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ARTICLE

Atypical and anaplastic meningiomas in a public hospital in São Paulo State, Brazil

Meningiomas atípicos e anaplásicos em um hospital público de São Paulo, Brasil

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ABSTRACT

Atypical/anaplastic (World Health Organization (WHO) grades II and III) are less common and have poorer outcomes than benign meningiomas. This study aimed to analyze the outcome of patients with these tumors. **Method:** Overall/recurrence-free survivals (RFS) and the Karnofsky Performance Scale of 52 patients with grades II (42) and III (9) meningiomas surgically treated were analyzed (uni/multivariate analysis). **Results:** Total/subtotal resections were 60.8%/35.3%. Patients <60 years-old and grade II tumors had longer survival. Grade II tumors, total resection and *de novo* meningioma had better RFS (univariate analysis). Patients >60 years-old, *de novo* meningioma and radiotherapy had longer survival and patients <60 years-old and with grade II tumors had longer RFS (multivariate analysis). Recurrence rate was 51% (39.2% Grade II and 66.7% Grade III). Operative mortality was 1.9%. **Conclusion:** Age <60 years-old, grade II tumors and *de novo* meningiomas were the main predictors for better prognosis among patients with grades II and III meningiomas.

Keywords: atypical and anaplastic meningiomas, surgical treatment, extent of resection, survival curves, recurrence survival curves.

RESUMO

Meningiomas atipicos/anaplásticos (graus II e III da *World Health Organization* (WHO)) são menos comuns e tem prognóstico pior que os benignos. Este estudo visa analisar o prognóstico de pacientes com estes tumores. **Método:** Sobrevida/sobrevida livre de doença (SLD) e índice de Karnofsky de 52 pacientes com meningiomas graus II (42) e III (9) tratados cirurgicamente foram avaliados (análises uni/multivariada). **Resultados:** Pacientes <60 anos e com tumores grau II tiveram sobrevida mais longa. Tumores grau II , ressecção total e meningioma *de novo* tiveram melhor SLD (análise univariada). Pacientes >60 anos, meningioma *de novo* e radioterapia tiveram sobrevida mais longa e, pacientes <60 anos e com tumores grau II tiveram SLD mais longa (análise multivariada). Recidiva ocorreu em 51% (39.2% Graus II e 66,7% Graus III). A mortalidade operatória foi 1,9%. **Conclusão:** Idade <60 anos, meningiomas grau II e *de novo* foram preditores de melhor prognóstico entre pacientes com meningiomas graus II/ III.

Palavras-chave: meningiomas atípicos e anaplásicos, tratamento cirúrgico, extensão da ressecção, curvas de sobrevida, curvas de sobrevida livre de doença.

Meningiomas constitute 13 to 26% of all intracranial tumors[1,2,3,4,5] Cushing and Eisenhardt[4], described meningiomas with more aggressive histopathological characteristics and worst clinical prognosis and classified them as malignant forms. Later, D`Arrigo et al.[6] described another subgroup of meningiomas, atypical, characterized by slower growth, but, with high recurrence rates. These tumors are included in grades II and grade III of the World Health Organization (WHO) classification[1,7]; they can originate from malignant progression of a benign meningioma that accumulates mutations. Atypical and anaplastic meningiomas account for 3.0-7.2% and 0.4-3.7%[1,3,5,8,9], respectively, of intracranial meningiomas. Female predominance is less marked and there is even male predominance among them[2,8,9,10], and they are more common in the cerebral convexities[2,9,10]. Although surgery is considered the primary treatment for these forms[10,11], the high recurrence rates requires other therapeutic modalities, such as radiation therapy, and chemotherapy. This study aimed to identify factors that influence the clinical outcome of patients with atypical and anaplastic meningiomas treated at our institution.

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METHOD

Patient population

This study was a retrospective review of the medical records of 52 consecutive patients with WHO Grade II or Grade III meningiomas who underwent surgery from 1984 to 2013 at the Division of Neurosurgery, Department of Surgery, Hospital das Clinicas, Ribeirão Preto Medical School - University of São Paulo (HCFMRP-USP). The study was approved by the Ethics in Research Committee of the HCFMRP-USP (Nº 736.988, 21/07/14). These patients comprised 10% (52 of 522) of patients with intracranial meningioma treated in the same period and 75% of the cases were operated on by the senior author (BOC). Diagnosis was performed using CT and/or MR imaging of the head. Tumors were more frequently located in the parasagittal region and on the convexity (Table 1). Tumors were classified according to the 2007 histopathological WHO criteria[1,7], (slides of patients operated in the first years were reviewed). Forty-three (82.7%) patients had Grade II meningiomas (37 atypical, 3 clear cell and 3 chordoid subtypes) and nine (17.3%) had Grade III (7 anaplastic, 1 papillary and 1 rhabdoid) meningiomas. Nine (17.3%) patients had multiple meningiomas (six with two, one with three and two with five tumors). One patient with multiple meningiomas had neurofibromatosis type 2. Forty-three (82.7%) were *de novo* meningiomas and nine (17.3%) were tumors with malignant progression. Among the later, four patients progressed from grade I to atypical grade II (0.8% of grade I meningiomas) after recurrence (at 39, 45, 84, and 195 months); the earlier, first biopsies of these 4 patients had focal areas of atypia not sufficient to be considered grade II. Two patients with grade I (0.4% of grade I meningiomas) and three with atypical grade II tumors progressed (7% of grades II meningiomas) to grade III after recurrence (at 4, 5, 12, and 26 months).

