[17, 20] Less frequently, CG demonstrated heterogenous enhancement on T1 weighted MRI, which was noted in 6 out of 56 patients (10.7%). Ring enhancement was noted in 1 patient. [22] On T2 weighted MRI, CG frequently appeared as hyperintense or isointense lesions that were homogenously enhancing. Mixed signal intensity was noted in 3 patients. [17, 29, 30] None of the tumors were hypointense. Edema on MRI was noted in 3 patients. [17, 25, 31] Less frequently, cystic components were noted on imaging in 9 patients. [4, 6, 10, 17, 23, 25, 31–36]

Histology

CG share nearly uniform pathological findings comprised of ovoid or polygonal epithelioid cells with abundant cytoplasm organized in clusters and chords. [5, 7, 18, 37] Cells are typically found within a mucinous vacuolated stroma. [5, 7, 18, 37] Tumor immunopositivity for GFAP, EMA, CD34, cytokeratin, S100, and vimentin is commonly present. [5, 11, 38–40] Some degree of lymphocytic infiltrate appears to be common. Of the 57 cases that elaborated on extent of lymphocyte infiltration, 4 reported sparse infiltrate (7.0%). [13, 19, 26] Of the remaining cases, extent of infiltration was highly variable, ranging from occasional [27, 41] to prominent infiltration. [4, 10, 42, 43] Distribution of tumor infiltrating lymphocytes was also highly variable, with peripheral [21], scattered [30], and focal appearance. [44] Mitoses were consistently low [7, 10, 24, 33, 45–48] or absent [35] when noted. Necrosis was not reported in any study. CG characteristically exhibit low MIB-1

labeling, with all but one case with MIB-1 5%. Mean MIB-1 was 2.5% (SD: 3.0%, range 0.3% to 20%) and was reported in 46 patients. Despite typically low proliferation indexes, Sanches et al. reported a case of a 59 year old female presenting with a 2 cm CG demonstrating GFAP and vimentin positivity, EMA negativity, and Ki67 expression in 20% of cells. [49]

Treatment

The most common surgical approaches described to resect CG include transcallosal in 7 [12, 29, 37, 43, 44, 50], transcortical in 5 [22, 31, 51, 52], and trans-lamina terminalis in 17 [4, 11, 13, 17, 20, 23, 42, 43, 46, 47, 53–55]. Surgical approach was not specified in 52 patients. Extent of surgical resection was reported in 75 cases, of which 10.7%, 45.3%, and 44.0% received biopsy, subtotal resection (STR), or gross total resection (GTR), respectively.

Radiotherapy for CG has largely been reserved as adjuvant therapy for the management of residual tumor following resection. However, the optimal role of radiotherapy remains unclear as reported experience in the literature is limited. Only patients who received either biopsies or STR received adjuvant radiotherapy. Specifically, 50% of biopsies (4/8) and 26.5% of STR (9/34) patients also received radiotherapy following resection. [7, 8, 19, 20, 29, 44, 46, 47] Although a number of radiation modalities have been reported, the most frequently cited was stereotactic radiosurgery, which was utilized in 8 cases. [7, 16, 20, 44, 46, 47] Marginal dose of radiosurgery ranged from 12 to 20 Gy. [16, 47] Kobayashi et al. reported on the long term safety and efficacy of Gamma Knife radiosurgery, delivering a lower marginal dose of 10.5 to 12 Gy following either subtotal resection or biopsy to minimize surgical morbidity.[47] Tumor size stabilized in one case and regressed in another at 70 and 66 months follow up, respectively. One patient died from causes unrelated to disease. However, Chung et al. reported recurrence at 8 months following Gamma Knife radiosurgery with a marginal dose of 20 Gy that eventually required subsequent surgery for recurrent disease.[16] Hanbali et al. reported use of focal fractionated radiotherapy delivering a total dose of 54 Gy in 30 fractions that resulted in recurrence at 7 months. [29] Kurian et al. reported poor outcomes following placement of radioactive iridium-192 seeds in 2 patients. One patient had hypothalamic dysfunction and poor clinical outcome at 15 months, while the other patient died shortly after repeat resection for recurrent disease at 9 months.[19] Further data is necessary to determine the optimal modality and dose of radiotherapy in the treatment of these rare tumors.

