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Predictors of recurrence in the management of chordoid meningioma

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Abstract

Introduction—Management of chordoid meningiomas (CMs) is complicated by high rates of recurrence, particularly following subtotal resection. Optimal management is not established given the paucity of published experience. To identify prognostic factors for recurrence following resection, the authors conducted the largest systematic review of CMs to date.

Methods—A comprehensive search on MEDLINE (OVID and Pubmed), Scopus, Embase, and Web of Science utilizing the search terms “chordoid” AND “meningioma” was performed to identify all reports of pathologically confirmed intracranial CMs.

Results—A total of 221 patients were included, comprising 120 females and 101 males. Mean age, MIB-1/Ki67, and tumor size was 45.5 years, 4.3% (range:0.1-26.6%), and 4.1 cm (range: 0.8-10 cm), respectively. 5-, and 10- year progression free survival (PFS) was 67.5%, and 54.4%, respectively. Gross total resection (GTR) and subtotal resection (STR) was achieved in 172 and 48 patients, respectively. Adjuvant radiotherapy (RT) was given to 30 patients. Multivariate analysis found GTR was strongly correlated with decreased recurrence rates (HR 0.04, p =<0.0001), while higher MIB-1 labeling index (≥5% vs <5%) was associated with increased recurrence (HR 7.08; p=0.016). Adjuvant RT, age, gender, and tumor location were not associated with recurrence.

Conclusion—GTR resection is the strongest predictor of tumor control, and should be the goal to minimize local progression. Additionally, higher MIB-1 labeling was associated with increased rates of tumor recurrence. Tumors that are subtotally resected or demonstrate higher MIB-1 are at greater recurrence and warrant consideration for RT and close long term follow up.

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Disclosures

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Author contributions to the manuscript are as follows: Conception and design (Ampie, Choy, Bloch), acquisition of data (Ampie and Choy), statistical analysis (Choy), interpretation of data (Choy and Ampie), drafting article (Choy and Ampie), revising the article (all authors).

Keywords

Chordoid; Meningioma; Surgery; atypical; radiation therapy

Introduction

Chordoid meningiomas (CM) are classified as grade II lesions under the World Health Organization classification of nervous system tumors due to the high recurrence rate after subtotal resection[1]. Other meningioma histological subtypes that are also classified as grade II include clear cell and atypical meningiomas. CM are rare tumors which constitute approximately less than 1% of intracranial meningiomas[2, 3]. The term was initially defined by Kepes et al. who defined it as having a chordoma-like histologic appearance with a clustering of tumor cells (some having single or multiple intracytoplasmic vacuoles) against a myxoid background[4]. The cohort in which they noted this tumor was composed of a pediatric population with associated iron refractory hypochromic anemia and other systemic findings. They proposed that the associated reactive peritumoral lymphoplasmacellular infiltrates found in CM induced the systemic manifestations of Castleman syndrome, a rare lymphoproliferative disorder, in pediatric patients. This association was later questioned with additional pediatric cases of CM presenting without adverse systemic effects.

The data for CM is sparse and restricted to case reports and retrospective case series. A void exists for the standardization of data in terms of important factors that may govern recurrence of these tumors after initial surgical intervention. Kozler et al. proposed that future reports on CM include important factors such as radicality of resection, presence or absence of peritumoral edema, vascular supply, and vascular endothelial growth factor (VEGF) expression of the tumor[5]. While most studies lack these variables, we present important tumor histological characteristics and clinical parameters that are present in CM and the role that they play in outcomes following resection through a systematic review of the literature.

Methods

Literature search

Two researchers (LA, WC) each performed independent literature searches on MEDLINE (OVID and Pubmed), Scopus, Embase, and Web of Science utilizing the search terms “chordoid” AND “meningioma” for all searched databases to identify all reports of CMs. The databases were searched on 7/1/15 and no publication date limitation was imposed on the study. Further refinement of the search was conducted by limiting to manuscripts published in English. Data sheets were constructed independently for each database searched which were utilized to remove duplicate papers shared by the databases and compared by the two researchers to agree on included studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was applied to this review. The protocol was not registered. **(Figure 1)**

Eligibility criteria

Only cases that were pathologically defined as CM were included. Reports which did not report individual disaggregated outcomes for patient treatment or clinical parameters were excluded. Non-intracranial cases which focused on systemic or orbital meningiomas were not included in this review.