Clinical findings

The most important demographic characteristics of patients are presented in Table 2 and Figure 1. There was a female predominance for all patients (1.3:1) and for patients with Grade II (1.5:1), and a slight male predominance among patients with Grade III tumors (0.8:1). The sex distribution was similar for patients with Grade II and Grade III tumors (p = 0.8732).

Age ranged from 16 to 89 years old (mean = 54.77 ± 15.91). Patients with Grade II were significantly younger than were patients with Grade III tumors (means: 53.86 vs 75.22 months, p = 0.0015, Kruskal-Wallis test, with Dunn's multiple comparison test); the same was observed for females (means: 51.96 vs 73.75 years, p = 0.0007, Kruskal-Wallis test, with Dunn´s multiple comparison test) and for males (means: 47.56 vs 76.40 years, p = 0.0034, Kruskal-Wallis test, with Dunn´s multiple comparison test). Follow-up ranged from 3 to 257 months (mean = 66.02 ± 59.96; median = 44.50 months).

The main clinical signs and symptoms at admission are summarized in Table 3. The most frequent were motor deficits, cranial nerve palsies and seizures.

Two male patients with grade II (atypical) meningiomas (falcine and petrous) underwent previous whole brain radiotherapy and chemotherapy (one 27-year-old for treatment of a medulloblastoma 8 years earlier; and another 23-year-old for lymphoid leukemia twice, 14 and 3 years earlier).

Management of the disease

Surgical Treatment: Surgery was performed using microsurgical techniques, with the aims of the most extensive safe resection possible and avoidance of new or increased neurological deficits. The extent of resection was assessed macroscopically during surgery and postoperatively using CT or MR imaging 48 hours and 6 months after operation categorized as radical removal (no evidence or doubt about residual tumor in the MR image); subtotal (resection >90%) and partial (resection was >90%).

Table 1. Location of grades II and III meningiomas in 50 patients operated on.

Location		WHO Histopathological Grades		
		Grade II	Grade III	Total
Parasagittal	Anterior Third	04		04
	Middle Third	06	01	07
	Posterior Third	01		01
Convexity	Fronto-Parietal	02	02	02
	Fronto-Temporal	01	02	03
	Parietal	04		04
Sphenoid Wing	Internal Third	02		02
	Middle Third	01		01
Diafragma Selae			01	01
Falx	Anterior Third	02		02
	Middle Third	01		01
Falco-Tentorial		01		01
Middle Fossa		02		02
Olfactory Groove		02		02

Table 2. Summary of demographic data in 50 patients with WHO grades II and III meningiomas.

Characteristic	Grade II Meningiomas atypical	Grade II Meningiomas other	Grade II Meningiomas total	Grade III Meningiomas	Total
Sex					
Female	22	5	27	4	31
Male	15	1	16	5	21
Female/male	1.5:1	5:1	1.7:1	0.8:1	1.5:1
Age (yrs)*	53.95 ± 14.70	53.33 ± 21.32	53.86 ± 15.47	75.22 ± 7.546	54.77 ± 15.91
Age range (yrs)	17-76	25-81	16-81	31-89	16-89
Female	25-64	65-68	25-68	69-81	25-81
Male	16-62	65-65	16-25	67-89	16-89
Follow-up (months)*	66.59 ± 59.85	59.17 ± 41.00	65.23 ± 57.56	78.25 ± 74.52	69.78 ± 74.20

* Values presented as the means ± standard deviation.

