Published in final edited form as:

J Neurosurg. 2009 September ; 111(3): 464–471. doi:10.3171/2009.2.JNS08877.

Bone Involvement Predicts Poor Outcome in Atypical Meningioma

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Abstract

Object—Identify clinical features associated with progression and death in atypical meningioma.

Methods—Forty-seven cases of primary atypical meningioma treated at Massachusetts General Hospital were retrospectively evaluated for clinical features. Associations with progression free survival (PFS) and overall survival (OS) were assessed.

Results—The estimated median PFS was 56 months (95% CI: 35-not estimable [NA]). Overall 3-year and 5-year PFS rates were 65% (95% CI: 44%-80%) and 48% (95% CI: 26%-67%), respectively. The median survival time and 5- and 10-year survival rates were 158 months (95% CI: 103-NA), 86% (95% CI: 69%-94%) and 61% (95% CI: 35%-79%), respectively. Subtotal versus gross total resection was associated with increased rate of progression ($p = 0.05$) and trended toward an association with decreased survival ($p = 0.09$). Bone involvement was associated with increased rate of progression ($p = 0.001$) and decreased survival ($p = 0.04$). Bone involvement remained significantly associated with progression after Bonferroni adjustment for multiple comparisons ($p = 0.008$) and in bivariate Cox regression models. Seventy-eight percent of patients with bone involvement at primary diagnosis recurred within bone whereas only 25% of patients without evidence of bone invasion at primary diagnosis experienced osseous recurrence.

Conclusions—Osseous involvement is associated with poor outcome in atypical meningioma and stresses the importance of bone assessment. Further investigation is warranted to assess the effectiveness of bone resection and/or bone-directed radiation therapy in improving outcome.

Keywords

atypical meningioma; bone invasion; subtotal resection; progression; survival

Meningiomas comprise up to 30% of intracranial neoplasms [1–3]. Approximately 10–40% of meningiomas correspond to atypical (grade II) and anaplastic (grade III) subtypes, which are associated with less favorable clinical outcomes [4–6]. These non-benign subtypes have been associated with two-fold increased relative risk of local failure and four-fold relative excess risk of death [7,8]. Among them, the atypical subtype (AtM; grade II) comprises up to 35% of meningiomas [3,6,9,10]. By the World Health Organization (WHO) criteria, grade II

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atypical meningiomas exhibit at least four mitotic figures per ten high-power fields or have at least three other histologic features associated with higher grade, including architectural sheeting, necrosis, prominent nucleoli, hypercellularity and high nuclear:cytoplasmic ratio. WHO grade III malignant meningiomas exhibit frank histological malignancy or twenty mitotic figures per 10 high-power fields. According to the 2000 and 2007 WHO classifications, brain invasion does not necessarily imply WHO grade III meningioma; in the absence of frank anaplasia, meningiomas exhibiting brain invasion behave most like atypical meningiomas [11]. These changes in the WHO grading system have resulted in increased diagnosis of the atypical subtype [3,6,10–12]. For example, upon re-assigning grade based on WHO 2000 criteria versus WHO 1993 criteria, 35% of previously diagnosed grade III meningiomas were re-assigned to grade II whereas few original grade II meningiomas had to be re-assigned [13]. Hence, understanding the pathogenesis and clinical course of the atypical subtype is of increasing importance.

AtM is characterized by heterogeneous treatment response whereas outcomes for the rarer anaplastic (malignant; grade III) subtype are uniformly poor [1,2,9]. A retrospective review of atypical and anaplastic meningiomas found that 50% of 108 patients responded just as well to treatment as those with benign tumors, 25% progressed slowly from atypical to anaplastic pathology and death, and 25% precipitously declined [5]. Progression free survival at 5 years after definitive treatment has been reported to be 20%-50% when atypical and anaplastic meningiomas are combined and 38%-62% when AtM is evaluated alone [1,2,14]. In addition, AtM is associated with 57% cause specific survival at 15 years, compared to 86% for benign meningioma [15]. Given the broad range of reported outcomes after radical surgery, it remains unclear which AtMs will recur and which patients will benefit from additional treatment options such as adjuvant postoperative radiation therapy. Such knowledge would help guide management, decrease inappropriate treatment, minimize treatment failure and reduce undue treatment-related toxicity. This study therefore sought to identify clinical features associated with tumor progression and death in AtM.