Data collection

The following variables were collected from each study: gender, tumor location, size, duration of symptoms before presentation, symptoms, systemic manifestations (i.e. anemia, fever), presence of Castleman's disease, radiologic findings, pathology findings (inclusive of the percentage of chordoid component), Ki-67/MIB-1 proliferation index, presence of lymphocytic infiltration, extent of resection, Simpson grade for resection, adjuvant radiotherapy, progression-free survival, recurrence status, follow-up time, follow-up condition, and the overall survival. Some of these components were not included in the case reports and retrospective studies encountered; we present the most common of these variables that were reported.

Statistical analysis

All statistical analysis was performed with SPSS version 20.0 (Armonk, NY, IBM Corp). Univariate evaluation of recurrence was performed through Kaplan Meier analysis and log rank test of the entire population, along with subgroups based on treatment type and putative prognostic factors. Outcomes between subgroups were assessed with chi squared test. Evaluation of differences within categorical data was made through fisher's exact tests. Log-rank tests were utilized on Multivariate Cox analysis of tumor recurrence. Tests were two tailed and P values <0.05 were considered statistically significant. Continuous data is presented as mean ± standard deviation

Results

A total of 221 patients met study criteria and were included in the analysis (**Table 1)**. Patient demographics are summarized in **Table 2**. There were a total of 120 females and 101 males. Mean age was 45.5 (SD:19.0, range 4-85 years) at time of surgery. Mean follow up was 36.5 months (SD: 42.7). Convexity meningiomas were the most common comprising 37.1% of all CMs reviewed in our series. The majority of tumors were not skull based (69.2%). Mean tumor size was 4.14 cm (SD: 2.5, range: 0.8-10 cm). MIB-1 proliferation index was reported in 127 patients. Mean MIB-1/Ki67 was 4.3% (SD:5.2%, range:0.1-26.6%). Histological reports in reviewed cases were largely heterogeneous, and percentage of chordoid elements was reported in 114 patients, of which 74 patients had specific values noted, with a mean of 60.9% (SD: 22.8, range: 20-100%). Of the remaining 30 patients, 6 and 34 patients were reported to have <50% and >50% chordoid component on histological analysis, respectively. For the 114 patients, 27 and 87 cases demonstrated <50% and >50% chordoid features on histology. Progesterone receptor positivity was specified in 6 patients.

Outcomes

All patients underwent tumor resection as part of their initial management. Simpson grade I and II resections were considered GTR. Gross total resection (GTR) and subtotal resection (STR) was achieved in 172 and 48 patients, respectively. GTR was achieved in 44 of 68 (64.7%) patients with skull base tumors and 128 of 153 (83.7%) patients with non-skull based tumors (p=0.0024). Within these two groups, 16 (9.3%) and 14 (29.2%) patients also received adjuvant radiation therapy, respectively. Tumor progression was noted in 51 patients, with median time to recurrence of 136 months. Three, five, and ten year progression free survival (PFS) was 76.0%, 67.5%, and 54.4%, respectively. **(Figure 2)** There were 18 deaths at last follow up, with 3, 5 and 10 year overall survival (OS) of 94.2%, 92.9% and 89.2, respectively. Six patients died shortly following surgery from postoperative complications from initial tumor resection. [6-9] Nine patients died from progression of disease and continued recurrence.[2, 7, 8, 10-15] The remaining 3 patients died from causes unrelated to disease.[6, 16, 17]

Prognostic factors

Results of multivariate analysis of prognostic factors for tumor recurrence following resection are summarized in **Table 2**. Greater extent of tumor resection (HR 0.04, CI 0.01-0.25; $p < 0.0001$) strongly predicted superior rates of tumor control in multivariable analysis. Of the 172 patients receiving GTR, regardless of radiotherapy, there were 24 cases of tumor recurrence. **(Figure 3)** For all GTR, median time to recurrence was 168 months. Mean follow up for the GTR group is 36.9 months. Within the GTR subgroup, 15 patients (62.5%) recurred within 24 months following resection.