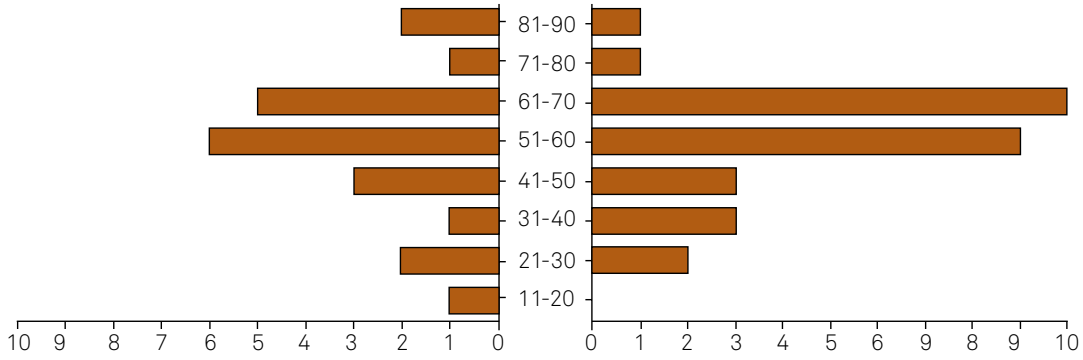

Figure 1. Age and sex distribution of WHO grades II and III meningiomas based on 50 cases treated at the Hospital das Clínicas, Ribeirão - Preto Medical School - University of São Paulo, Ribeirão Preto, São Paulo, Brazil.

Table 3. Initial signs and symptoms in 51 patients with grades II and III meningiomas.

Histological grade	OMS II	OMS III	Total
Motor deficit	9 (21.4%)	0	9 (17.7%)
Cranial nerve deficits	9 (21.4%)	3 (22.2%)	12 (23.5%)
Seizures	8 (19.1%)	1 (11.1%)	9 (17.7%)
Protusion of the skull	5 (11.9%)	0	3 (05.9%)
Intracranial hypertension	4 (09.5%)	1 (11.1%)	4 (07.8%)
Superior cortical function deficits	3 (71.4%)	0	4 (07.8%)
Headache	3 (71.4%)	2 (22.2%)	3 (05.9%)
Incidental	1 (02.4%)	2 (22.2%)	5 (09.8%)
Total	42	9	51

Twenty (36.5%) patients (16 with Grade II and 4 with Grade III meningiomas) underwent adjuvant radiotherapy. Nineteen were submitted to external beam fractionated radiotherapy and one to conformational radiotherapy (doses: 4,500 to 6,000 cGy). Twelve patients were treated after the first surgery (all Grade II) and 8 after the first recurrence.

Functional outcome

Functional outcomes were compared between patients with histopathological Grades II vs III tumors and between atypical and other subtypes of Grade II tumors. The preoperative, postoperative (first 10 days) and the follow-up outcome were analyzed using the Karnofsky Performance Scale (KPS) for 48 patients. Patients were classified into one of three functional status categories: 1) Normal function or minimal symptoms and ability to work (KPS 80-100), 2) Independent but not able to work (KPS 70), and 3) Moderate or severe disability (KPS <70. For patients with tumor recurrence and clinical deterioration, the highest KPS score obtained during the follow-up evaluations was used. Two patients did not attend the 6 months follow-up and did not receive a KPS score at this time.

Survival analysis was performed using Kaplan-Mayer overall survival (censoring event: death), and recurrence-free survival (RFS) curves (censoring event: recurrence) and rates in relation to sex, age, histopathological grade, and extent of resection, use of radiation therapy, and malignant progression.

Statistical analysis

Statistical analyses was performed using the Chi-square and Fisher's exact tests to compare proportions, the Kruskall-Wallis non-parametric test and the analysis of variance (ANOVA) to compare medians, and the log-rank test to compare overall and RFS curves using the Graph Pad PRISM (version 3.0; Graph Pad Software Inc. San Diego, CA). Multivariate analysis for selected clinical variables was performed using Cox-Regression (SPSS-Version 21.0, IBM Corporation, Armonk, NY). An α-error probability not exceeding 5% was considered significant for two-tailed probability tests.

RESULTS

Summary of surgical treatment

Thirty-five (67.3%, 29 Grade II/6 Grade III) patients underwent radical tumor resection, fourteen (26.9%, 10 Grade II/4 Grade III) had subtotal and three (5.8%, Grade II) had partial resection.

Survival: Tables 4 (univariate analysis) and 5 (multivariate analysis) presents the results of the analysis of factors evaluated for an association with the overall survival of patients with WHO grades II and III meningiomas. Patients <60-years-old survived longer than did patients >60-year-old (univariate - Figure 2, and multivariate analysis), and patients with grade II tumors survived longer than did patients with grade III tumors (univariate analysis - Figure 3). Histological progression, radiotherapy and recurrence were predictors for longer survival (multivariate analysis).

Recurrence: The results of the analysis of factors that can influence the RFS of patients with WHO grades II and III meningiomas are presented in Tables 4 (univariate) and 5 (multivariate). The recurrence rates during follow-up were 50% (26/52 patients), 46.5% (20/43 patients) and 66.7% (6/9 patients), respectively, in all patients, in patients with WHO Grade II and with III meningiomas. Among patients with Grade II tumors, 16 (80%) recurred in the first 5 years and the other 4 (20%) recurred after 10 years. All six recurrences in patients with Grade III meningiomas occurred in the first 3 years.