Complications

Postoperative complications were noted in 31 cases, and are summarized in Table 4. There were 18 cases of hypothalamic dysfunction, of which 13 were new onset diabetes insipidus and 3 were syndrome of inappropriate antidiuretic hormone (SIADH). Less frequently, panhypopituitarism [15, 43] was noted in 2 and weight gain was noted in another 2 cases. [34, 43] New onset seizures were noted 2 days following STR in a 36 year old male.[42] Short-term memory deficits were present in 7 (8.8%) patients postoperatively. In particular, one of these patients continues to have severe amnesia at last follow up of 40 months. [43] Non-neurologic complications including hematoma formation [6, 31, 47] and bacterial

meningitis [4, 50] were also reported. There were 5 reported cases of pulmonary embolism (6.3%). [7, 8, 24, 29, 44]

Incidence of postoperative morbidity was not associated with age (< 50 vs $\; 50$ years old, p=0.77) or tumor size (< 3 vs $\; 3$ cm, p=1.00). The rate of overall complications was 39.4% and 42.9% within the GTR and STR/biopsy groups, respectively, with no statistical difference between groups (p=0.82). While there was a higher incidence of DI following GTR compared to biopsy/STR (24.2% vs 9.5%), these differences were not statistically significant (p=0.12).

Of the cases in which surgical approach was specified, rate of postoperative complication were 75.0%, 71.4%, and 29.4% for transcortical, transcallosal, and trans-lamina terminalis approaches, respectively. Compared to transcortical and transcollasal approaches, translamina terminalis demonstrated a strong trend towards decreased overall rates of postoperative morbidity (p=0.051), although this difference did not quite meet statistically significance. Of note, data on surgical approach was only available in the minority of cases.

Recurrence and Survival

There were a total of 9 tumor progressions noted with a mean follow up of 14.9 months. The rate of 1, 3, and 5 year progression free survival (PFS) was 88.4%, 82.5%, and 70.7%, respectively, for all patients. For the 9 patients with progression, time to progression ranged from 4 to 96 months postoperatively. Progression was noted in 25% following biopsy and 14.7% of patients following STR. There were no progressions within the group of patients receiving GTR. In one patient with progression, extent of resection for initial resection was not reported. [56] Four patients had repeat resections for progressive disease following initial surgery. [16, 19, 29, 56].Of these, 2 later died from causes unrelated to disease, and 1 remains disease free at 29 months of follow up.[16] One 13 year old female had 2 repeat resections for recurrent disease at 8 and 9 years following initial resection.[56]

The extent of tumor resection was the most robust predictor of improved rates of tumor control (Figure 2). GTR was associated with improved outcomes compared to both STR and biopsy alone (p=0.028) (Table 4). Within the subset of patients with STR, rates of 1, 3, and 5 year PFS was 85.2%, 71.0%, and 35.5%, respectively. Of the 8 patients that received biopsy, rates of 1, 3, and 5 year PFS were all 60.0%. Differences in rates of progression were not statistically significant between STR and biopsy groups (p= 0.86), likely related to small sample size. When controlling for extent of resection, adjuvant radiotherapy did not predict rates of disease progression (p=0.11). Additionally, patient age (p=0.61), tumor size (p=0.48) and MIB-1 labeling (p=0.38) also did not predict progression rates on univariate analysis.