Within the GTR-only group without adjuvant therapy, there were 19 out of 156 recurrences (12.2%). Of the 48 patients receiving STR, either with or without RT, there were 26 cases of tumor progression (54.2%) at last follow-up. Median follow up within this group was 36.5 months. Median time to recurrence for all STR and GTR, regardless of adjuvant RT, was 40 and 168 months, respectively ($p<0.001$). On subgroup analysis of surgery only patients, EOR remained a robust prognostic factor (p=0.0002), **(Figure 4)**.

Additionally, higher MIB-1 labeling Index (MIB-LI) (≥5% vs<5%) was associated with increased rates of recurrence (HR 7.08, CI 1.43-35.02; p=0.016) **(Figure 5).** While there was no differences in tumor size based a MIB-LI cut off of 5%, those with higher proliferation indexes tended to be younger, with mean ages of 46.0 vs 54.1years, (p=0.018). There were 15 (17.2%) and 13 (35%) recurrences within the low and high MIB-LI groups, respectively. Median time to progression was 81 and 168 months (p=0.036) within the high and low MIB-LI groups. Within the 24 patients that recurred following GTR, 15 of these patients recurred within a 24 month time span. Time to recurrence for the remaining 9 patients was 90.4 months. Mean MIB-LI was 10.3% and 2.7% for the early and late recurrence groups respectively (p=0.016).

Of the other covariates within our multivariate analysis, adjuvant RT did not improve rates of tumor control (p= 0.633). There was no differences in age (p=0.33), size (p=0.58) or MIB/Ki-67 (p=0.50) between those who did and did not receive adjuvant radiation therapy.

Additionally, age, gender, size and tumor location (skull base vs non-skull base) did not predict rates of recurrence.

Discussion

Surgery remains the mainstay of treatment for CM, with reasonable rates of long term tumor control. Overall survival at 5 and 10 years was 92.9% and 89.2% for all patients in our analysis. Despite an apparent slow growing course, recurrence remains high following subtotal resection. Our review of literature corroborates the relationship between EOR and local tumor control in the surgical management of CMs as previously reported.[2, 3, 6, 7, 18-20] While the majority of reports were single case studies and small retrospective series, our systematic review demonstrates that GTR results in better rates of long term tumor control (5- and 10-year PFS of 80.2 and 70.3%, respectively). Thus, GTR is the goal for the surgical management of primary CMs and remains the strongest predictor of long term rates of tumor progression. [2, 8] However, complete resection may not always be safely achievable, and may depend on a number of factors such as tumor location and involvement of neurovascular structures. While GTR was achieved in a majority of cases within our review (78.2%), lower rates of GTR were achieved in tumors of the skull base (64.7%), as expected.

In one of the larger studies to date, Couce et al. reviewed 42 CMs and reported 14 recurrences (39%) in patients with 1-16 years of follow up.[2] All 13 patients who had a STR had tumor recurrence at last follow up, while only 1 out of the 29 patients receiving GTR recurred. [2] Smaller retrospective series have similar outcomes following GTR. In a recent study, Zhu et al. reviewed the outcomes of 17 patients with CM. Excluding 1 patient with postoperative mortality, there was only 1 recurrence following GTR.[8] However, as with the majority of other published series, the study was underpowered for a comparison based on EOR. Whether resection of affected bone and dura (Simpsons grade I vs II) has prognostic significance remains unclear, as distinctions between Simpsons grading were inconsistently and incompletely reported in literature, precluding a meaningful analysis.