Clinical Methods and Materials

The Massachusetts General Hospital Brain Tumor Repository contained 85 cases of AtM treated surgically between August 1987 and September 2006. Thirty-eight cases were excluded for the following reasons: recurrent tumor (23 cases), history of prior irradiation (8 cases), lack of follow-up (6 cases), age < 18 years (1 case). For each of the remaining 47 cases, the diagnosis of AtM was confirmed by review of hematoxylin and eosin-stained sections, and hospital records, operative notes, office notes, pathology reports and neuroradiology reports were reviewed. Comorbidities at initial diagnosis were scored in a weighted scale as follows: cardiovascular disease, cerebrovascular disease and cancer were each given a score of 3; cardiovascular/cerebrovascular/cancer risk factors were each given a score of 1 [16]. No major pulmonary, hepatic or renal disease was present in this cohort.

Tumors were classified into the following locations based on neuroradiographic findings and operative notes: convexity, parasagittal region, falx, olfactory groove, sphenoid region, orbit, skull base (not otherwise specified), and cerebellopontine angle. Extent of resection was documented as gross total or subtotal (GTR vs STR) based on the surgeon's impression in the operative report with post-operative radiographic confirmation of absence or presence of residual disease. The GTR designation included Simpson grade I-III excisions. STR denoted Simpson grade IV excision. Bone involvement and parenchymal brain involvement were coded as positive if described in neuroradiographic, operative and/or pathology reports.

The primary endpoint was progression free survival (PFS), calculated from date of primary surgery until the date of first documented radiographic recurrence of tumor after GTR or growth

of residual disease after STR. This was determined on contrast-enhanced magnetic resonance imaging (MRI) or, less commonly, computed tomography (CT) evaluation. Patients not having experienced progression were censored at the date of most recent available neuroradiographic imaging. PFS was never censored by a death time; when censored, it was always at a date of last imaging. The secondary endpoint was overall survival measured from the date of primary surgery to the date of death as recorded in the Social Security Death Index (SSDI). Patients not recorded as having experienced death were censored at the date of latest SSDI search (May 1, 2007). For patients not recorded as having died, SSDI search was performed again 10 months after the initial search to account for the possible latency of data entry into the SSDI; no additional deaths were recorded during this 10 month interval. Survival of the one patient without a Social Security number was confirmed by date of most recent clinical follow-up.

Statistical analysis

Associations between bone involvement and other clinical features at diagnosis were assessed using Fisher's exact test. Distributions of time to progression and time to death were estimated using the Kaplan-Meier method and compared between independent groups using the log-rank test. Unadjusted p-values are reported; Bonferroni adjustment requires multiplication by eight. Median follow-up times for radiographic progression and overall survival were estimated using the Kaplan-Meier method, with progression and death serving as "censoring" variables in these analyses. Univariate Cox proportional hazards models were fit to assess the impact of clinical features at surgery on progression and death. Bivariate models that included bone involvement and each of the remaining clinical features, one at a time, were fit to assess the association of bone involvement with outcome, after adjusting for the other features. Larger multivariate models were not considered because of the relatively small sample size. Kaplan-Meier estimates were calculated using GraphPad Prism version 5.0 software (San Diego, CA). Fisher exact tests and Cox model analyses were performed using the R programming language (<http://www.r-project.org/>).

Results

Patient and tumor characteristics

The 47 AtM cases consisted of 25 males (53%) and 22 females (47%) (Table 1). Ninety percent of patients (42/47) were Caucasian. Median age at diagnosis was 59 years (range, 31–90 years). Seventy-four percent (34/46) of patients had no or only minor comorbidities (comorbidity score 0, 1). Twenty-six percent (12/46) of patients had multiple/major comorbidities (comorbidity scores >1). Information about tumor size was available in the neuroradiology or operative reports for 41/47 cases. Median tumor diameter was 5.5 cm (range, 2–11.6 cm) based on these reports. The majority of tumors were located in the convexity (28%) and parasagittal (28%) regions. Other regions of involvement included the falx (17%), sphenoid (15%), skull base (6%), olfactory groove (2%), orbit (2%) and cerebellopontine angle (CPA; 2%). GTR was achieved in 74% of cases (35/47), compared with 26% (12/47) STR. Bone involvement was documented in 32% of cases (15/47). Radiographic evidence of bone involvement included hyperostosis, bone sclerosis and/or osteolytic lesions. Intraoperative evidence of bone involvement included hyperostosis, extension of tumor mass into bone, and/or bony destruction. Bone samples were sent for histopathologic evaluation in 8/15 cases of bone involvement, with 100% concordance. Brain invasion was noted in only 4% (2/47). Adjuvant postoperative radiation therapy was performed in 23% of cases (11/47). Fifty-nine percent (28/47) of patients received no radiation therapy and 18% (8/47) of patients received only salvage radiation therapy for disease progression.