Although there were 18 deaths (22.2%) at last follow up, the majority of deaths were not related to disease progression. Nine deaths occurred within 18 days of surgery. Four patients died from pulmonary embolism postoperatively[1, 7, 20, 24], 4 from infectious causes [6, 9, 26, 40], two from myocardial infarction.[5, 21] No deaths from tumor progression were reported in any study. Age, tumor size, MIB, EOR, and RT did not predict survival. For all patients 1 and 5 year overall survival was 78.2% and 63.7%, respectively.

Discussion

Chordoid gliomas are relatively rare tumors considered to be indolent, but still carry an increased risk of recurrence in cases of sub-optimal resection. They are classified as grade II tumors by World Health Organization (WHO) and the current mainstay of treatment consists of surgical intervention with the possibility of post-operative radiotherapy in cases of STR. The lesion itself appears pathologically akin to chordomas, possessing clusters and cords, also similar to chordoid meningiomas. The hallmark of this neoplasm is the specific suprasellar and anterior third ventricular region from which it originated. Additionally, these lesions may be adhered to the hypothalamus, which has been thought to carry a greater risk of hypothalamic-associated complications in cases where total resection is attempted. The majority of published studies have been small case series, which makes risk assessment and outcomes of patients with CG unclear and difficult to determine. The present comprehensive literature review represents the largest summarized report of this tumor, reporting 80 distinct cases of CG.

While CG is classified as a WHO grade II neoplasm [57], rates of tumor progression, particularly following STR or biopsy remain very high in a relatively short follow-up period. [47] The 3 and 5 year PFS rate was 71.0% and 35.5% for patients with STR. Therefore, the standard of care for CG remains surgery, and GTR should be the goal when it can be safely performed. There were no reports of recurrence following GTR in any study reported in the literature. However, it is unclear whether GTR is truly curative, as the majority of cases lacked long term follow up. For those patients who did have progression, specifically within the STR group, time to progression ranged from 4 months to 4 years. The limited follow up for select patients undergoing GTR[7, 13, 14, 21, 38, 39, 41, 50, 53] may have precluded detection of later recurrences.

However, treatment should be tailored to individual patients, and GTR may not be safely achievable in select cases of CG. GTR was only achieved in 44% of patients with CG in our analysis. Although extent of resection did not predict postoperative morbidity and mortality in our analysis, complications were frequent following resection. Hypothalamic dysfunction was present in 22.2% of all patients, and most frequently comprised transient DI, which occurred at a rate of 16.0% overall. Other hypothalamic complications include SIADH[22, 29], temperature dysregulation [19], and panhypopituitarism.[15, 43] Surgical approach appears to play a more prognostic role in dictating postoperative morbidity. In our analysis of the studies with adequate reporting of surgical technique, the trans-lamina terminalis approach demonstrated a strong trend toward decreased rates of adverse effects compared to transcortical and transcallosal approaches. The trans-lamina terminalis approach was the most frequently cited surgical approach and demonstrated a complication rate of 29.4% overall, while rates of complications were 75.0% and 71.4% for transcortical and transcollosal approaches. Thus, surgical approach appears to be a stronger predictor of postoperative mobidity than extent of resection. A caveat to this conclusion is the limited number of studies that reported their surgical approach. Of the 81 reported cases within the literature, surgical approach was specified in only 28 patients. Given the limited number of studies that specify surgical approach, statistical analysis of individual complications were insufficiently powered to correlate complication rates to surgical technique. Hypothalamic

deficits were reported in only 2 out of 17 trans-lamina terminalis cases, although differences were not statistically significant between surgical approaches. Moreover, surgical approach did not predict rates of memory deficits or seizures.