Adjuvant RT for atypical meningiomas has mainly been utilized in the management of residual disease following subtotal resection[9, 21-23]. Given the increased rates of tumor recurrence compared to benign meningiomas, some authors have advocated the use of postoperative RT regardless of EOR to minimize risk of recurrence. [7, 24] However, its role is less clear in the specific management of chordoid meningiomas. Within a series of 30 patients with CM, Wang et al noted a trend towards improved tumor control following adjuvant RT. Rates of tumor recurrence with and without RT were 11.1% and 22.2%, and 5 year PFS rates were 80.0% and 63.0%, respectively. However, differences were not statistically significant.[7] While some case studies have advocated for the role of RT [9, 15, 25, 26], our multivariate analysis did not demonstrate a benefit with adjuvant RT. The rarity of this entity has limited the accumulation of experience in the literature, and larger prospective studies will be needed to further delineate the role of RT, including timing and modality. Presently, the role of RT should depend on factors including extent of resection, MIB-1 proliferation, and both patient and physician preference.[9, 27]

The MIB-LI is a histological marker for proliferative capacity, and correlated with rates of tumor control within our review. Higher MIB-LI has been noted to correlate with recurrent meningiomas [28-30], and has also been correlated with increasing WHO grade, with up to 1.35% for benign, up to 9.3% for atypical and up to 19.5% for anaplastic meningiomas.[12, 29, 31, 32] Despite this established trend, MIB-LI for CMs in the literature have been controversial for 2 reasons: reported ranges of MIB-LI are highly variable within studies, and a lack of correlation with outcomes. Couce et al reported a mean MIB-LI of 5.2% with a range of 0.4-11.4%.[2] Wang et al similarly reported a mean MIB-LI of 2.0% in 30 patients with a range of 1-10%, and found no correlation with outcomes.[7] Di Ieva et al. reported a mean MIB-LI of 2.3% in 9 patients, with a range of 0.6-6.5%, and found no correlation with recurrence.[9] Recently, Jee et al reported a mean MIB in 11.56% in 16 patients, ranging from 1-26.6%, without correlation to clinical outcomes.[12] Our data reflect the high variability reported in literature, with a mean MIB-LI of 4.4 and a wide range of 0.1-26.6%.

The high variability of MIB-LI in may suggest that CMs comprise a diverse group of tumors with variable clinical behaviors. While the rarity of this tumor has limited smaller retrospective studies from establishing its prognostic significance, MIB ≥ 5.0% strongly predicted recurrence within our multivariate analysis. The majority of recurrences following GTR occurred within 24 months following resection, suggesting that these early recurrences comprise a more clinically aggressive group of tumors. Indeed, those early recurrences had a significantly higher MIB-LI compared to the late recurrences group, and the time to recurrence varied drastically between the early and late recurrences. Thus, the use of MIB-LI can be used to risk stratify those patients, following resection, who are at higher risk for early recurrences and warrant closer clinical follow up.

Extent of chordoid composition has been another histological feature suggested to be correlated with outcomes in select reports. A series reported by Lin et al. (2012) composed of 17 patients noted that in 12 patients with tumors harboring greater than 50% chordoid features, 9 (75%) underwent recurrence. In contrast, only 1 (20%) patient out of 5 with chordoid features less than 50% recurred. Statistical analysis in their series noted that tumors with a chordoid element ≥50% was statistically significant in its association with recurrence (p=.049). Our review included 114 patients who had a defined chordoid component to their CM. We noted that a chordoid element greater or equal to 50% was not correlated to recurrence on multivariate (p=.481) or univariate (p=.871) analysis. Other important histological variables such as necrosis and mitotic count were only mentioned in a few select studies and they were not included in our analysis. Additionally, some reports noted the presence of lymphocytic infiltrates but they were reported in a non-uniform manner with some studies simply stating that there was minimal, mild, or moderate associated infiltration while other studies just stated that they were present.

There are a few important limitations of our study worth noting. A limitation of this study is derived from reports generated near the time the term CM was coined. Other papers may have reported cases of CM but not utilized the nomenclature, these studies would have failed to show up on our search. As a retrospective review, this analysis carries biases inherent to studies of this nature. Reporting of select measures, including tumor size, volume, MIB-LI, and radiographical features were not completely and consistently reported in all studies

included within our study. Consequently, features with either heterogeneous or insufficient reporting were excluded within our multivariate analysis. Similarly, length of follow up was highly variable between published reports, which may limit our assessment of clinical course of these tumors in the long term. However, our study, the largest comprehensive review of literature to date, provides valuable insight into the clinical and prognostic features of chordoid meningiomas that smaller studies cannot due to the rarity of these tumors.