Univariate analysis of factors in relation to radiographic progression

Median radiographic follow-up was 29 months (95% CI: 24-55). Thirteen patients experienced radiographic progression (Table 2). The estimated median PFS time for all subjects was 56 months (95% CI: 35-not estimable [NA]). Three-year and 5-year PFS rates for the entire cohort were 65% (95% CI: 44%-80%) and 48% (95% CI: 26%-67%), respectively. STR was associated with increased rate of progression compared with GTR ($p = 0.05$; Figure 1A; Table 2). Four of 12 cases progressed after STR, with a corresponding median PFS time of 32 months (59% CI: 17-NA), a PFS rate of 30% at 3 years (95% CI: 1%-71%). In contrast, 9/35 cases progressed after GTR, with median PFS time not estimable, a PFS rate of 73% (95% CI: 49%-87%) at 3 years and a PFS rate of 53% (95% CI: 28%-73%) at 5 years. Patients had a 72% lower instantaneous risk of progression after GTR compared to STR [hazard ratio: 0.28; 95% CI: 0.08-0.99]. Evidence of bone involvement was also associated with increased rate of progression ($p = 0.001$; Figure 1B; Table 2). Nine out of 15 cases with bone involvement progressed, with corresponding median PFS time of 32 months (95% CI: 23-51), PFS rate of 33% (95% CI: 8%-62%) at 3 years and PFS rate of 17% (95% CI: 1%-49%) at 5 years. In contrast, 4/32 cases without evidence of bone involvement progressed, with median PFS time not estimable, PFS rate of 83% (95% CI: 55%-95%) at 3 years and PFS rate of 76% (95% CI: 46%-91%) at 5 years. Patients with bone involvement experienced a seven-fold increased instantaneous risk of progression [hazard ratio: 7.06; 95% CI: 2.13-23.38]. Pattern of failure analysis revealed that 78% (7/9) of patients with evidence of bone invasion at primary diagnosis recurred within bone. In contrast, only 25% (1/4) of patients with no evidence of bone invasion at primary diagnosis exhibited bone involvement at recurrence. Gender, age at diagnosis, comorbidity, tumor size, tumor location and adjuvant radiation therapy revealed no significant association with radiographic progression.

Univariate analysis of factors in relation to overall survival

Median follow-up for survival was 66 months (95% CI: 54-96). Ten patients died during the follow-up period (Table 3). The median survival time and 5- and 10-year OS rates for the entire cohort were 158 months (95% CI: 103-NA), 86% (95% CI: 69%-94%) and 61% (95% CI: 35%-79%), respectively. Age ≥ 65 years at diagnosis was associated with decreased OS ($p = 0.02$) (Figure 2). Six of 15 patients died in the ≥ 65 year old group with a median survival time of 102 months (95% CI: 52-NA), OS of 62% (95% CI: 13%-82%) at 5 years and OS rate of 41% (95% CI: 8%-73%) at 10 years. In contrast, 4/32 patients died in the < 65 year old group with a median survival time of 158 months (95% CI: 107-NA), OS rate of 100% at 5 years and OS rate of 73% (95% CI: 36%-91%) at 10 years. Patients ≥ 65 years old at diagnosis experienced five-fold increased instantaneous risk of death [hazard ratio: 5.50; 95% CI: 1.36-22.36]. The presence of major or multiple comorbidities (comorbidity score > 1) was associated with decreased OS compared (comorbidity score ≤ 1) ($p = 0.02$). Four of 12 patients with major/multiple comorbidities died during the follow-up period with a median survival time of 107 months (95% CI: 57-107), OS rate of 63% (95% CI: 17%-88%) at 5 years. In contrast, 6/35 patients without major/multiple comorbidities died over the follow-up period. This corresponded to a median survival time of 158 months (95% CI: 103-NA), OS rate of 92% (95% CI: 73%-98%) at 5 years and OS of 71% (95% CI: 42%-88%) at 10 years. Patients with major/multiple comorbidities at diagnosis experienced five-fold increased instantaneous risk of death [hazard ratio: 4.79; 95% CI: 1.24-18.48]. There was a trend toward an association between STR and decreased survival ($p = 0.09$; Figure 2A; Table 3). Four out of 12 patients receiving STR died over the course of follow-up compared with 6/35 patients who received GTR. Median survival time, OS rates at 5 years and OS at 10 years for STR compared with GTR were 107 months (95% CI: 50-NA) versus 158 months (95% CI: 107-NA), 77% (95% CI: 31%-94%) versus 89% (95% CI: 69%-96%) and 25% (95% CI: 1%-66%) versus 74% (95% CI: 45%-89%), respectively. Patients experienced 68% decreased instantaneous risk of death after GTR compared with STR [hazard ratio: 0.32; 95% CI: 0.09-1.21]. Evidence of bone