RFS was longer for patients with grade II than with grade III meningiomas (univariate - Figure 4, and multivariate analysis), for patients who underwent total resection than with subtotal resection, for patients with de novo than in patients with malignant transformation (univariate analysis - Figures 5 and 6), and for patients >60-years-old (multivariate analysis).

Mortality and morbidity

One patient (grade II) died in the first postoperative month after surgery, due to pulmonary embolism. Two patients (grades II and III) died, respectively, three and two months after surgery due to pulmonary infection and 13 patients died during the follow-up period (operative mortality: 2 [3.9%] patients; surgery related mortality: 3 [5.8%] patients; and overall mortality: 16 [30.8%] patients). During follow-up, nine deaths occurred due to progression of Grades II (five patients) and III (four patients) tumors and four deaths were not related to tumor.

Transient (5 [9.6%] patients) or permanent (6 [11.5%] patients) neurological postoperative complications occurred in 11 (21.2%) patients (10 with Grade II and one with Grade III tumors). The most frequent complication were hemiparesis in six (11.5%) patients (four transient [75%] and two [25%] permanent), and cranial nerve deficits in 3 (5.8%) patients (II/III/IV/VI in one; V/VII in the second; and V/VI/VII in the third patient). Two patients had deep venous thrombosis, one of them developed pulmonary embolism. Another patient had osteomyelitis.

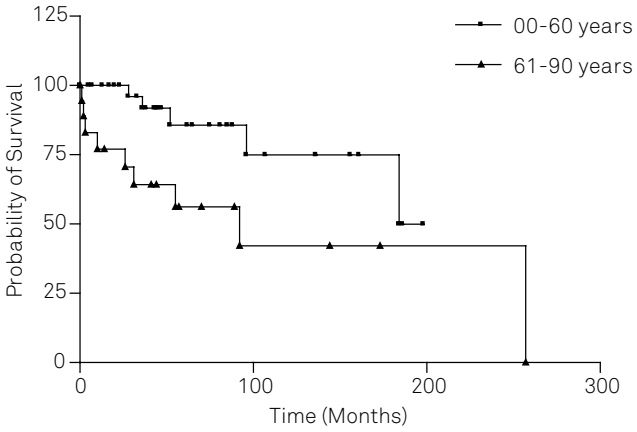

Figure 2. Survival curves for patients with WHO grades II and III according age (≤60 years-old vs >60 years old). Significant difference (p = 0.0221, df = 1, [log-rank test].

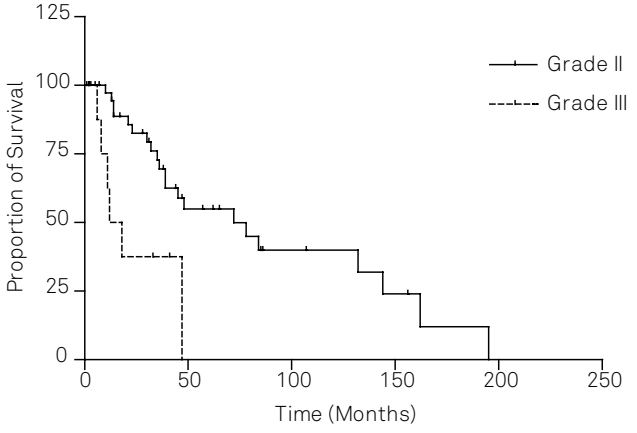

Figure 3. Survival curves for patients according WHO histological grades. Significant difference (p = 0.0034, df = 1, log-rank test).

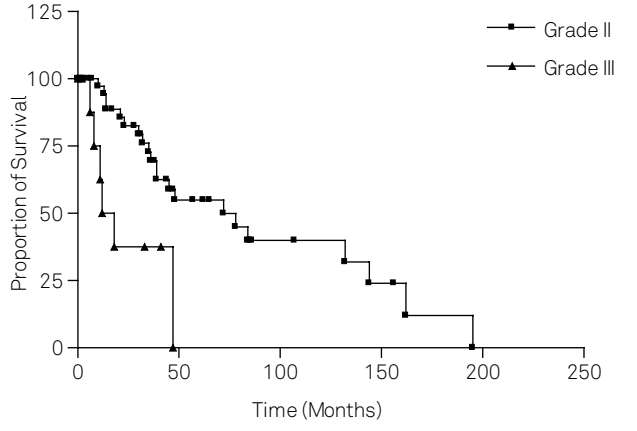

Figure 4. Recurrence-free survival curve for patients with WHO grades II and III. Significant difference (p = 0.0030, df = 1, log-rank test).