When a complete resection could not be accomplished, adjuvant radiotherapy or radiosurgery was occasionally administered. The use of adjuvant radiotherapy in literature has been solely reserved for the management of residual disease, either in the setting of biopsy [16, 47] or STR. [19, 20, 46] Kobayashi advocated the role of adjuvant Gamma Knife radiosurgery with lower marginal doses to the hypothalamus and optic nerves in the management of these tumors to minimize adverse neuroendocrine sequelae.[47] Two patients underwent biopsy followed by Gamma Knife, delivering a maximal dose of 21 tyo 22 Gy and a maginal dose of 10.5 to 11 Gy. These two patients were alive without disease progression or radiation toxicity at last follow up. A patient who underwent STR received a marginal dose of 12 Gy, with less than 10 Gy to the optic nerve, and eventually died of causes unrelated to tumor progression. Tumor size was noted to have decreased at 5 months following radiosurgery. In all cases, adjuvant therapy was given within 4 months postoperatively.

Other series have reported the safe management of CG with fractionated radiotherapy [19, 20, 44] [7], and benefits of RT have been demonstrated in the management of other low grade gliomas involving the hypothalamus and optic nerves.[58] The use of adjuvant radiotherapy may allow minimization of surgical complications, and result in improved tumor control or even regression. [47] However, due to the small number of patients in literature, the present study is underpowered to definitively delineate the role of radiotherapy in the management of CG. The use of adjuvant chemotherapy for CG has not been reported in literature.

Although CG appears to be highly recurrent in cases of STR, and a number of deaths were reported, no death was attributed to disease progression. A total of 18 deaths were reported, with 15 (83.3%) deaths occurring within 13 months and 9 (50%) within 18 days of surgery. Most common causes of death were pulmonary embolism [7, 8, 24], myocardial infarction [5, 21], and infection [6, 9, 26]. Pulmonary embolism was reported in 5 patients (6.3%), of which 4 resulted in death. Two patients died within a few days of surgery [7, 8], and the remaining two within 14 days [7] and 15 days [24] of surgery. Proper prophylaxis for thromboembolic events is critical for patients with CG given its high reported incidence. [43] The high rate of postoperative mortality associated with a low-grade tumor that carries a low rate of disease-associated mortality should be carefully considered when planning surgery and peri-operative care. Although better tumor control can be achieved with more aggressive resection, early complications may negate the benefit of a more aggressive approach.

While our analysis comprises the largest literature review of CG, there are several important limitations to consider given our methodology and design. As an analysis of cases presented in literature, our review carries biases inherent to all retrospective studies. Given the rarity of this tumor type, the number of patients receiving adjuvant radiotherapy is limited, and larger studies will be critical in elucidating the role of radiotherapy in the treatment of CG.

Additionally, while there was no reported local progression following GTR, length of follow-up may be too limited to capture late recurrences.

Conclusion

CG is a rare subtype of low grade glioma typically located within the third ventricle. Surgical intervention remains critical in the management of these tumors. GTR should be the primary goal, as it is associated with improved rates of tumor control and has not been shown to increase rates of postoperative complications. However, GTR may not always be achievable given the proximity to sensitive neurovascular structures. The application of adjuvant radiotherapy has mainly been utilized in the management of residual disease in cases where GTR may not be achievable. The true benefits of radiotherapy remain unclear. To minimize postoperative complications, a greater emphasis should be placed on surgical approach and perioperative management. Morbidity remains high, and future studies will be critical in optimizing the use radiotherapy and surgical techniques to improve outcomes while minimizing complications.

Author (year)	# of patients	Average Age	Extent of Resection (initial tumor)	Reported # that underwent radiotherapy†	Reported patient recurrences	Reported deaths
Al-Zubidi et al. (2014)[41]	1	37	STR	0	0	0
Kobayashi et al. (2013)[47]	3	49	Bx (n=2) STR (n=1)	3	0	1
Ni et al. (2013)[18]	4	40	GTR (n=4)	0	0	0
Shiramizu et al. (2013)[54]	1	49	GTR	0	0	0
Scheurkogel et al. (2012) [55]	1	30	STR	0	0	0
Romero-Rojas et al. (2012) [14]	1	39	GTR	0	0	0
Can et al. (2012)[38]	1	37	GTR	0	0	0
Ghosal et al. (2012)[59]	1	48	STR	0	0	0
Vij et al. (2011)[17]	1	48	STR	0	0	0
Liu et al. (2011)[31]	1	45	STR	0	0	0
Tu et al. (2010)[12]	1	46	STR	0	0	0
Horbinski et al. (2009)[15]	5	47	GTR (n=1) NA (n=4)	0	0	0
Dziurzynski et al. (2009)[23]	1	41	Bx	0	0	0
Kawasaki et al. (2009)[27]	2	47	GTR (n=1) STR (n=1)	0	0	1
Vanhauwaert et al. (2008) [52]	1	58	GTR	0	0	0