involvement was associated with decreased OS compared to absence of bone involvement ($p = 0.04$; Figure 2B; Table 3). Seven of 15 patients with bone involvement died during the follow-up period resulting in a median survival time of 103 months (95% CI: 78-158), OS rate of 83% (95% CI: 47%-96%) at 5 years and OS rate of 28% (95% CI: 4%-60%) at 10 years. In comparison, the median survival time was not estimable for patients without bone involvement; and 5-year and 10-year OS rates were 88% (95% CI: 67%-96%). Patients with bone involvement experienced a four-fold increased instantaneous risk of death [hazard ratio: 4.09; 95% CI: 1.05-15.89]. Gender, tumor size, tumor location and adjuvant radiation therapy revealed no significant effect on survival.

Regression analysis of bone involvement and other factors

Regression analyses focused on the strong univariate finding of bone involvement (Table 4). First, Fisher's exact test revealed that none of the other baseline factors were significantly associated with bone involvement. Bivariate Cox models for progression and survival were fit one at a time for bone involvement and each of the other predictors. This was selected over more detailed multivariate analysis because of the relatively small number of events. Bone involvement remained significantly associated with progression in these models. This is also illustrated in Kaplan Meier curves grouped according to bone involvement and extent of resection, and analyzed by a stratified log rank test (Figure 3).

Discussion

This retrospective study to identify clinical features associated with progression and death in AtM reveals that bone involvement is associated with increased tumor progression and decreased overall survival. Furthermore, subtotal resection is associated with increased tumor progression and possibly with survival. Gender, age at diagnosis, tumor size, and tumor location are not significantly associated with progression in this cohort. Age and multiple/major comorbidities at diagnosis are associated with decreased survival but are not significantly associated with progression. Among all of these findings, only the association between bone involvement and progression is retained after Bonferroni adjustment for multiple comparisons. Adjuvant postoperative radiation therapy is not significantly associated with progression or survival in this cohort; however, the sample size is small and mostly patients with high-risk features, such as subtotal resection, were given immediate postoperative radiation.

The importance of extent of resection in outcome for meningioma has been well established [1,5,17,18]. Simpson's retrospective study graded meningiomas of various histologies based on degree of surgical excision and reported 5-year recurrence rates of 9% for GTR including surrounding dura and bone (grade I resection), 16% for GTR involving dural cauterization (grade II resection), 29% for GTR with microscopic residual disease (grade III resection), 49% for extended biopsy with macroscopic resection (grade IV resection), and 77% for simple decompression with or without biopsy (grade V resection). Although the series was reported prior to the advent of CT, MRI and microsurgery, the importance of extent of resection on outcome has been confirmed in multiple modern series [1,5,18].

With respect specifically to non-benign meningiomas, Palma *et al* conducted a retrospective study of 42 cases of atypical and 29 cases of malignant meningioma, revealing that radical resection (Simpson grade I vs. II-III) and histology (AtM vs. malignant meningioma) were significantly related to progression and survival [5]. Many of the "malignant" cases were classified based on the presence of brain invasion and, hence, may actually represent AtMs based on current WHO classification. Outcomes with AtMs were heterogeneous and after incomplete surgical excision patients with AtMs fared only marginally better than those with malignant meningiomas. Therefore, although the prognosis with AtM was better than with malignant meningioma, the risk of poor outcome after incomplete resection was substantial.

