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Research Article

Recurrence of Surgically Treated Meningiomas: Experience of a Single Brazilian Tertiary Center with 757 Consecutive Tumors

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Abstract

Background: Meningiomas are the most common tumors of the central nervous system. Despite being mostly benign, some of them can recur even when totally resected. We aimed to determine the surgical/tumor characteristics of recurrence in meningiomas.

Methods: This was a retrospective analysis of nongenetic-molecular surgical tumor characteristics that influenced recurrence in 757 operated meningiomas.

Results: Recurrences predominated in males between 0-9-years-old and in tumors subtotally and partially resected, with the rates being similar for tumors of convexity and of the skull base. Recurrences occurred between 1-203 months and at rates of 33%, 64%, and 95.6% at 2, 5, 10, and 20 years, respectively. There was a tendency to observe fewer recurrences in the most recent decades for totally resected tumors. In intracranial tumors, recurrences occurred in 13.6%, 33.8%, and 33.3% of total, subtotal, and partial tumor resections, respectively. This correlated to 12.5%, 17.6%, 34.6%, and 32.9% of cases with Simpson grades I, II, III, and IV resections, respectively. There was two recurrences (2/34=5.8%) among spinal tumors. Recurrences increased by features of histopathological World Health Organization grades (14.6%, 41.8%, and 50.0% for grades I, II, and III, respectively).

Conclusions: Over time, meningiomas exhibited a tendency toward recurrence. Extension of the resection, histological grade, tumor size, and age were independent factors for recurrence in patients treated exclusively by surgery, as has been observed in other large studies. In addition, the male sex and atypia in histological grade I tumors were identified as being independent factors for recurrence.

Keywords: *Vaccination; COVID-19; Herpes Simplex Reactivation*

Introduction

Meningiomas are the most common tumors of the central nervous system (CNS), accounting for 35.8% of all CNS tumors and more than 53% of benign CNS tumors (CBTRUS Statistical Report) [29]. They are more common in women, and their frequency increases with age; moreover, the TUMORs can be classified into World Health Organization (WHO) histological grades I, II, and III, most of which are benign [30]. Despite these facts, a certain percentage of meningiomas which had been completely or partially surgically removed may relapse or progress. The relationship between the extent of resection (EOR) and the rate of recurrence of meningiomas has been clearly

demonstrated in 1957 by Simpson [37], who established a I to V regressive classification system to describe various grades of resection. This descriptive system has been widely used until today. Demographic characteristics, such as age and sex, as well as histological findings and factors related to the surgical treatment of the tumor, such as the EOR, are considered predictive factors for recurrence of meningiomas [17,24,31]. In this study, we analysed such characteristics that are not related to genetic-molecular characteristics in recurrencing meningiomas in a cohort of 763 patients who were surgically treated in a single Brazilian public institution.

Materials and Methods

Patient population

The medical records of 835 patients with CNS meningiomas who underwent operations at the Hospital das Clínicas, Ribeirão Preto Medical School, University of São Paulo, were retrospectively analysed between May 1984 and December 2019 to identify the characteristics of the tumor and the surgical treatments which may correlate to tumor recurrences. Forty-four (6.0%) patients had multiple meningiomas, resulting in a total of 835 operated tumors. The epidemiological data of the patients were reported in a previous paper [7]. The tumors were classified according to the last WHO histological criteria [30]. The histopathological examinations of 6 meningiomas could not be revised and were excluded. Ten patients had 11 tumors submitted to conventional adjuvant radiotherapy and were excluded from this analysis because radiotherapy (as a primary or adjuvant treatment) is not part of routine meningioma management in our hospital. Thirty-three patients died in the first three months (due to brain ischemia and pneumonia in 10 each, pulmonary embolism in 3, circulatory chock and sepsis in 2 each, and due to brain edema, hemorrhagic brain contusion, aneurysmatic hemorrhage, intracranial hematoma, respiratory failure and not identified in one patient each), and 28 patients did not return after surgery. The remaining 685 patients with 757 operated tumors had a follow-up of ≥ 3 months. The clinical course of these patients was assessed by using the rates and estimates of recurrence/regrowth and recurrence-free survival (RFS) curves after the first surgery. Recurrences, defined as growth on postoperative imaging after gross total resection (GTR) and or increasing size of residual after subtotal resection (STR), were detected by the systematic employment of computed tomography (CT)/magnetic resonance imaging (MRI) performed 3 months after surgery followed by annually or biannually examination.

Follow-up period ranged from 3 - 426 months (mean: 113.3 ± 301.0 months; median: 87 months). The tumors were identified and located by using CT/MRI. Within our study cohort, 254 (30.4%) tumors were classified by size as being small (< 3 cm), 351 (42.0%) medium (> 3 and < 5 cm), and 230 (27.6%) large (≥ 5 cm), according to their largest crossectional diameter.

Specific genetic/molecular characteristics of the tumors were not analysed because these tests were not routinely performed in our hospital. The study was approved by the Research Ethics Committee of our institution (No. 736,988).

Statistical analysis were performed by using the chi-square test, Fisher's exact test, and log-rank (Mantel-Cox) test with (GraphPad Software, San Diego, CA 92108). A significant difference was considered when the error $\alpha = 0.05$.