Table 4. Summary of the analysis of survival curves according factors that can influence the overall survival of patients with WHO grades II and III meningiomas.

	5y RFE	10y RFE	Median survival	Analysis
Age				
Decades of life	-	-	-	p = 0,1012, log-rank test, df = 7
>60 years-old	85.7 vs 56.2%	75.0 vs 42.1%	-	p = 0.0212*, log-rank test, df = 1
Sex (female vs male)				
All patients	73.7 vs 63.1%	55.3 vs 47.7%	Undef vs 136.0y	p = 0.6511, log-rank test, df = 1
Grade II	73.0 vs 78.4%	58.4 vs 58.8%	Undef vs Undef	p = 0.7281, log-rank test, df = 1
Grade III	50.0 vs 0.0%	50.0 vs 0.0%	147.0 vs 36.0y	p = 0.3261, log-rank test, df = 1
WHO Histopathological grade				
G II, G II-atypical, G II-other subtype, G III)	75.7 vs 75.1%	51.1 vs 47.7%	-	p = 0.5823, log-rank test, df = 3
All Patients(G II vs G III)	85.7 vs 56.2%	75.0 vs 42.1%	184.0 vs 92.0y	p = 0,0221*, log-rank test, df =1
De Novo vs malignant progression	72.9 vs 46.9%	63.0 vs 31.3%	Undef vs 96.0y	p = 0.1955, log-rank test, df = 1
Extent of resection (radical, subtotal)				
Grades II and III	82.8 vs 61.4%	63.1 vs 40.9%	Undef vs 96.0y	p = 0.2322, log-rank test, df = 2
Grade II	88.4 vs 61.0%	64.4 vs 61.0%	Undef vs Undef	p = 0.6880, log-rank test, df = 1
Grade III	50.0 vs 30.0%	50.0 vs 30.0%	111.0 vs 96.0y	p = 0.6823, log-rank test, df = 1
RT After 1st surgery (RT vs No RT	52.7 vs 78.6%	52.7 vs 62.8%	186.0y vs Undef	p = 0,6698, log-rank test, df = 1
KPS at admittance (≤70 vs >70)	74.3 vs 75.8%	37.1 vs 65.0%	96.0 vs Undef	p = 0.5267. log-rank test, df = 1

RFE: recurrence-free estimate; Undef: undefined; WHO: World Health Organization; y: year; * significant difference.

Table 5. Summary of the analysis of factors that can influence the overall recurrence-free survival of patients with WHO grades II and III meningiomas.

	5y RFE	10yr RFE	Median Survival	Analysis
Recurrence/Regrowing rate GII vs G III (46.5% vs 66.7%)	-	-	-	p = 0.4654, Fisher's exact test
Age				
Decades of life	-	-	-	p = 0.7799, log-rank test, df = 7
>60 years-old	45.9 vs 53.0%	25.5 vs 12.9%	48.0 vs 84.0y	p = 0.9469, log-rank test, df = 1
WHO Histopathological grade				
Grades (II vs III)	55.1% vs 0.0%	32.1 vs 0.0%	78.0 vs 15.0y	p < 0.0030*, log-rank test, df = 1
Atypical vs other subtypes G II	52.1 vs 10.5%	26.0 vs 32.5%	72.0 vs Undef	p < 0.2033, log-rank test, df = 1
De Novo vs Malignant progression	51.1 vs 0.0%	31.8 vs 0.0%	72.0 vs 15.0y	p = 0.0010*, log-rank test, df = 1
Sex				
All patients,	53.7 vs 32.2%	25.6 vs 32.2%	72.0 vs 45.0%	p = 0.7396, log-rank test, df = 1
Patients with grade II	64.3 vs 32.5%	30.6 vs 32.5%	78.0 vs 45.0y	p = 0.5612, log-rank test, df = 1
Patients with grade III	0.0 vs 0.0%	0.0 vs 0.0%	15.0 vs 29.0y	p = 0.7675, log-rank test, df = 1
Extent of resection (radical, subtotal)				
All patients	65.4 vs 33.0%	46.5 vs 0.0%	-	p = 0.011*9 log-rank test, df = 1
Patients with grade II	64.8 vs 45.5%	42.6 vs 15.4%	132.0 vs 36.0y	p = 0.2968, log-rank test, df = 1
Patients with grade III	0.0 vs 0.0%	0.0 vs 0.0%	11.5 vs 32.5y	p = 0.3948, log-rank test, df = 1
RT After 1st surgery (RT x No RT)	29.2 vs 57.4%	29.2 vs 0.0%	36.0 vs 72.0y	p = 0.4895, log-rank test, df = 1
KPS at admittance (≤70 vs >70)	31.1 vs 54.9%	15.6 vs 27.4%	39.0 vs 78.0y	p = 0.4719 log-rank test, def = 1

RFE: recurrence-free estimate; Undef: undefined; WHO: World Health Organization; y: year; * significant difference.