Conclusion

CMs comprise a rare subtype of WHO grade II meningiomas. This study reviewed all reported cases of CMs within literature and represents the largest series to date on these rare tumors. Within our series, GTR resection strongly predicted improved rates of tumor control, and should be the primary goal in the surgical management of these neoplasms to minimize local progression. GTR was able to achieve acceptable rates of long term tumor control. Additionally, higher MIB-LI was associated with increased rates of tumor recurrence. Other factors including patient age, extent of chordoid component, and tumor location were not predictive of recurrence following surgery. The role of adjuvant radiotherapy remains controversial. While its utility in the management of atypical meningiomas in general has been establish, the optimal use of RT in CMs remains unclear and may be indicated in patients with subtotal resection and higher MIB-LI. Indeed these two significant prognostic factors may identify a subset of patients in which closer long term follow up is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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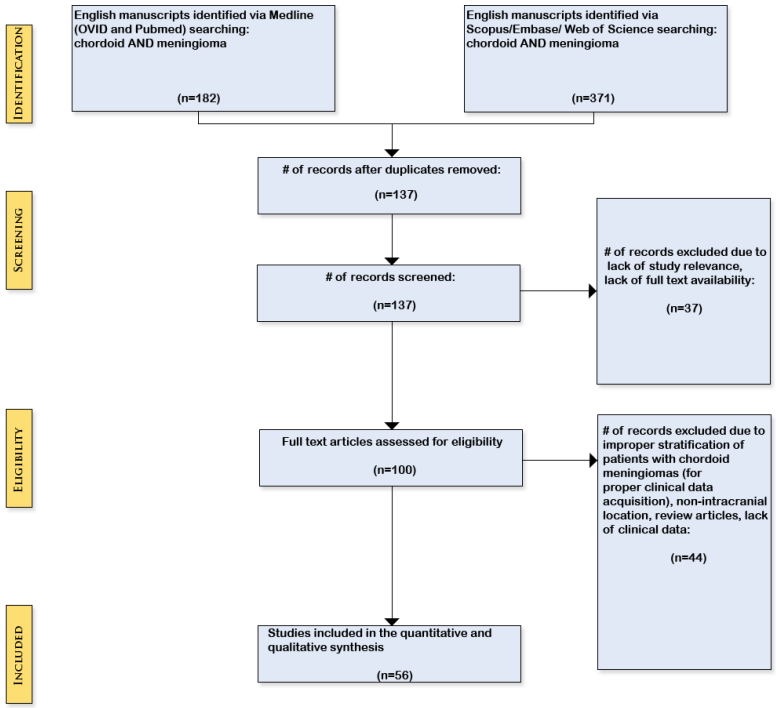

