Risk of Recurrence in Operated Parasagittal Meningiomas: A Logistic Binary Regression Model

José Alberto Escribano Mesa[1], Enrique Alonso Morillejo[3], Tesifón Parrón Carreño[2], Antonio Huete Allut[1], José María Narro Donate[1], Paddy Méndez Román[1], Ascensión Contreras Jiménez[1], Francisco Pedrero García[1], José Masegosa González[1]

■ BACKGROUND: **Parasagittal meningiomas arise from the arachnoid cells of the angle formed between the superior sagittal sinus (SSS) and the brain convexity. In this retrospective study, we focused on factors that predict early recurrence and recurrence times.**

■ METHODS: **We reviewed 125 patients with parasagittal meningiomas operated from 1985 to 2014. We studied the following variables: age, sex, location, laterality, histology, surgeons, invasion of the SSS, Simpson removal grade, follow-up time, angiography, embolization, radiotherapy, recurrence and recurrence time, reoperation, neurologic deficit, degree of dependency, and patient status at the end of follow-up.**

■ RESULTS: **Patients ranged in age from 26 to 81 years (mean 57.86 years; median 60 years). There were 44 men (35.2%) and 81 women (64.8%). There were 57 patients with neurologic deficits (45.2%). The most common presenting symptom was motor deficit. World Health Organization grade I tumors were identified in 104 patients (84.6%), and the majority were the meningothelial type. Recurrence was detected in 34 cases. Time of recurrence was 9 to 336 months (mean: 84.4 months; median: 79.5 months). Male sex was identified as an independent risk for recurrence with relative risk 2.7 (95% confidence interval 1.21–6.15), $P = 0.014$. Kaplan–Meier curves for recurrence had statistically significant differences depending on sex, age, histologic type, and World Health Organization histologic grade. A binary logistic regression was made with the Hosmer–Lemeshow test with $P > 0.05$; sex, tumor size, and histologic type were used in this model.**

■ CONCLUSIONS: **Male sex is an independent risk factor for recurrence that, associated with other factors such tumor size and histologic type, explains 74.5% of all cases in a binary regression model.**

INTRODUCTION

Parasagittal meningiomas arise from the arachnoid cells of the angle formed between the superior sagittal sinus (SSS) and the brain convexity. They comprise 20%–30% of all intracranial meningiomas. Considering the symptoms and the surgical aspects, we divide these tumors into anterior, middle, and posterior thirds of the SSS. The sinus can be partially or completely occluded by the tumor's growth. Sometimes only the lateral wall of the sinus is involved.[1]

Angiography or angio-magnetic resonance imaging (angio-MRI) usually is needed to assess the status of the SSS and the relationship of the meningioma with the cortical veins, this information is vital, particularly in middle and posterior-third lesions to decide what to do with the SSS during surgery. Many authors have carefully approached this aspect, and they all agree

Key words
- Operated meningiomas
- Parasagittal meningiomas
- Parasagittal meningiomas recurrence
- Superior sagittal sinus

Abbreviations and Acronyms
Angio-MRI: Angio-magnetic resonance imaging
CI: Confidence interval
CT: Computed tomography
MRI: Magnetic resonance imaging
PR: Progesterone receptor
RR: Relative risk
RS: Radiosurgery
RT: Radiotherapy
SSS: Superior sagittal sinus
WHO: World Health Organization

From the [1]Department of Neurosurgery, Complejo Hospitalario Torrecárdenas; Departments of [2]Health Science, and [3]Psychology, University of Almería, Almería, Spain

To whom correspondence should be addressed: José Alberto Escribano Mesa, M.D. [E-mail: dr.j.a.escribano@gmail.com]

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that it is vital to conserve the cortical drainage veins to avoid a venous stroke.

In cases in which occlusion of the sinus is total, it is possible to bind the sinus if blood flow is absent when demonstrated by angiography. Some authors have proposed as a valid method reconstruction of the SSS if permeability still exists, its invasion makes a tumor progression very predictable despite a subtotal resection of the meningioma.

All these considerations are important because a subtotal resection typically is associated with a greater rate of tumor recurrence. A subtotal resection is accepted by the scientific community as a risk factor but nowadays some studies put in fabric of judgment this affirmation, with a large number of cases and no statistical significance between Simpson Grade of resection and rate of recurrence. Other risk factors for recurrence have been described in published studies such as age, tumor size, sex, World Health Organization (WHO) grading, and histologic type.[2,3] In this retrospective study, we focused on aspects relating to factors that predict an early recurrence of this type of meningioma and progression time.

MATERIALS AND METHODS

We have researched all parasagittal meningiomas operated from 1985 to 2014. We studied in our hospital data base (Hospital Torrecárdenas, Almería) the following variables: age, sex, location (anterior, middle, or posterior third of the SSS), laterality (right, left, or bilateral), date of surgery, histology, surgeons, degree of invasion of the SSS (total, partial, or no invasion), Simpson removal grade, follow-up time, angiography, previous tumor embolization, radiotherapy (RT) after surgery, recurrence, recurrence time, reoperation, neurologic deficit at diagnosis, and level of dependence as measured by the functional independence measure before, after surgery, and at the end of the patient follow-up, which evaluates the patient according to the areas of feeding, locomotion, expression, transfer mobility, and social interaction. Scores are comprise the following groups: 1 (complete dependence), 2 (modified dependence), 3 (modified independence), and 4 (complete independence).[4] Also studied was the status of the patients at the end of the follow-up: living free of disease, alive with recurrence, perioperative death, death due to tumor progression, death due to another reason, and death due to age.