Results

Demographics and the characteristics of tumors of this series is presented in table 1. Most of the operated patients were females (557/172 = 1: 3.2) with a peak incidence in the 5^{th}-6^{th} decades of life (48.9%).

Anatomical location and recurrence

Of the 757 tumors, 723 (95.5%) were intracranial (19.6% over the convexity, 19.2% parasagittally, 1.5% in the ventricles, and 57.0% at the base of the skull) and 34 (4.5%) were intradural extramedullary located in the spinal canal. The rate of EOR and the related recurrence rates according to tumor locations is shown in table 2.

	Excluded			Follow-Up > 3 Months				Total		
Sex	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**		**Female**	**Male**	**Total**
	31	47	78	582	175	757		613	222	835
Age										
	55.23 ± 12.82	57.67 ± 14.99	55.35 ± 13.63	52.22 ± 13.60	46.83 ± 17.56	50.97 ± 14.78		52.37 ± 13.53	49.02 ± 19.66	51.55 ± 15.31
	53.5	58	54	54	50	52		54	51	53
Size										
Small	7	2	9	163	58	221		170	60	230
Medium	22	14	36	243	72	315		265	86	351
Large	22	11	33	163	58	221		185	69	254
Total	51	27	78	569	188	757		620	215	835
Location										
Cranial	50	26	76	553	170	723	95.5%	603	196	799
Spinal Canal	1	1	2	29	5	34	4.5%	30	6	36
Total	51	27	78	582	175	757		575	201	835
Cavernous Sinus	2		2	10	5	15	2.1%	12	5	17
Convexity	7	4	11	103	39	142	19.6%	110	43	153
Falx	3		3	13	6	19	2.6%	16	6	22
Forame Magnum	1		1	17	2	19	2.6%	18	2	20
Olfactory Groove	8	2	10	26	6	32	44%	34	8	42
Superior Sagittal Sinus	4	7	11	86	28	120		90	35	131
Petroclival	2	6	8	9	2	11	1.5%	11	8	18
Petrous	4	2	6	22	5	27	37.3%	26	7	33
Sphenoid-Orbital				34	4	38	5.3%	34	4	38
Sphenopetrous	3	1	4	9	12	15	2.1%	12	13	25
Sphenoid Wing	8		8	81	20	101	13.0%	89	20	109
Spinal Canal	1	1	2	29	5	34	4.7%	30	6	36
Tentorium	4	2	6	55	12	67	9.3%	59	14	73

Tuberculum Sellae	3	2	5	51	13	64	8.9%	54	15	69	
Ventricular				7	4	11	1.5%	7	4	11	
Other	1		1	28	14	42	5.8%	29	14	43	
Total	51	27	78	580	177	757		631	204	835	
Skull Base	35	20	55	325	93	412	57.0%	360	127	487	
WHO Grades											
I	41	25	66	540	132	672		581	157	738	
II	4	4	8	39	40	79		43	44	87	
III	2	2	4	3	3	6		5	5	10	
Total	47	31	78	582	175	757		629	206	835	
	Excluded			**Follow-Up > 3 Months**				**Total**			
Extent of Resection	**Total**	**Subtotal**	**Partial**	**Total**	**Subtotal**	**Partial**	**Biopsy**		**Total**	**Subtotal**	**Partial**	**Biopsy**
Intracranial	40	29	7	557	149	15	2	723	597	178	22	2
	52.6%	38.2%	9.2%	77.0%	20.6%	2.1%	0.3%		76.7%	22.8%	2.8%	0.3%
Spinal Canal	2			30	3	1		34	32	3	1	0
	100 %			88.2	8.8%	2.9%			88.9%	8.3%	2.8%	0
Total	42	29	7	587	152	16	2	757	629	181	23	2
	53.8%	37.2%	9.0%	77.7%	20.1%	2.1%	0.3		75.3%	21.7%	2.8%	0.2%

Table 1: *Demographic data of patients, tumor characteristics and extent of resection of the entire cohort of operated patients with meningiomas.*

Extent of resection	**Total**		**Subtotal**		**Partial**		**Biopsy**		**Total**			
	Ext Res	**Rec**	**Ext Res**	**Rec**	**Ext Res**	**Rec**	**Ext Res**	**Rec**	**Ext Res**		**Rec**	
Location												
Intracranial	558 (77.2%)	76/558 13.6%	148 (20.5%)	50/148 33.8%	15 (2.1%)	5/15 33.3%	2 (0.3%)	1/2 50%	723 (95.6%)		132/723 18.%	
Spinal Canal	30 (88.2%)	1/30 (3.3%)	3 (8.8%)	1/3 33.3%	1 (2.9%)	0/1 0%	0	0	34 (4.4%)		2/34 5.9%	
Total	588 (77.2%)	77/588 (13.1%)	151 (20.3%)	51/151 (33.8%)	16(2.2%)	5/16 (31.3%)	2 (0.3%)	1/2 (50%)	754		134/757= (17.7%)	
Simpson´s Grades	**I**		**II**		**III**		**IV**		**V**		**Total**	
Intracranial	439 (60.27	55/439= (12.5%)	108 (14.9%)	19/108= 17.6%	26 (3.6%)	9/26= 34.6%	146 (20.2%)	48/146= 32.9%	4 (0.6%)	1/4= 25%	723 (95.5%	134/723 18.5%
Spinal Canal	7 (20.6%)	1/7 20.6%	24 (70.6%)	1/24 4.2%	0 (0%)	0 0%	3 (8.8%)	1/3 33.3%	0 (0.0%)	0	34 (4.5%)	2/34 5.9%
Total	446 (58.9%)	56/446 12.6%	132 (17.4%)	20/132 15.2%	26 (3.4%)	9/26 34.6%	149 (19.7%)	49/149 32.9%	4 (0.5%)	1/4= 25%	757	134/757 17.7%