In a subsequent retrospective study of 22 patients with AtM, Goyal *et al* (2000) reported 87% local control at 10 years after GTR compared to 17% after STR [1]. GTR in their study was comprised entirely of Simpson grade II or III resection. Several studies suggest that Simpson grade II or III excision is sufficient for durable local control and many studies classify Simpson grade I-III resection into one category of complete resection [1,15]. This may have resulted in clinical practice in which treatment of bone has become less aggressive. The current study supports the conclusion that extent of resection is an important predictor of outcome and suggests that Simpson grade I resection may need greater consideration for better disease control.

Meningioma has long been known to induce changes in adjacent bone, including hyperostosis and direct invasion [19,20]. Although some studies have implicated hyperostosis as a secondary manifestation involving humoral mechanisms without neoplastic invasion [21,22], the evidence indicates that it results from direct tumor invasion into bone [19,23–27]. One study postulated that the new bone growth probably results from periosteal stimulation by tumor invasion [28]. Another report correlating radiographic evidence of hyperostosis with histopathology identified tumor invasion in the resected bone biopsies of 25/26 patients with radiographically identified hyperostosis [27]. In addition, histological tumor invasion of bone was identified in 9 patients who did not show evidence of hyperostosis on preoperative neuroradiological evaluation, indicating that it is difficult to delineate the extent of bone involvement definitively even with modern radiographic techniques. Additional studies involving histopathologic examination of hyperostotic bone have revealed bone infiltration by meningioma cells in 4/5 cases [29] and 12/13 cases [30], supporting the direct tumor infiltration hypothesis of hyperostosis.

The importance of bone involvement as a prognostic factor in meningioma is not universally accepted [31]. Furthermore, the role of bone involvement in clinical outcome specifically in AtM has not previously been reported. A study of 657 patients with seemingly complete removal of histologically benign intracranial meningioma reported overall recurrence rate of 19% at 20 years [32]. Tumor attachment to bone was identified as a strong and independent risk factor for recurrence on multivariate analysis. Furthermore, another report noted that hyperostosis was a significant prognostic factor for excess mortality in patients who survived the first postoperative year [8]. This retrospective study of 936 meningioma cases revealed 67% relative survival rate at 15 years for patients with hyperostosis compared to 81% at 15 years for patients without hyperostosis. The impact of hyperostosis became apparent only after the 7th follow-up year. Patients with hyperostotic tumors lost 16% of their expected length of life and had a 2.1-fold relative excess risk of death, while those with no hyperostosis lost only 9% of their expected length of life. Except for hyperostosis, no attachment into adjacent structures proved significant for long-term survival. 4.7% (44 patients) of the patients were categorized as having AtM. Hyperostosis adjacent to the tumor was encountered in 20% of all patients. Because stratification by histologic grade was not reported, it remains unclear whether the effects of hyperostosis on survival differed between AtM and benign meningioma. The current study shows that bone involvement, including hyperostosis, is indeed associated with increased recurrence/progression and decreased survival in an AtM cohort.

The observation that bone invasion affects clinical outcome in AtM raises a number of biological possibilities. For example, worse outcomes with bone-invasive AtMs may reflect a more aggressive tumor biology compared to those that do not invade bone. Alternatively, poor outcomes may result from failure to treat diseased bone. Indeed, pattern of failure analysis in this cohort revealed osseous relapse in 78% of cases that initially involved bone compared to only 25% osseous relapse in cases that did not initially exhibit bone involvement. The majority of cases in this study were thought to have undergone gross total resection, i.e., the tumor and attached dura mater were apparently completely removed. However, surgical treatment of bone

in this cohort varied, some receiving aggressive removal and/or cranioplasty and others not. It is possible that, in cases with bone involvement, remaining tumor cells in the surrounding bone made visual estimates of complete removal misleading. Post-operative radiographic imaging may lack sensitivity to detect residual tumor cells in bone and determination of margin status in bone is not straightforward, making it difficult to assess the radical extent of bone resection. Hence, the high recurrence rates observed after surgery may reflect subclinical bony disease that would be best addressed with adjuvant radiation therapy with fields encompassing surrounding bony areas. None of the cases with bone involvement received post-operative radiation directed specifically to the remaining bone.