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Carrasco et al. (2008)[4]	1	53	GTR	0	0	0
Jain et al. (2008)[6]	2	31	GTR (n=2)	0	0	1
Gallina et al. (2007)[11]	1	56	GTR	0	0	0
Goyal et al. (2007)[5]	1	5	STR	0	0	1
Jung et al. (2006)[26]	1	50	STR	0	1	1
Nga et al. (2006)[51]	1	49	NA	0	1	1
Leeds et al. (2006)[48]	1	57	Bx	0	0	0
Baehring et al. (2006)[32]	1	71	Bx	0	0	0
Kurian et al. (2005)[19]	2	35	STR (n=1) Bx (n=1)	2	1	1
Buccoliero et al. (2004)[10]	1	56	GTR	0	0	0
Suh et al. (2003)[33]	1	48	GTR	0	0	0
Taraszewska et al. (2003) [21]	2	57	GTR (n=2)	0	0	1
Sato et al. (2003)[40]	1	65	STR	0	0	1
Raizer et al. (2003)[50]	1	57	GTR	0	0	0
Nakajima et al. (2003)[44]	1	49	STR	1	0	0
Grand et al. (2002)[34]	1	41	STR	0	0	0
Pasquier et al. (2002)[35]	2	37	STR (n=2)	0	0	0
Hanbali et al. (2001)[29]	1	57	STR	1	1	1
Castellano- Sanchez et al. (2001)[28]	1	12	STR	0	0	0
Galloway et al. (2001)[13]	1	54	GTR	0	0	0
Cenacchi et al. (2001)[24]	3	39	GTR (n=3)	0	0	1
Castellano- Sanchez et al. (2000)[42]	1	36	STR	0	0	0
Ricoy et al. (2000)[53]	1	41	GTR	0	0	0
Tonami et al. (2000)[20]	1	42	STR	1	0	0
Reifenberger et al. (1999) [7]	4	52	GTR (n=3) STR (n=1)	1	0	2
Vajtai et al. (1999)[45]	1	60	STR	0	0	1
Brat et al. (1998)[8]	8	47	GTR (n=2) STR (n=6)	2	3	3

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Tanboon et al. (2014)[30]	1	29	GTR	0	0	0
Sanches et al. (2012)[49]	1	59	Bx	0	0	0
Xian et al. (2012)[39]	1	53	GTR	0	0	0
Kim et al. (2010)[22]	1	27	STR	0	0	0
DeSouza et al. (2010)[60]	2	42	GTR (n=1) STR (n=1)	0	0	0
Sugita et al. (2010)[37]	1	55	STR	0	0	0
Hsu et al. (2005)[36]	1	50	GTR	0	0	0
Chung et al. (2007)[16]	1	48	Bx	1	1	0
Bastin et al. (2012)[25]	1	31	STR	0	0	0
Molnar et al. (2008)[9]	1	34	STR	0	0	1
Kochi et al. (2000)[46]	1	51	STR	1	0	0
Morais et al. (2015)[56]	1	13	NA	0	2	0