Table 2: *Extent of resection and recurrence rates of tumors of 757 patients with ≥ 3 month follow up according location (intracranial x spinal canal).*

Resections for intracranial tumors followed for ≥ 3 months were total, subtotal, and partial in 77.2%, 20.5%, and 2.4%, respectively. When classified according to Simpson's grades I, II, III, IV, and V grades this showed as 60.7%, 14.9%, 3.6%, 20.2%, and 0.6%, respectively.

In spinal tumors, the resections were total, subtotal, and partial at rates of 88.2%, 8.8%, and 2.9%, respectively. Associated Simpson's grades I, II, and IV were seen in 20.6%, 70.6%, and 8.8%, respectively.

The recurrence rates for all lesions were 13.1%, 33.8%, 31.8 and 50% for total, subtotal, partial resections and biopsy respectively, which correlated to 12.6%, 15.2%, 34.6%, 32.9, and 25.0% for Simpson's I, II, III, IV and IV grades respectively. Specifically, for intracranial tumors, the rates were 13.5%, 33.8%, 33.3, and 50.0% for total, subtotal, and partial resections and biopsy respectively, with rates of 12.5%, 14.6%, 34.6%, 32.9%, and 25.0% for Simpson I, II, III, and IV resections respectively. There were two recurrences among the spinal tumors, after a total/Simpson I and a subtotal/Simpson IV resections (3.3% each).

The recurrence rates and the RFS curves for convexity and skull base tumors were similar (14.1% and 20.5%, respectively, p = 0.1256, Fisher's exact test; p = 0.2956, Log-rank [Mantel Cox] test). Recurrence rates according to the tumors anatomical locations are shown in figure 1. Recurrences predominated in tumors of the ventricles, optic canal, floor of the middle fossa, and sphenopetrous region.

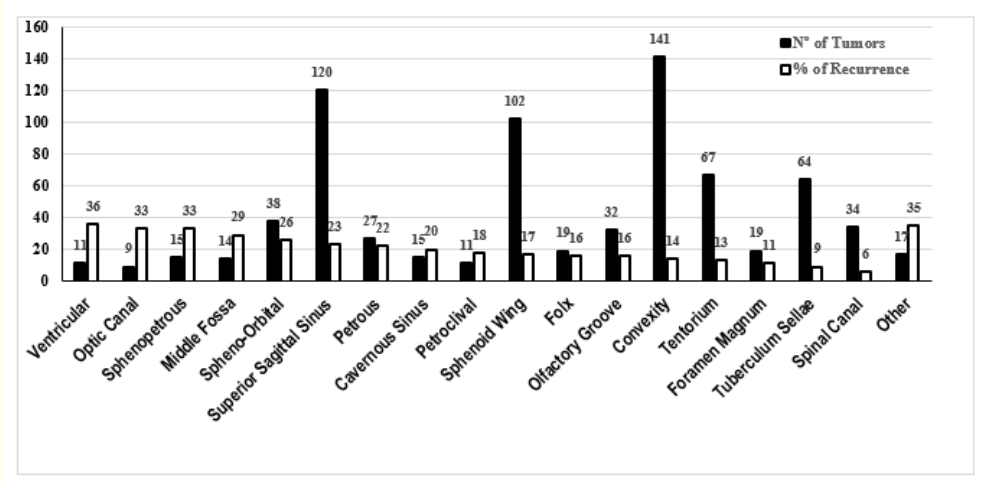

Figure 1: *Recurrence rates of meningiomas according the anatomical location for patients with ≥ 3 months follow-up.*

Age and sex and recurrence

Figure 2A shows the recurrence rates by the age groups of patients. Recurrence predominated in the first decade of life (p < 0.0001, chi-square test). Recurrences among tumors of patient with follow-up ≥ 3 months and among intracranial tumors were higher in men (25.1% vs 15.5% and 25.9% vs. 16.3%, respectively, p = 0046 and p = 0.0090, Fisher's exact test, respectively) and the RFS curve (Figure 2B) for intracranial tumors was better in females (p = 0.0044, log-rank [Mantel-Cox] test). In spinal tumors, recurrences occurred in one female and in one male patient.