The presence or absence of bone involvement may explain the heterogeneous treatment outcomes observed in AtM. If so, modifying clinical management to better address bony disease may be indicated. For example, patients with AtM might benefit from preoperative nuclear bone scanning or fine-cut computed tomographic imaging to better evaluate the extent of bone involvement and help guide treatment strategy. In addition, fluorescence-guided resection with 5-aminolevulinic acid may be useful to visualize minute areas of residual tumor along bone and guide complete removal [33,34]. An important future challenge in AtM management is to investigate the degree to which clinical outcome correlates with extensive bone removal and/or postoperative irradiation of the surrounding bone in cases with osseous involvement. Aggressive bone removal with wide exeresis, cranioplasty, and/or adjuvant bone irradiation could potentially improve treatment outcome in this heterogeneous disease.

Conclusion

Bone involvement is an important predictor of poor treatment outcome in AtM. Careful preoperative bone assessment and aggressive bone removal and/or adjuvant radiation therapy targeting the cranium may be warranted to decrease the risk of tumor recurrence in cases involving bone. Future investigation is warranted to assess the effectiveness of aggressive bone-directed treatment in improving the heterogeneous outcomes in this disease.

Acknowledgments

The authors thank Shumin Dong, Anna Levitz, Gayatri Mohapatra, Andrew Potts, Candice Romany, Jennifer Roy, David Sher and Abram Recht for histopathology expertise, technical support, software management and constructive comments. DG was supported by NIH T32CA09216.

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Figure 1.
Kaplan-Meier curves reveal that (A) extent of resection and (B) bone involvement are associated with progression.

Figure 2.

Kaplan-Meier curves reveal (A) a trend toward association between extent of resection and overall survival and (B) association between bone involvement and overall survival.

Figure 3.

Bone involvement (A) remains significantly associated with progression and (B) trends toward an association with survival when patients are grouped by extent of resection.

Table 1

Patient and tumor characteristics

Characteristic	Number of patients	Adj RT	No Adj RT
All	47	11	36
Gender			
Male	25 (53%)	4 (36%)	21 (58%)
Female	22 (47%)	7 (64%)	15 (42%)
Race			
Caucasion	42 (90%)	9 (82%)	33 (92%)
African American	1 (2%)	0 (0%)	1 (3%)
Asian	2 (4%)	0 (0%)	2 (6%)
Hispanic	2 (4%)	2 (18%)	0 (0%)
Median age	59 yrs (range, 31–90)	63 yrs	58 yrs
Comorbidity Score			
0, 1	34 (74%)	8 (73%)	27 (75%)
> 1	12 (26%)	3 (27%)	9 (25%)
Median tumor size	5.5 cm (range, 2 cm –11.6 cm)	6 cm	5 cm
Tumor location			
Convexity	13 (28%)	4 (36%)	9 (25%)
Falx	8 (17%)	1 (9%)	7 (19%)
Sphenoid	7 (15%)	1 (9%)	6 (17%)
Skull base	3 (6%)	1 (9%)	2 (6%)
Parasagittal	13 (28%)	3 (27%)	10 (27%)
Olfactory groove	1 (2%)	1 (9%)	0 (0%)
Orbit	1 (2%)	0 (0%)	1 (3%)
CPA	1 (2%)	0 (0%)	1 (3%)
Resection			
GTR	35 (74%)	5 (45%)	30 (83%)
STR	12 (26%)	6 (55%)	6 (17%)
Brain invasion			
Yes	2 (4%)	0 (0%)	2 (6%)
No	45 (96%)	11 (100%)	36 (94%)
Bone involvement			
Yes	15 (32%)	4 (36%)	11 (31%)
No	32 (68%)	7 (64%)	25 (69%)
RT			
None	28 (59%)	-	-
Adjuvant	11 (23%)	-	-
Salvage	8 (18%)	-	-