[†] Radiation soon after initial resection

Abbreviations: GTR=Gross Total Resection/STR=Subtotal Resection/Bx=Biopsy

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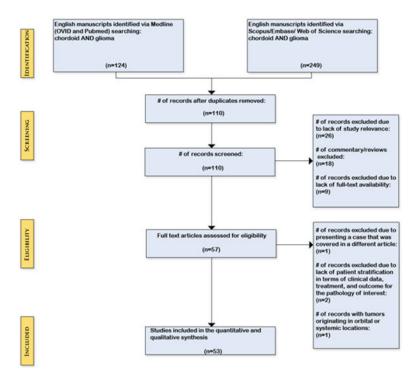


Figure 1.Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

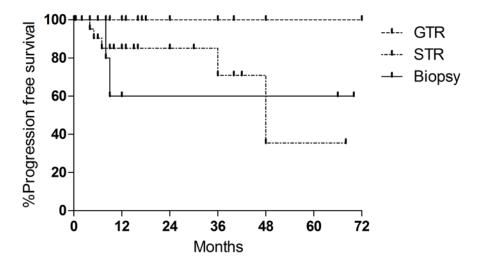


Figure 2.Kaplan Meier analysis of recurrence free survival (PFS) based on extent of resection. STR: subtotal resection. GTR: gross total resection. There were no recurrences within the GTR group. 1-, 3-, and 5 year PFS for STR was 85.2%, 71.0%, and 35.5% respectively. GTR was associated with an improved rate of tumor control than STR and biopsy (p= 0.0276).

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Table 1

Summary of studies and patients included within analysis.

Morais et al. (2015)[56] Tamboon et al. (2014)[30] Al-Zubidi et al. (2014)[41] I 33 Kobayashi et al. (2013)[47] Ni et al. (2013)[17] Can et al. (2012)[18] Sanches et al. (2012)[49] Xian et al. (2012)[49] Xian et al. (2012)[24] I 55 Sanches et al. (2012)[49] Xian et al. (2012)[29] I 64 Wije t al. (2011)[13] I 74 Autorian et al. (2010)[71] I 1 44 Autorian et al. (2010)[71] I 1 44 Autorian et al. (2010)[71] I 22 Autorian et al. (2000)[21] Autorian et al. (2000)[22] Autorian et al. (2000)[25] Autorian et al. (2000)[21] Autorian et al. (2000)[25] Autorian et al. (2008)[25] Autorian et al. (2008)[15] Autorian et al. (2008)[15]	13 NA	c	,	0
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1	29 GTR	0	0	0
1 3 65] 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	37 STR	0	0	0
55] 1 1 25] 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	49 Bx (n=2) STR (n=1)	2) 3 1)	0	1
1	40 GTR (n=4)	4) 0	0	0
55] 1 1010] 1 1 1 1 1 1 1 1 1 1 1 1 1 2 2 2 2	49 GTR	0	0	0
)[10]	30 STR	0	0	0
1 1 1 1 1 1 1 1 1 1 1 1 1 2 2 2 2 2 1	39 GTR	0	0	0
1 1 1 1 1 1 1 1 1 1 2 2 2 2 2 1 1 1 1 1	37 GTR	0	0	0
1 1 1 1 1 1 1 1 2 2 2 2 2 1 1 1 1 2 2 2 3 1 1 1 1	59 Bx	0	0	0
1 1 1 1 1 1 1 1 2 2 2 2 1 1 1 1 1 2 2 1	53 GTR	0	0	0
1 1 1 1 1 2 2 2 2 1 1 5 2 1 1 2 2 1 1 1 1	31 STR	0	0	0
1 1 1 1 2 2 1 1 5 2 2 2 2 2 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1	48 STR	0	0	0
1 1 1 2 2 1 1 5 2 1 2 2 2 2 1 1 1 1 1 1	48 STR	0	0	0
1 1 2 2 1 1 5 2 2 2 2 2 3 5 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	45 STR	0	0	0
2 2 2] 1 2] 1 55] 1 52] 1	46 STR	0	0	0
2 1 2] 1 2] 2 52] 1	27 STR	0	0	0
1 5 22] 1 22 2 52] 1	42 GTR (n=1) STR (n=1)	1) 0 1)	0	0
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2 8)[52] 1 1	41 Bx	0	0	0
8)[52] 1	47 GTR (n=1) STR (n=1)	1) 0	0	1
1	58 GTR	0	0	0
	34 STR	0	0	_
Carrasco et al. (2008)[4] 1 53	53 GTR	0	0	0
Jain et al. (2008)[14] 2 31	31 GTR (n=2)	2) 0	0	-