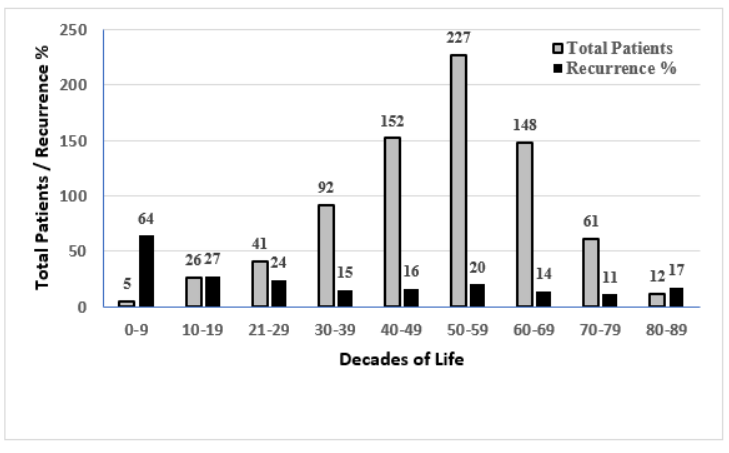

Figure 2A

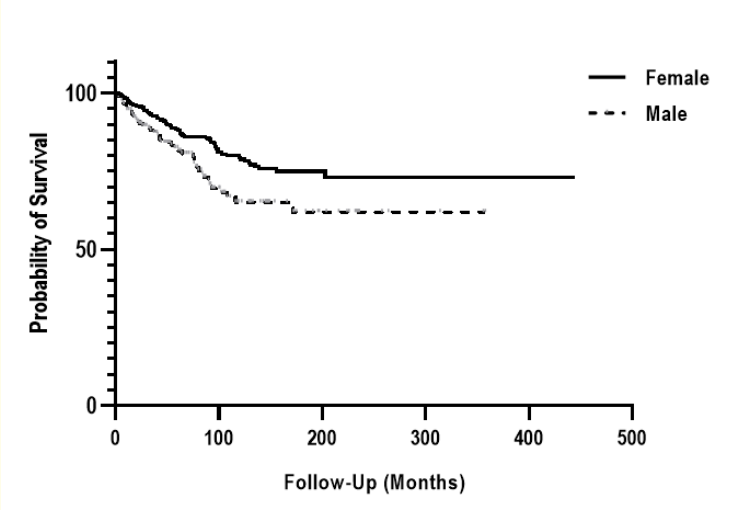

Figure 2B

Figure 2: *Recurrence rates of intracranial tumours according decades of life (A) and recurrence-free survival curves according sex (B) for intracranial tumors with follow-up ≥ 3 months.*

Size of tumors and recurrence

The recurrence rates according to tumor size and WHO grades are shown in table 3. Recurrences predominated in large tumors, and the RFS curve was worse for large tumors.

WHO Grades	Tumor Size	Nº of Patients	Recurrence		Comparison	p - Rates Fisher exact test	p-RFS Log-rank (Mantel-Cox) test
			Nº	%			
I	Small	210	24	11.4	Small x Medium	0.5842	0.5116
	Medium	285	38	13.4	Small x Large	0.0171*	0.0526
	Large	180	37	20.4	Medium x Large	0.0516	0.1269
	Total	675	99	14.7		0.0275*	0.0464*
II	Small	11	4	36.4			
	Medium	30	15	50.0			
	Large	38	14	36.8			
	Total	79	33	41.8			
III	Small						
	Medium	1	1	100.0			
	Large	2	1	50.0			
	Total	3	2	66.7			
Total	Small	221	28	12.7	Small x Medium	0.1803	0.2823
	Medium	316	54	17.1	Small x Large	0.0043*	0.0129*
	Large	220	52	23.6	Medium x Large	0.0780	0.0866
	Total	757	134	17.7		0.0108*	0.0342*

Table 3: *Size and recurrence rates of 757 tumors with follow-up ≤ 3 months.*

Abbreviations: *Nº: Number; RFS: Recurrence free-survival curve; *Significant difference.*

Follow-up and recurrence

The distribution of recurrences throughout the follow-up is shown in figure 3. Recurrences occurred between 3-203 months (mean = 50.9 ± 38.5, median = 43 months), and 32.6%, 45.4%, 53.0%, 62.9%, and 94.7% occurred at 2, 3, 4, 5, and 10 years, respectively.

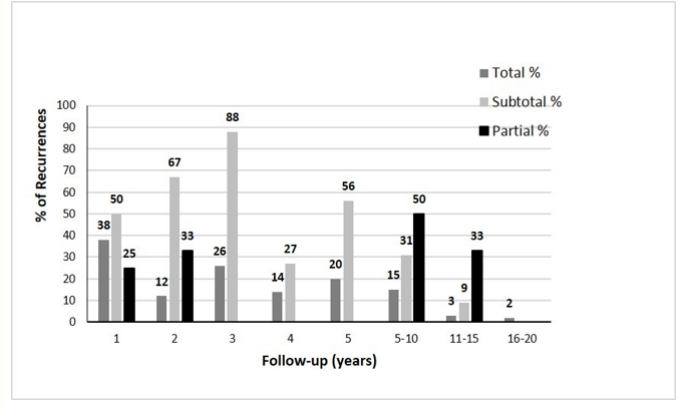

Figure 3: *Distribution of recurrence rates (percentages) for intracranial tumours according the extent of resection along the follow-up in patients with follow-up ≥ 3 months.*

Recurrence by decades of study

Total, subtotal, and partial resections for the entire cohort were obtained in 75.3%, 21.7%, and 2.8% (Table 1), and Simpson's grades I, II, III, IV, and V were obtained in 56.9%, 17.4%, 3.4%, 21.9%, and 0.5%, respectively The EOR in patients with intracranial tumors per decade of study is shown in table 4.