Figure 1.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

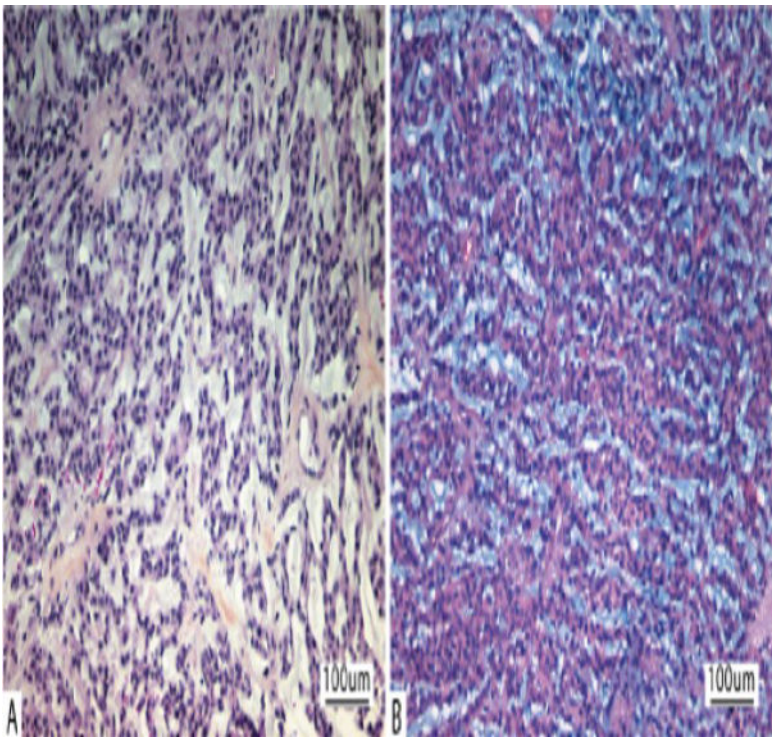

Figure 2.

Kaplan Meier curve for all patients included within the study. 3- and 5- year PFS was 76.0% and 67.5%, respectively.

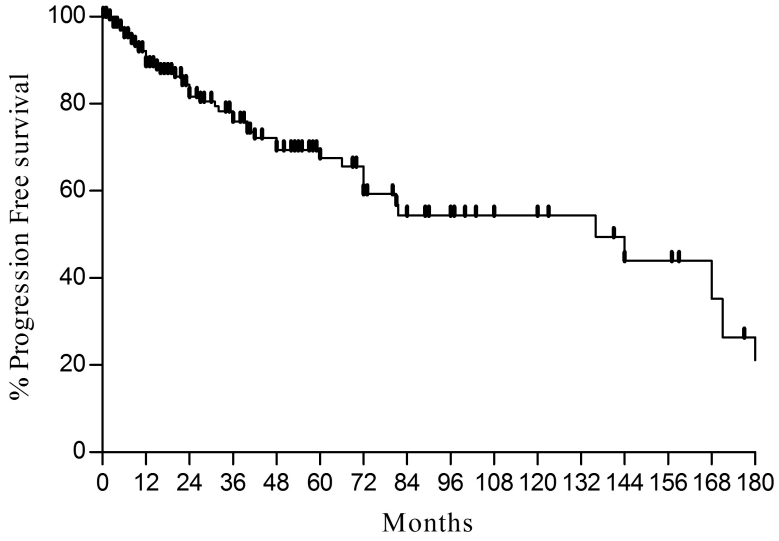

Figure 3.

Kaplan Meier analysis of recurrence free survival following either gross (GTR) to subtotal (STR) resection. Greater extent of surgery was associated with improved rates of tumor control. For GTR, 3- and 5- year PFS was 85.3% and 80.8%, respectively. For STR, 3- and 5- year PFS was 50.7 and 33.8%, respectively, $p < 0.001$.

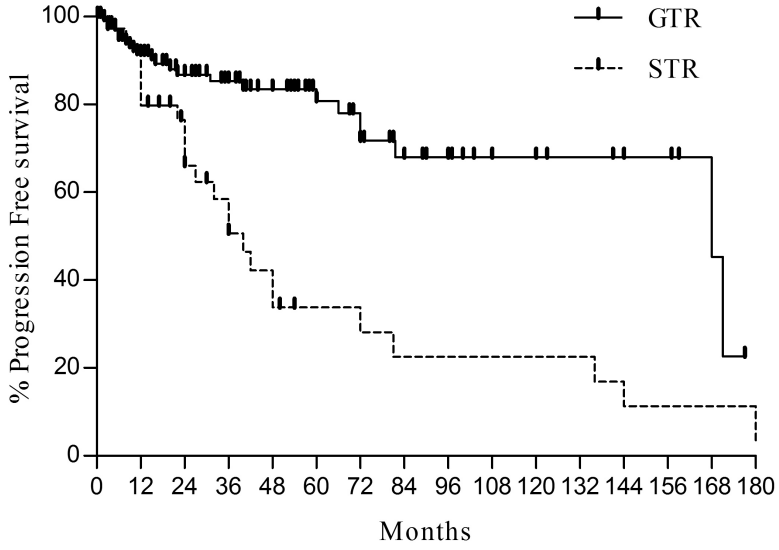

Figure 4.