Table 2

Univariate analysis to evaluate factors related to progression

Factor	Patients (n)	Progressions (#)	Median TTP (mos)	3-yr PFS (%)	5-yr PFS (%)	p	HR [95% CI]
Overall	47	13	56	65	48	-	-
Gender						0.20	2.17 [0.67–7.05]
Male	25	9	51	51	32		
Female	22	4	NR	82	70		
Age						0.94	0.96 [0.31–2.95]
≥ 65 yrs	15	5	NR	63	51		
< 65 yrs	32	8	56	68	47		
Comorbidities						0.55	0.53 [0.07–4.21]
> 1	12	1	NR	89	89		
0,1	35	12	56	63	45		
Tumor size						0.83	0.88 [0.24–2.97]
< 5.5 cm	20	5	NR	82	56		
≥ 5.5 cm	21	5	56	58	44		
Tumor location						0.39	
Convexity	13	5	51	52	35		1.47 [0.48–4.51]
Falx	8	1	NR	80	80		
Sphenoid	7	1	NR	83	83		
Parasagittal	13	4	38	74	25		1.61 [0.49–5.24]
Resection						0.05	0.28 [0.08–0.99]
GTR	35	9	NR	73	53		
STR	12	4	30	25	0		
Bone involvement						0.001	7.06 [2.13–23.38]
Yes	15	9	32	33	0		
No	32	4	NR	83	76		
Adjuvant RT						0.83	0.85 [0.19–3.86]
Yes	11	2	NR	56	56		
No	36	11	56	66	47		

TTP = time to progression. NR = not reached. HR= hazard ratio. CI = confidence interval.

p-values and HRs for convexity and parasagittal locations are versus/relative to all other locations.

Table 3

Univariate analysis to evaluate factors related to survival

Factor	Patients (n)	Deaths (#)	MST (mos)	5-yr OS (%)	10-yr OS (%)	p	HR [95% CI]
Overall	47	10	158	86	61	-	-
Gender						0.11	3.54 [0.74–17.00]
Male	25	8	158	81	50		
Female	22	2	NR	92	77		
Age						0.02	5.50 [1.36–22.36]
≥ 65 yrs	15	6	102	62	41		
< 65 yrs	32	4	158	100	73		
Comorbidities						0.02	4.79 [1.24–18.48]
> 1	12	4	107	63	0		
0,1	35	6	158	92	71		
Tumor size						0.98	1.02 [0.28–3.69]
< 5.5 cm	19	5	158	93	61		
≥ 5.5 cm	22	4	NR	73	73		
Tumor location						0.71	-
Convexity	13	2	NR	89	59		0.53 [0.11–2.64]
Falx	8	1	NR	80	-		
Sphenoid	7	2	102	86	43		
Parasagittal	13	4	157	81	65	0.64	1.37 [0.38–4.95]
Resection						0.09	0.32 [0.09–1.21]
GTR	35	6	158	89	74		
STR	12	4	107	77	25		
Bone involvement						0.04	4.09 [1.05–15.89]
Yes	15	7	103	83	28		
No	32	3	NR	88	88		
Adjuvant RT						0.81	1.32 [0.14–12.19]
Yes	11	1	NR	75	-		
No	36	9	158	87	62		

MST = median survival time. NR = not reached. HR = hazard ratio. CI = confidence interval.

p-values and HRs for convexity and parasagittal locations are versus/relative to all other locations.

Table 4

Bivariate analysis of factors for radiographic progression and survival in relation to bone involvement.

Factors in Relation to Bone Involvement	Fisher's Exact Test <i>p</i>	Progression Analysis HR for BI [95% CI]	Survival Analysis HR for BI [95% CI]
Bone Involvement			
Yes vs No	-	7.06 [2.13–23.38]	4.09 [1.05–15.89]
Gender			
Male vs Female	0.22	6.6 [1.86–23.40]	3.01 [0.68–13.42]
Age			
≥ 65 yrs vs < 65 yrs	0.74	7.39 [2.18–25.11]	6.44 [1.52–27.31]
Comorbidities			
0 vs > 0	1.0	6.69 [1.92–23.30]	3.91 [0.96–15.89]
Tumor size			
< 5.5 cm vs ≥ 5.5 cm	1.0	7.46 [2.22–25.09]	4.25 [1.07–16.82]
Tumor location			
Convexity vs others	0.5	7.09 [2.14–23.50]	3.95 [0.95–16.44]
Parasagittal vs others	1.0	6.87 [2.04–23.04]	4.35 [1.04–18.31]
Resection			
GTR vs STR	0.46	6.59 [1.96–22.24]	3.5 [0.87–14.01]
Adjuvant RT			
Yes vs No	1.0	7.04 [2.13–23.29]	4.08 [1.05–15.85]