Extent of Resection	Total		Subtotal		Partial		Biopsy		Total			
	Rec/Nº	%	Rec/Nº	%	Rec/Nº	%	Rec/Nº	%	Rec/Nº		%	
Decades												
1984-1989	4/22	18.2	3/7	42.9	1/2	50.0	0	0	8/31		25.8	
1990-1999	11/92	12.0	10/20	50.0	2/6	33.3	0	0	23/118		19.5	
2000-2009	32/175	18.3	18/50	36.0	0/3	0	1/1	100	51/230		22.2	
2010-2019	29/298	9.7	22/75	29.3	1/3	33.3	0/1	0	52/378		13.8	
Total	76/587	13.0	52/152	34.2	4/14	28.6	1/2	50.00	134/757		17.7	
Simpson´s Grades	**I**		**II**		**III**		**IV**		**V**		**Total**	
	Rec/Nº	**%**	**Rec/Nº**	**%**	**Rec/Nº**	**%**	**Rec/Nº**	**%**	**Rec/Nº**	**%**	**Rec/Nº**	**%**
1984-1989	2/15	13.3	2/7	28.6	0/1	50.0	4/8	50.0	0	0	8/31	25.8
1990-1999	7/70	10.0	3/20	15.0	1/3	33.3	12/25	48.0	0	0	23/118	19.5
2000-2009	25/131	19.1	7/43	16.3	3/7	42.9	15/48	31.3	1/1	100.00	51//230	22.2
2010-2019	22/230	9.56	8/61	13.1	4/15	26.7	18/69	26.1	0/3	0	52/378	13.8
Total	56/446	12.56	20/131	11.36	8/26	30.8	45/150	30,9	1/4	25.00	134/757	17.7

Table 4: *Recurrence rates of 757 tumors of patients with ≥ 3 months of follow-up according the extent of resection and decades of the study.*

The recurrence rates for patients with intracranial tumors (according to the EOR) per decade of study are shown in table 4. The overall recurrence rate was 18.1%, which was distributed in 13.6%, 32.1%, and 46.2% for total, subtotal, and partial resections, respectively, and in 12.5%, 16.7%, 29.4%, 34.4%, and 0% for Simpson's grades I, II, III, IV, and V, respectively. There was a tendency to observe a lower recurrence rate in the most recent decade for totally resected tumors.

The RFS curves according to the EOR for intracranial tumors are shown in figure 4. The RFS estimates at 5, 10, 15, and 20 years, respectively, were 91.0%, 78.0%, 76.0% and 72.0% for the total resections; 73.0%; 56%, 52.0% and 52.0% for the subtotal resections; and 82.0%, 44.0%, 22.0%, and 22.0% for the partial resections (Figure 4). The RFS curves were significantly better for GTR than for subtotal and partial resections ($p < 0.0001$ and $p = 0.0178$, respectively; log-rank [Mantel-Cox]). The RFS curves were better for Simpson I vs III and IV, as well as for grades II vs IV ($p = 0.0013$, $p < 0.0001$, and $p = 0.0042$, respectively; Mantel-Cox log-rank test, respectively).