Postoperative functional outcome

Preoperative, immediate postoperative and follow-up functional disabilities assessed by KPS are presented in Table 6. The proportions of patients in the functional categories were similar in all evaluations (p = 0.5107 for all patients, p = 0.4694 for patients with Grade II tumors, and p = 0.9056 for patients with Grade III tumors). Preoperatively 12 (27.9%) patients had KPS scores ≤ 70, and postoperatively 14 (32.6%) had similar KPS scores (p = 0.5059). Three (5.9%) patients (two with Grade II and one with Grade III) experienced postoperatively deterioration (KPS score ≤70) and one Grade III (1.9%) experienced improvement (KPS ≥80). Assessment at 6 months identified 5 additional patients (four Grade II and one Grade III) with KPS score ≤70. There was no significant differences between the overall survival and RFS curves for patients with KPS score ≤70 and with KPS >70 on admission (respectively, p = 0.5107 and p = 0.4719) Tables 4 and 5.

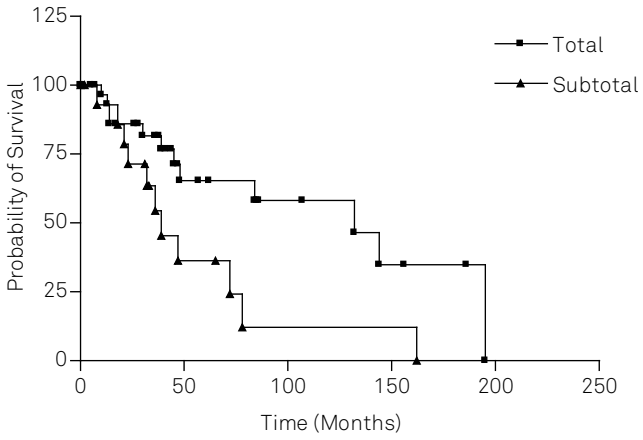

Figure 5. Recurrence-free survival curves for patients according the extent of resection. Significant difference (p = 0.0192, df = 2, log-rank-test.

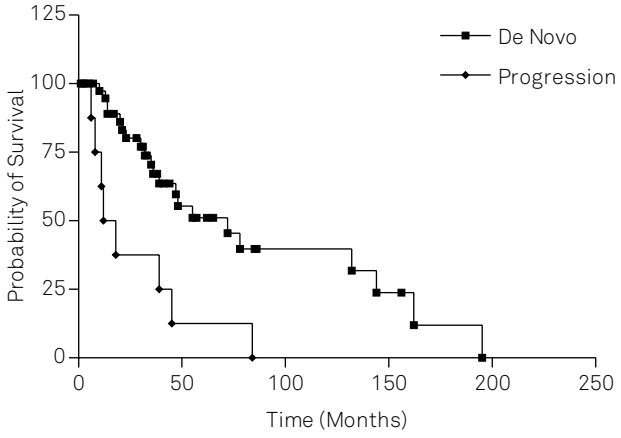

Figure 6. Recurrence-free survival curves for patients with de novo and for patients with progression meningiomas. Significant difference (p = 0.0010, df = 1, log-rank-test.

Table 6. Preoperative, postoperative, and follow-up functional status*.

Functional status	KPS Score	WHO Histopathological Grade								
		Preoperative			Immediate Postoperative			Follow-Up		
		Grade II	Grade III	Total	Grade II	Grade III	Total	Grade II	Grade III	Total
No. of patients		43	09	52	43	09	52	39	08	47
Normal/minimal symptoms & working	80-100	31 (72.1%)	06 (66.7%)	37 (71.1%)	29(67.4%)	6 (66.7%)	35 (67.3%)	31 (79.5%)	6 (66.7%)	37 (78.7%)
Independent, not working	70	12 (27.9%)	03 (33.3%)	15 (28.9%)	14 (32.6%)	2 (22.2%)	16 (30.8%)	08 (20.5%)	2 (22.2%)	10 (21.3%)
Moderate or severe disability	<70					1 (11.1%)	1 (1.9%)			

KPS: Karnofsky Preformance Scale; WHO: World Health Organization.

DISCUSSION

Epidemiology

The wide range in the relative frequency of atypical (3.6 and 7.5%) and anaplastic meningiomas (0.4 to 2.8%)[1,2,3,5,8,9,10,11], can be explained by variable pathological criteria for their classification. However, the use of the WHO criteria improved comparisons among more recent series. We found 8.2% of patients with grade II and 1.7% with grade III (10% of the patients with meningiomas surgically treated), data similar to the recent series. Benign meningiomas predominates in patients of female sex; in contrast, gender distribution has been reported similar or even with male predominance among patients with Grades II/III[2,8,12,13,14,15]. Our results kept this tendency for patients with grade II and III tumor. Atypical meningiomas have been reported to occur after cranial irradiation for other tumors or conditions[16,17]. We observed two patients (3.8%) with radiation-induced grade II (atypical) meningiomas.