Kaplan Meier analysis of recurrence free survival for patients who have undergone surgery only without adjuvant radiotherapy. Greater extent of surgery was associated with improved rates of tumor control. For GTR only, 3- and 5- year PFS was 86.4% and 83.5%, respectively. For STR only, 3- and 5- year PFS was 53.3% and 29.6%, respectively, $p < 0.001$.

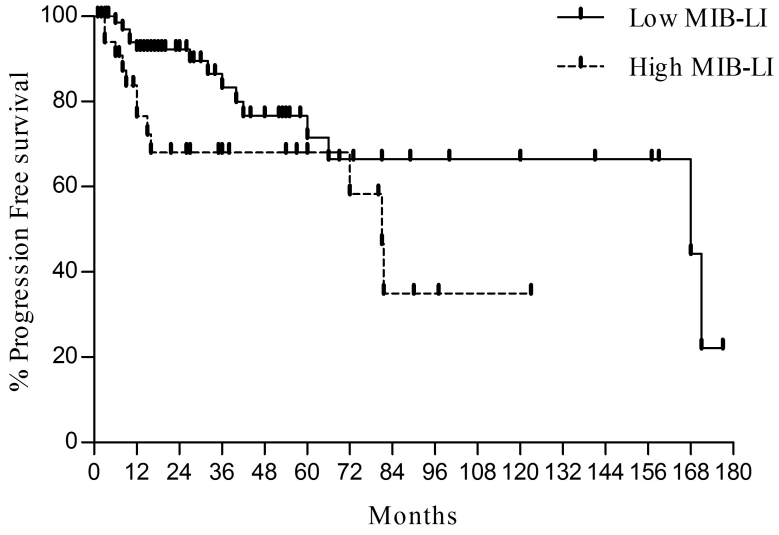

Figure 5.

Kaplan Meier analysis of recurrence free survival based on MIB Labeling index (<5% vs ≥5%). Higher MIB-LI was associated with poorer rates of tumor control. Within the low MIB-LI group, 3- and 5- year PFS was 83.3% and 71.5%. Within the high MIB-LI group, 3- and 5- year PFS was 68.0% and 68.0%, respectively p= 0.03.

Table 1

Clinical features of included patients from studies which met inclusion criteria

Author (year)	N	Mean Age	Extent of Resection	Patients undergoing RT†	Number of recurrence	Deaths
Di Ieva et al. (2014)[9]	9	60	GTR (n=5) STR (n=3) NA (n=1)	0	3	1
Jee et al. (2014)[12]	16	42	GTR (n=14) STR (n=2)	6	6	1
Lee et al. (2014)[33]	1	17	STR	0	0	0
Duric et al. (2014)[34]	1	13	GTR	0	1	0
Yang et al. (2013)[35]	1	20	GTR	0	0	0
Sriram et al. (2013)[36]	1	38	STR	0	0	0
Passacantilli et al. (2013)[37]	7	52	GTR (n=5) STR (n=2)	1	2	0
Lee et al. (2013)[38]	1	23	GTR	0	0	0
Wang et al. (2013)[7]	30	48	GTR (n=5) STR (n=5)	9	1	2
Zhu et al. (2013)[8]	17	51	GTR (n=15) STR (n=2)	4	1	1
Nambiar et al. (2012)[26]	1	11	GTR	0	1	0
Xi et al. (2012)[39]	1	66	GTR	0	0	0
Lin et al. (2012)[16]	17	57	GTR (n=13) STR (n=4)	1	9	3
Zhao et al. (2011)[40]	1	42	GTR	0	0	0
Campos-Franco et al. (2011)[41]	1	59	GTR	0	1	0
Kaloshi et al. (2011)[42]	2	48	GTR (n=2)	0	0	0
Malloy et al. (2011)[43]	1	51	STR	1	0	0
Jeon et al. (2010)[44]	1	15	GTR	0	0	0
Lin et al. (2010)[6]	11	61	GTR (n=9) STR (n=2)	0	2	2
Wind et al. (2010)[45]	1	23	GTR	0	0	0
Kano et al. (2009)[10]	1	64	STR	1	1	1
Fukushima (2008)[46]	1	22	STR	0	0	0
Song (2008)[47]	1	12	GTR	0	0	0
Scott (2008)[48]	1	44	STR	1	0	0
Kozler (2008)[5]	2	44	GTR (n=2)	0	0	0
Marhx-Bracho (2008)[49]	1	4	GTR	0	0	0
Liu (2007)[50]	2	34	GTR (n=2)	0	0	0
Lui (2007)[51]	4	61	GTR (n=1) STR (n=3)	3	0	0
Hasegawa (2006)[17]	1	77	GTR	0	0	1