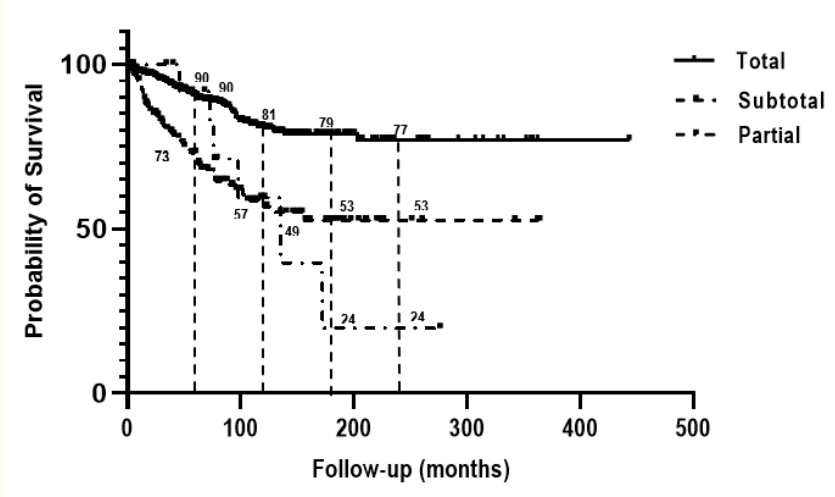

Figure 4A

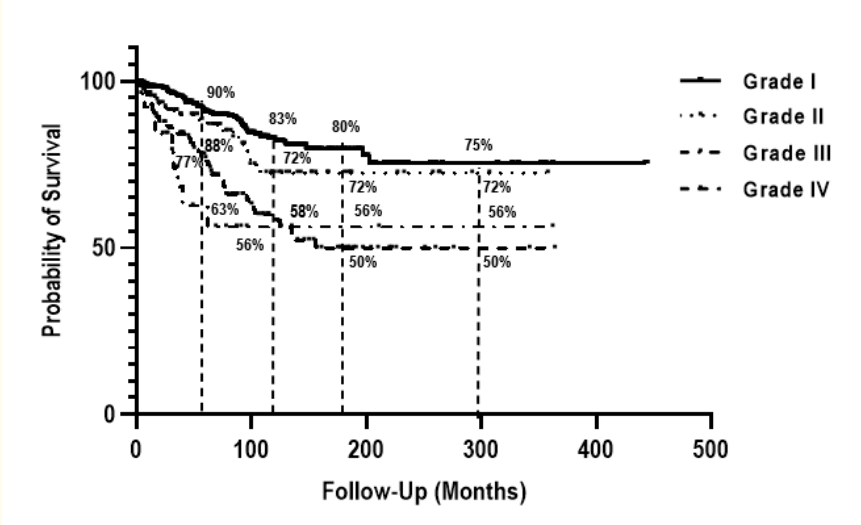

Figure 4B

Figure 4: *Recurrence-free survival curves according the extent of resection for patients with intracranial tumours with follow-up ≥ 3 months. A. Total, subtotal and partial resection, and B. Simpson's grades resection.*

Histological grade and recurrence

The histological grades of the tumors and recurrences are shown in table 5. Grade I was assigned in 88.2% and 88.8% of specimens, grade II in 10.9% and 10.4% for intracranial and for the entire cohort, respetively, and grade III in 0.8% for both. In grade I, the transitional

(41.4% and 41.1%) and meningothelial (32.1% and 32.8%) subtypes predominated for the entire cohort and for intracranial tumors, respectively; in grade II, 91.1% were atypical; and in grade III, the anaplastic (50%) subtype predominated for both groups of tumors. All of the spinal tumors were grade I (47.1% were transitional, 23.5% were psammomatous, and 20.6% were meningothelial).

Location	Intracranial			Spinal Canal			Total		
WHO Grade	Nº of Tumors	Recurrence		Nº of Tumors	Recurrence		Nº of Tumors	Recurrence	
		Number	%		Number	%		Number	%
Grade I									
Transicional	262	45	17.2	16	2	5.9	278	47	16.9
Meningothelial	209	34	16.3	7			215	34	15.8
Fibroblastic	64	4	6.3	2			67	4	6.0
Psammomatous	28	1	3.6	8			36	1	2.8
Sincitial	21	5	23.8				21	5	23.8
Angiomatous	18	3	16.7				17	3	17.7
Microcystic	13	1	7.7				13	1	7.7
Mixed	14	1	7.1				11	1	9.1
Secretory	10	1	10.0				10	1	10.0
Lipoblastic	1						1		
Lymphocitic	1						1		
Metaplastic	1	1	100.0	1			2	1	50.0
Total Grade I	638 88.24%	96	13.9	34 4.7%	2	5.9	672 88.77%	98	14.6
Grade II									
Atypical	72	31	43.1				72	31	43.1
Chordois	4	1	25.0				4	1	25.0
Clear Cell	3	1	33.3				3	1	33.3
Total Grade II	79 10.93%	33	41.8				79 10.44%	33	41.8
Grade III									
Anaplastic	3	2	66.7				3	2	66.7
Papillary	1						1		
Rhabdoid	2	1	50.0				2	1	50.0
Total Grade III	6 0.83%	3	50.0				6 0.79%	3	50.0
Total	723	132	18.3	34	2		757	134	17.7
Comparisons (Fisher's exact and Qui-square tests)	Grades I x II Grades I x III Grades II x III		p < 0.0009* p < 0.0497* p + 0.0.006*		Grades I x II Grades I x III Grades II x III		p < 0.0001* p = 0.0519 p = 0.6948		

Table 5: *Distribution of operated meningiomas according the WHO histopathological grades and recurrence of meningiomas of patients with ≥ 3 months follow-up.*

Recurrences rates were practically similar in the entire cohort and in intracranial tumors for grade I, II and III tumors (14.6%, 41.8%, and 50.0% vs. 13.9%, 41.8%, and 50.0%), with predominance for grades II and III in relation to grade I and grade III in relation to grade II. Two grade I spinal tumors exhibited recurrence (5.9%). Figure 5 shows the RFS curves for intracranial tumors (according to histopathological grades). The RFS curves were better for patients with grade I intracranial tumors than for patients with grade II and III intracranial tumors ($p < 0.0001$) and were similar for grade II and III intracranial tumors ($p = 0.6969$, log-rank [Mantel-Cox] test). The RFS rates at 5, 10, 15, and 20 years were 89.9%, 80.3%, 76.1%, and 74.7%; 68.4%, 44.6%, 40.6%, and 40.6%; and 50%, 0%, 0%, and 0%, respectively, for WHO grades I, II, and III, respectively.