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Gallina et al. (2007)[6]	-					
	٦	26	GTR	0	0	0
Chung et al. (2007)[13]	1	48	Вх	1		0
Goyal et al. (2007)[27]	1	5	STR	0	0	-
Jung et al. (2006)[25]	1	50	STR	0	-	
Nga et al. (2006)[51]	-	49	NA	0	_	-
Leeds et al. (2006)[48]	1	57	Вх	0	0	0
Bachring et al. (2006)[32]	1	71	Вх	0	0	0
Hsu et al. (2005)[36]	1	50	GTR	0	0	0
Kurian et al. (2005)[18]	2	35	$\begin{array}{c} \text{STR} \; (n{=}1) \\ \text{Bx} \; (n{=}1) \end{array}$	2	-1	1
Buccoliero et al. (2004)[5]	-	99	GTR	0	0	0
Suh et al. (2003)[33]	-	48	GTR	0	0	0
Taraszewska et al. (2003)[20]	2	57	GTR (n=2)	0	0	-
Sato et al. (2003)[40]	1	92	STR	0	0	-
Raizer et al. (2003)[50]	1	57	GTR	0	0	0
Nakajima et al. (2003)[44]	-	49	STR	1	0	0
Grand et al. (2002)[34]		41	STR	0	0	0
Pasquier et al. (2002)[35]	2	37	STR (n=2)	0	0	0
Hanbali et al. (2001)[29]	_	57	STR	1	-	-
Castellano-Sanchez et al. (2001)[28]		12	STR	0	0	0
Galloway et al. (2001)[8]	-	54	GTR	0	0	0
Cenacchi et al. (2001)[23]	3	39	GTR (n=3)	0	0	-
Kochi et al. (2000)[46]	-	51	STR	1	0	0
Castellano-Sanchez et al. (2000)[42]	1	36	STR	0	0	0
Ricoy et al. (2000)[53]	_	41	GTR	0	0	0
Tonami et al. (2000)[19]	_	42	STR	1	0	0
Reifenberger et al. (1999)[16]	4	52	GTR (n=3) STR (n=1)	1	0	2
Vajtai et al. (1999)[45]	_	09	STR	0	0	П
Brat et al. (1998)[9]	∞	47	GTR (n=2) STR (n=6)	2	3	8

Abbreviations: GTR=Gross Total Resection/STR=Subtotal Resection/Bx=Biopsy

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Table 2
Summary of patient demographics and tumor characteristics

	Median	Range
Age	48	5 to 72
Sex		
Female	48	
Male	33	
Tumor diameter (cm)	3	1.5 to 7
MIB-LI	1.7	1 to 20
Treatment		
BX	8 (9.9%)	
STR	34 (42.0%)	
GTR	33 (40.7%)	
Unknown	6 (9.9%)	
Recurrences	8	
Death	18	

Table 3

Frequency of presenting symptoms

Symptoms	n	<u>%</u>
Headache	33	40.7
Visual deficits	29	35.8
Mental status/memory changes	22	27.2
Nausea/Vomiting	11	13.6
Lethargy/somnolence	9	11.1
Ataxia	7	8.6
Amenorrhea	4	4.9
Diabetes Insipidus	4	4.9
Seizures	2	2.5
Syncope	2	2.5
Hypothyroidism	2	2.5
Psychotic features	2	2.5
Speech difficulty	1	1.2
Incidental	3	3.7