Histopathological features

Several histopathological classifications were proposed for more aggressive meningiomas[2,18], however, these classifications are potentially subjective. Perry et al.[19,20], elaborated a simple and reproducible grading scheme for meningiomas (The Mayo Clinic Scheme), based primarily on histological features in patients who underwent total resection. They defined the following criteria for the diagnosis of 1) atypical meningiomas: (≥4 mitoses/10 HPF, ≥2.5/mm2) or at least three of the following features: sheeting, macronuclei, small cell formation, hypercellularity (≥53 nuclei/HPF, ≥118/mm2), and brain invasion; 2) anaplastic meningiomas (≥20 mitotic figures/10 HPF, ≥12.5 mm2), or focal or diffuse loss of meningothelial differentiation (carcinoma-, sarcoma-, or melanoma-like appearance).

The WHO classifications[1,7] incorporated the Mayo Clinic criteria for grading atypical and anaplastic meningiomas (proliferation index, brain invasion and mitotic activity), and emphasized more strict and objectives histological criteria. Grade II tumors included atypical tumors with three or more of the following features: increased mitotic activity (≥4 mitoses/10 HPF), increased cellularity, small cells with a high nuclear:cytoplasmic ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of necrosis. Grade II also includes clear cell and chordoid subtypes. Grade III tumors had obvious malignant cytology resembling that of carcinoma, melanoma or high-grade sarcoma or a markedly elevated mitotic index (≥20 mitoses /10 HPF). Grade III also includes rhabdoid and papillary subtypes.

Histopathological progression of meningiomas from Grade I to II and from Grade II to III has been reported in 0.16 to 2% of cases[8,13,15,18,19,21]. We found 9 patients (1.7% of all meningiomas and 17.3% of Grades II and III meningiomas) that had tumor progression at time of their recurrence. All patients progressing from Grade I to II had focal atypia in the first biopsy slides not considered sufficient to classify them initially as atypical. This observation should be considered at least as an alert: patients with Grade I meningiomas with focal atypia deserve close follow-up imaging looking for recurrence.

Some authors postulated that genetic changes in meningiomas progress stepwise, from grade I to III[1,22,23]. This is supported by histopathological progression of benign meningioma at recurrence[11]. However, other authors[15] genetic changes in tumor cells already present in the biopsies of benign recurrent progressing tumors, a finding inconsistent with the stepwise progression.

Prognostic factors

In addition to the histopathological features, several other factors were reported to influence the prognosis of the patients with atypical and anaplastic meningiomas. Age at diagnosis is a recognized prognostic factor for patients with intracranial tumors, including grades II and III meningiomas[8,10,12,14,19]. Among our patients, age <60-years-old was also a prognostic factor for overall survival, but not for RFS. Although some authors report that female sex is an unfavorable prognostic factor[2], more evidence indicates that gender does not influence prognosis of patients with grades II and III meningiomas[10,12,13,14], including our results. Some authors[21] found that patients with Grade II tumors progressing to Grade III have shorter overall survival than patients with "de novo" grade II meningioma and our results support these findings.

Extent of resection is considered a strong prognostic factor in several studies. Recurrence rate is lower for patients submitted to total (17%) compared with subtotal (87%) resection[3]. Survival is longer in patients that had Simpson 1 resection[13], and RFS is longer in patients with total resection[3]. Total or subtotal resections did not influence the survival of our patients and the RFS was longer for patients with total resection only on univariate analyis.

Molecular markers were also reported to be related to prognosis. Poor prognosis may be associated with a high MIB-1 labeling index. However, this index ranges overlap considerably for benign, atypical, and anaplastic meningiomas[11,19,20], and it is only valuable to evaluate tumors with borderline atypia. In such a case, an index of ≥ 4.2% would classify the tumor as atypical[11,19,20].

Surgical treatment

Surgery is the primary treatment for atypical and anaplastic meningiomas aiming a definitive diagnosis, reducing any mass effect and alleviating symptoms. Complete resection is the goal and the involved dura mater and bone should also be resected to prevent recurrence. Repeated surgery should be considered in cases where subtotal resection is required to avoid neurological deficits, such as for tumors of the cranial base and tumors with dense cortical adherence[11].