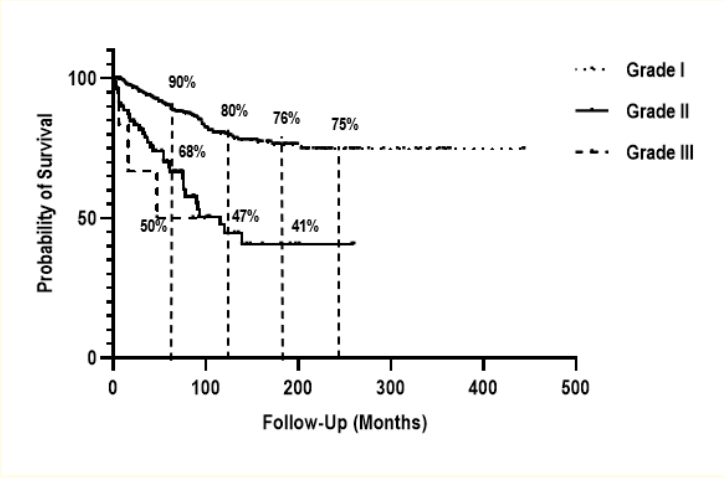

Figure 5: *Recurrence-free survival curves according the histological type of tumours for patients with intracranial tumors with follow-up ≥ 3 months.*

Among patients with WHO grade I tumors, 25 (3.8%) had focal atypia. The recurrence rate among them was 24% versus 3.5% for those who did not have atypia ($p = 0.0001$, Fisher's exact test). There was no difference between the RFS curves for either group ($p = 0.0965$, log-rank test [Mantel-Cox]).

Discussion

The information obtained in this study resulted from the retrospective analysis of a large series of patients with CNS meningiomas who were treated via surgical resection alone. This study exhibits the limitations that are inherent to a retrospective study, which must be considered when interpretating the results. Another limitation of this study is the lack of genetic data from the tumors, a problem of public hospitals in developing countries.

Symptomatic recurrences of intracranial meningiomas have been demonstrated to be related to histopathological aggressiveness and incomplete resections as early as 1938 by Cushing [9], who emphasized the need to remove the bone and dura adjacent to the tumor. In the pre-CT era, the recurrence rates for CNS meningiomas detected by clinical manifestations or at autopsies ranged from 12.9 - 16.2%, as well as from 5 - 14.6% for intracranial tumors [16,19,37]. These rates are underestimated because recurrences were diagnosed by clinical symptoms or at death, and there is no record regarding the extension of the resections (complete or incomplete). Simpson [37], in his seminal 1957 paper, correlated the EOR with meningioma recurrence in a clear manner.

The uses of CT and MRI have improved the diagnosis of the recurrence of meningiomas, with overall rates of 22% (11% for total resections and 37% for partial resections) [5]. With the use of a life table analysis, recurrences were reported in 19% in 20 years and in 32% in 15 years [18,26]. Currently, the probability of recurrence of meningiomas after incomplete or total resections is widely recognized [5,8,11,17-18,24,26,31,32,38].

By using a systematic surveillance approach employing consecutive CT/MRI, we observed symptomatic/asymptomatic global recurrence/regrowth rates of 17.4% and 18.1% for all tumors and for intracranial tumors, respectively (13% and 30.8% for complete resections, respectively, and 13.5% and 33.3% for incomplete resections, respectively) during long-term follow-up (3 - 426 months; mean: 91.5 ± 72.7 months).

Both younger patients and female patients with meningiomas have been identified as showing better survival [4,34]. In our study, global recurrence was higher and the RFS curves were worse in men for both total tumors and for intracranial tumors. Despite the small number of tumors, recurrence was also greater in the first decade of life. These facts were likely due to the predominance of the more aggressive tumors in this group.

Tumor sizes greater than 5 cm were identified as the factor correlating with the highest recurrence rates and the worst RFS in univariate and multivariate analysis, which is likely due to the greater difficulty of a complete resection [2,14,17]. We observed higher rates of recurrences and worse RFS curves in tumors > 5 cm for our cohort of patients and for patients with WHO grade I tumors.

After the introduction of CT, there was an improvement in the EOR and a reduction in the mortality of operated meningiomas; however, comparisons between more recent periods have shown no significant differences between recurrence rates and between RFS [34,36]. We observed a progressive increase in the rate of accomplished total resections/Simpson I and II grade resections from the beginning to the last decade of the study, which can be explained by the improvement of the diagnostic methods and microsurgical techniques, as well as the enhancement of the expertise of surgeons. In contrast, the recurrence rates for tumors with total/grade I/II resections have shown greater variability; however, there was a tendency to these rates to decrease in the last decade, which can be explained by the increase in the extent of the resection and by the progressive reduction of the follow-up period.

Recurrences for intracranial meningiomas are more frequent than for those found in the spine [2,13,18,19,26,33,35], where they appear to be related to factors other than the extent of the resection. Therefore, some authors have proposed not attempting a Simpson I resection if there is a risk of cerebrospinal fistula or neurological worsening [41]. Recurrences are more frequent for intracranial meningiomas, and RFS curves are worse for tumors that are located in regions where total resections are less likely, such as at the base of the skull (17 - 54% recurrence), compared to other locations, such as the convexity (1.8 - 25% recurrence in 5 years) [1,5,20,21,24,27]. Furthermore, for meningiomas outside of the base of the skull, histopathological grades and MIB-1 were higher in recurrence than tumors at the base of the skull [28]. Parasagittal/falcine tumors are also significant for having high recurrence rates (18-29%) and worse RFS curves (an estimated 33% at 5 years) [5,25,26,31]. We did not observe any difference between recurrences or between RFS curves for tumors of the base of the skull and convexity.