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Table 4

Postoperative complications stratified by EOR and surgical approach

	0	Overall		GTR	S	STR/Bx	Tra	nscortial	Tran	Transcortial Translaminar	Tra	Transcallosal	_	Other
Number of patients		81		33		42		4		17		7		53
Number of complication	31	38.3%	13	39.4%	18	42.9%	3	75.0%	5	29.4%	5	71.4%	18	34.0%
Hypothalamic dysfunction	18	22.2%	∞	24.2%	6	21.4%	_	25.0%	2	11.8%	4	57.1%	Ξ	20.8%
DI	13	16.0%	∞	24.2%	4	9.5%	-	25.0%	2	11.8%	3	42.9%	7	13.2%
SIADH	3	3.7%	0	0.0%	\mathcal{S}	7.1%	_	25.0%	0	0.0%	2	28.6%	-	1.9%
Hypothermia	2	2.5%	2	6.1%	_	2.4%	0	%0.0	0	0.0%	0	%0.0	2	3.8%
Panhypopituitarism	2	2.5%	2	6.1%	0	0.0%	0	%0.0	П	5.9%	0	0.0%	-	1.9%
Weight gain	2	2.5%	_	3.0%	_	2.4%	0	%0.0	-	5.9%	0	0.0%	-	1.9%
Hypothyroidism	2	2.5%	_	3.0%	0	0.0%	0	%0.0	0	0.0%	0	%0.0	2	3.8%
Organic psychosis	2	2.5%	_	3.0%	_	2.4%	0	%0.0	0	%0.0	0	%0.0	2	3.8%
Memory deficits	7	8.6%	2	6.1%	7	16.7%	0	%0.0	-	5.9%	0	%0.0	9	11.3%
Seizures	-	1.2%	0	0.0%	_	2.4%	0	%0.0	П	5.9%	0	0.0%	0	0.0%
Hematoma	3	3.7%	-	3.0%	2	4.8%	-	25.0%	-	5.9%	0	%0.0	-	1.9%
Meningitis	2	2.5%	2	6.1%	0	0.0%	0	%0.0	0	0.0%	0	%0.0	-	1.9%
Myocardial infarction	2	2.5%	-	3.0%	-	2.4%	0	%0.0	-	2.9%	-	14.3%	0	0.0%
Atrial fibrillation	-	1.2%	-	3.0%	0	0.0%	0	0.0%	0	%0.0	1	14.3%	0	0.0%
Pulmonary embolism	S	6.2%	2	6.1%	33	7.1%	0	%0.0	0	%0.0	1	14.3%	4	7.5%
Stroke	-	1.2%	0	0.0%	-	2.4%	0	%0.0	0	%0.0	-	14.3%	0	0.0%
Somnolence/lethargy	3	3.7%	-	3.0%	2	4.8%	-	25.0%	1	8.9%	0	%0.0	-	1.9%
Persistent hydrocephalus	_	1.2%	0	0.0%	_	2.4%	0	%0.0	0	%0.0	-	14.3%	0	0.0%
Visual deficits	_	1.2%	0	0.0%	-	2.4%	0	0.0%	0	0.0%	0	0.0%	_	1.9%

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Table 5

Univariate Kaplan Meier analysis for tumor recurrence. Analysis of radiotherapy compared STR only to STR + RT, and excluded patients with GTR as no patients with GTR received adjuvant therapy.

Factor	Hazard Ratio	95% CI	p
Age (>50 vs 50years)	0.77	0.16-3.71	0.618
Tumor diameter (3 vs <3cm)	0.33	0.01 - 7.36	0.484
MIB-LI (2.5 vs <2.5%)	0.25	0.01-5.75	0.383
EOR (GTR vs STR/Bx)	0.18	0.04-0.83	0.028
Radiotherapy	0.16	0.03-0.82	0.114