Radiation therapy

Conventional fractionated radiation therapy

Results of fractionated radiation therapy for atypical and anaplastic meningiomas are difficult to evaluate because of the variation of histopathology, the small number of cases and other variables, such as extent of resection and brain invasion[11]. The 5-year survival rate for patients with atypical and anaplastic meningiomas was found to be 58% and the 5-year RFS rate was 48%[24], the 2-year RFS rate was 89% for irradiated patients compared to 50% for patient not irradiated. The overall survival rate was better for patients submitted immediately to radiation therapy[3]. Therefore, the consensus favors fractionated radiation therapy for patients submitted to total or subtotal resection of atypical and anaplastic meningiomas[11], even though this recommendation is not supported by prospective controlled trials. We find better overall survival favoring patients submitted to fractionated radiation therapy on multivariate analysis but no difference was found between the RFS curves.

Stereotatic radiosurgery

Some authors have reported good results using stereotactic radiosurgery to treat benign, atypical and anaplastic tumors, 10-year survival rates of 59% for atypical and of 59 and 0% for anaplastic meningiomas, and 5-year RFS rates of 83 and 72% for atypical and anaplastic meningiomas, respectively[25]. However, another report did not support these favorable results for stereotatic radiosurgery showing a very poor result for anaplastic lesions[26]. Tumor size is a limiting factor for stereotactic radiosurgery[25,27]; lesions >3 cm in size do not respond to this treatment[25] and radiation necrosis occurs in 23% of the cases, with a few cases requiring surgery[27].

Based on the fairly good results reported in the literature and because complications are considered uncommon[11], except when radiosurgery is administered after conformal radiation therapy[26], stereotactic radiosurgery probably could be administered to patients with nodular residual atypical or anaplastic meningiomas along with fractionated radiation therapy to the tumor bed, even though no prospective controlled studies support this approach[11].

CHEMOTHERAPY

Anti-progesterone agents, interferon alfa-two-B, hydroxyurea and a combination of cyclophosphamide, adriamycin and

vincristine, were used to treat unresectable benign, atypical and anaplastic meningiomas and produced tumor shrinking or stabilization in most cases in preliminary studies. The initial results were not reproduced and none of these agents has shown convincing results in the treatment of atypical and anaplastic meningiomas[11].

Molecular biology suggested new options for the management of atypical and anaplastic meningiomas. Vascular Endothelium Growth Factor (VEGF) and Platelet-Derived Growth Factor (PGDF)-A and B and PDGF-β-receptor cause increased cell division and tumor proliferation[28], and their expression are increased in atypical and in anaplastic meningiomas[29]. Based on this knowledge, inhibitors of VEGF or VEGF receptors (vandetanib, vatalanib, bevacizumab, AEE788, and IMC-1C11), and VEGF receptor antagonists (bevacizumab and erlotinib), are available and some of them are being tested in phase II trials[11].

Atypical and anaplastic meningiomas are distinct entities with poorer prognosis than benign meningiomas when treated with the current therapeutic options. Objective classification systems to grade meningiomas, which were improved by the Mayo Clinic scheme followed by the WHO grading system, which was based on the former, allow better comparison between different series. The algorithm for treatment of atypical and anaplastic meningiomas proposed by Perry et al.[20], and modified by Modha & Gutin[11] is a reasonable option for treating these patients (Figure 7).

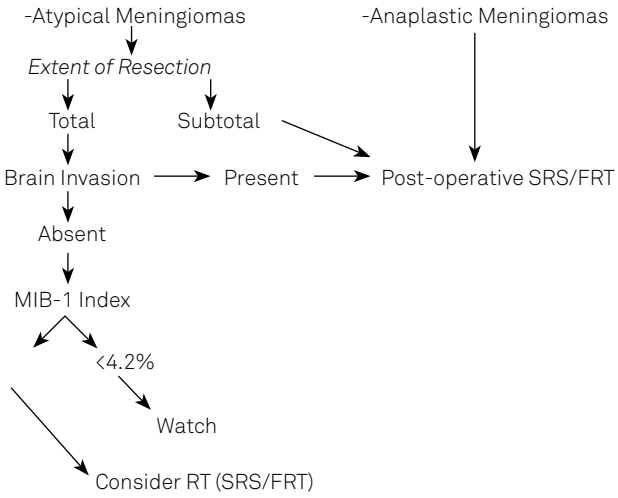

Figure 7. Algorithm for treatment of atypical and anaplastic meningiomas. Adapted from Modha & Gutin, 2005[14]. RT - radiation therapy; SRS - stereotactic radiosurgery; FRT - fractionated radiation therapy.

In conclusion, in this study we found that age under sixty-years old, grade II tumors, *de novo* meningiomas and total resection were main predictors for better prognosis factors among patients with atypical and anaplastic meningiomas. The treatment of atypical and anaplastic meningiomas remains a challenge for neurosurgeons, and new strategies should be developed to reduce recurrence and improve the prognosis of patients harboring these tumors.

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