The EOR and the histopathological degree have been considered to be the strongest predictive factors for recurrence of meningiomas [8,11-12,14,18,21,24,26,31,32,38]. However, some authors have argued the need for Simpson I resection in the post-RM era against the risk of neurological worsening to achieve this effect [8,15,39,40]. The overall recurrence rate of intracranial meningiomas in our patients was 17.4%, with an increase in tumor recurrence for total/Simpson's grade I-II resections to subtotal and partial/Simpson's III-IV resections based on a long-term follow-up. These numbers are similar to those observed in post-CT publications [5,8,11-12,17,18,24,26,31,32,38]. The absence of recurrence among patients with tumors with Simpson's grade V resections can be explained by the small number of cases.

The average time for detecting recurrences of meningiomas before and after the use of CT was 5.9 years and 2.9 years, respectively [5]. For benign intracranial meningiomas, this time period ranged from 26 months to 21 years (mean: 90 months) [18], with late recurrences reported at 17 years and 25 years of follow-up [9,13,18,31]. For Simpson's grade I and II resections, the recurrence time was 13 and 26 months to 13.5 and 13 years, with averages of 62 and 57 months, respectively [37]. Predominance of later recurrences in less aggressive tumors (grade I with proliferation index < 2%) was also observed by others [31]. By using analyses with a life table, the risk of recurrence at 5, 10, and 15 years was 7%, 20%, and 32% and 37%, 55%, and 91%, respectively, for total and subtotal resections, respectively [26]. In our study, recurrences of intracranial meningiomas occurred between 1-203 months (36% in the first 5 years and 60% in the first 10 years). In the first two years, recurrences predominated, and RFS curves were worse in patients with subtotal resections, compared to total resections. Likewise, for total tumors and for intracranial tumors, the rate of recurrences increased, and the RFS curves progressively worsened according to Simpson's I to IV resections.

The relationship between more aggressive histological grade and greater recurrence and lower RFS was reported by Cushing [9]. This phenomenon was also reported later by other authors, wherein it was observed to range from 0% for benign tumors to 50% for malignant tumors [13,19,37]. The WHO histological classification made the evolution of meningiomas more comparable in the literature. Global recurrence rates are now referenced as 7.5 - 11.0% for grade I, 25.5 - 59.0% for grade II (14% with total resection and 37% with partial resection), and 25-94% for grade III [3,6,7,10,22]. The survival rates of 5 years and 10 years are reported to be 90% and 81%, respectively, for grade I meningiomas, 80% and 61% for grade II meningiomas, respectively, and 30% and 15% for grade III tumors, respectively [2,12,17]. RFS curves have been observed to decrease with the progression of the histological grade (means of 54.1%, 11.9 - 30.1%, and 10.5% months for grades I, II, and III, respectively) [10,22,28]. Among the intracranial tumors, we observed lower recurrences rates between grades I/II tumors than among grade III, and between grade II and grade III. We also observed better RFS curve for patients with grade I tumors than for patients with grade II/III tumors.

The presence of focal atypia characteristics (mitotic activity, increased cellularity, nuclear pleomorphism, and necrosis) ane is associated with progression/recurrence (1- and 5-year actuarial rates of 9.6% vs 1.4% and 30.8% vs 13.8% for tumors with and without signs of atypia, respectively) [23]. Our tumors with WHO grade I focal atypia in the first biopsy had a higher rate of recurrence; however, they presented RFS curves that were similar to those that did not present atypia. It is possible that genetic data can characterize better the behavior of these tumors.

Radiotherapy as a primary or adjuvant treatment is not part of routine meningioma management in our hospital and, because of this 10 patients underwent adjuvant radiotherapy were excluded from this analysis aiming to avoid contamination of the results of surgical treatment that was the main objective of this study.

Despite the development of diagnostic methods and surgical techniques, the factors that determine the recurrence of meningiomas in histological grade I tumors continue to be a problem in their management. In addition to the classic factors, the identification of genetic-molecular factors and the use of algorithms involving clinical, radiomic, and tumor-related information represent hopes for a better characterization of the evolution of these tumors [12,14,17,36]. As the reality for many developing countries do not allow the identification of the genetic-molecular factors of meningiomas, the results obtained with the analysis of this large cohort can contribute for the comparison with other similar series.

Conclusion

The characteristics of recurrences of CNS meningiomas (the EOR, histological grade, tumor size, and age) in our patients who were exclusively treated via surgery were similar to those observed in other large studies. In addition, the male sex and atypia in histological grade I tumors were identified as being independent factors for recurrence. Despite the development of diagnostic methods and surgical techniques, the recurrence of meningiomas has exhibited only a slight decreasing trend in recent decades.

Conflict of Interest

The authors have no financial interest or any conflict of interest to declare.

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