Author (year)	N	Mean Age	Extent of Resection	Patients undergoing RT†	Number of recurrence	Deaths
Barresi (2006)[11]	1	75	GTR	0	0	1
Mullassery (2006)[15]	1	12	GTR	1	1	1
Donato (2006)[52]	1	55	GTR	0	1	0
Epari (2006)[3]	12	32	GTR (n=11)	0	0	0
			STR (n=1)			
Takei (2006)[53]	1	45	STR	0	0	0
Matyja (2006)[54]	2	47	GTR	2	0	0
Mitsuhashi (2006)[55]	1	69	GTR	0	0	0
Purkayastha (2005)[56]	2	18	GTR (n=2)	0	0	0
McIver et al. (2005)[20]	1	23	STR	0	0	0
Denaro et al. (2005)[57]	1	30	GTR	0	0	0
Arima et al. (2005)[19]	1	37	GTR	0	0	0
Ozen et al. (2004)[58]	1	48	GTR	0	0	0
Murali et al. (2004)[59]	1	61	STR	0	0	0
Varma et al. (2003)[60]	2	25	GTR (n=2)	0	0	0
Yeon et al. (2003)[61]	1	33	GTR	0	0	0
de Tella et al. (2003)[14]	2	36	GTR (n=1)	0	1	1
			STR (n=1)			
Haque et al. (2002)[62]	1	34	GTR	0	0	0
Mori et al. (2001)[63]	1	62	GTR	0	0	0
Lee et al. (2001)[64]	1	55	GTR	0	0	0
Wada et al. (2000)[65]	1	45	GTR	0	0	0
Yano et al. (2000)[66]	1	44	GTR	0	0	0
Couce et al. (2000)[2]	40	48	GTR (n=28)	0	13	2
			STR (n=12)			
Kobata et al. (1998)[67]	1	15	GTR	0	0	0
Kumar et al. (1996)[13]	1	5	GTR	0	1	1
Glasier et al. (1993)[68]	1	15	GTR	0	0	0
Kepes et al. (1988)[4]	7	15	GTR (n=5)	0	0	2
			STR (n=2)			

Abbreviations: GTR=Gross Total Resection/STR=Subtotal Resection/ RT=radiotherapy/n = number of patients

†Radiation soon after initial resection

Table 2

Summary of Patient Demographics

	Mean
Gender	
Male	120
Female	101
Age (years)	45.6
MIB-LI	4.34
Tumor size (cm)	4.14
Treatment	
GTR	156
GTR + RT	16
STR	34
STR + RT	14
Follow up (months)	36.5
Death	18
Recurrence	51

Table 3

Multivariate analysis of factors predicting rates of recurrence

Prognostic factor	HR	CI	P
Age <50 vs >50 years	1.36	0.33-5.46	0.665
Size ≤3.5 vs> 3.5	0.89	0.21-3.74	0.869
GTR vs STR	0.04	0.01-0.25	<0.0001
Radiotherapy	1.49	.29-7.68	0.633
MIB-LI >=5 vs <5	7.08	1.43-35.02	0.016
Skull Based Location	0.74	0.17-3.31	0.695