There were 125 patients with parasagittal meningiomas who underwent operation. All were studied with a previous contrast computed tomography (CT) scan and magnetic resonance imaging (MRI). Angiography was performed in 75 cases and 10 were previously embolized, and 50 were studied only with angio-MRI. Since 2007, tumor location is determined intraoperatively with a neuronavigation system. A standardized technical process is performed in our department: great craniotomy, dura opening in a C-shape fashion with its base toward the SSS, an initial debulking of the tumor with bipolar and ultrasonic suction, dissection of the tumor's lateral walls with cottoned and water jet dissection, middle wall coagulation, and removal of tumor implantation around the sinus (SSS) area.

The degree of resection was evaluated 24 hours after surgery with a contrast CT scan and 2 months after surgery with a gadolinium-contrast MRI. Statistical analysis was performed with SSPS 22.0 Statistical Software (IBM Corp., Armonk, New York, USA). We made an analysis of frequency of variables. A comparison between qualitative variables was made with the χ^2 test, and Kaplan–Meier curves with a long-rank test (Mantel-Cox) have been done to see the influence of diverse variables and the recurrence of the tumor or patient's survival. Using the same software, we made a binary logistic regression model with the Hosmer–Lemeshow test to accept it.

RESULTS

Patient Characteristics

The age range of patients was 26–81 years (mean: 57.86 years; median: 60 years). There were 44 men (35.2%) and 81 women (64.8%). Time to follow-up ranged from 13 to 340 months (mean: 105.79 months; median: 96 months).

Clinical Presentation

There were neurologic deficits in 57 patients (46.2%). The most common presenting symptoms were motor deficit (41 patients; 32.8%), followed by headache (34 patients; 27.2%), seizures (25 patients; 20%), mental symptoms (16 patients; 12.8%), dysphasia (6 patients; 4.8%), visual loss (4 patients; 3.2%), and head tumescence (2 patients; 1.6%). Diagnosis was incidental in 7 patients (5.6%).

Histology

Tumors were classified and divided into histologic subtypes according to the WHO criteria. WHO grade I tumors were identified in 104 patients (84.6%) the majority were the meningothelial type, followed by transitional and fibroblastic; "atypical" meningiomas (WHO grade II) were diagnosed in 16 patients (13%), and malignant meningiomas (WHO grade III) were diagnosed in 3 patients (2.4%).

Tumors Characteristics

Tumor size ranged from 2 to 8.6 cm (mean: 4.86 cm; median: 5 cm). Table 1 lists the patients depending on tumor laterality (right, left, or bilateral), sinus invasion, histologic grade (WHO grades I, II, or III), Simpson removal grade (Grades I, II, III, or IV), functional outcome before, after surgery, and at the end of follow-up (functional independence measure grades I, II, III, or IV), and final status of the patients according to the tumor location along the SSS (anterior, middle, and posterior third).

In the majority of cases (68 patients; 54.4%) the location of the tumors was in the middle third of SSS, the others cases were in the anterior third (37 patients; 29,6%) and in the posterior third (20 patients; 16%). There were 55 patients (44%) with tumors on the right side, 51 patients (40.8%) with tumors on the left side, and 19 (15.4%) patients with bilateral tumor extension. After we evaluated the preoperative images (MRI, CT scan, angio-MRI, and angiography) and after confirming it intraoperatively, the SSS was

Table 1. Characteristics Depending on Tumor Location

	Tumor Location			
Characteristics	**Anterior Third, *n* (%)**	**Middle Third, *n* (%)**	**Posterior Third, *n* (%)**	**Total (100%)**
Laterality				
Right	18 (32.7)	31 (56.4)	6 (10.9)	55
Left	10 (19.6)	29 (56.9)	12 (23.5)	51
Bilateral	9 (47.4)	8 (42.1)	2 (10.5)	19
Sagittal sinus invasion				
No invasion	18 (24)	43 (57.3)	14 (18.7)	75
Partial invasion	8 (26.7)	17 (56.7)	5 (16.7)	30
Total invasion	11 (57.9)	7 (36.8)	1 (5.3)	19
Histologic grade				
WHO grade I	30 (28.8)	58 (55.8)	16 (15.4)	104
WHO grade II	6 (37.5)	7 (43.7)	3 (18.7)	16
WHO grade III	1 (33.3)	1 (33.3)	1 (33.3)	3
Simpson removal grade				
Grade I	11 (64.7)	4 (23.5)	2 (11.8)	17
Grade II	26 (27)	55 (57.3)	15 (15.6)	96
Grade III	0 (0)	0 (0)	0 (0)	0
Grade IV	0 (0)	5 (83.3)	1 (16.6)	6
Dependence level before surgery				
I — Complete dependence	3 (27.3)	8 (72.7)	0 (0)	11
II — Modified dependence	2 (8.7)	19 (82.6)	2 (8.7)	23
III — Modified independence	6 (30)	13 (65)	1 (5)	20
IV — Complete independence	26 (37.1)	27 (38.6)	17 (24.3)	70
Dependence level after surgery				
I — Complete dependence	1 (14.3)	5 (71.4)	1 (14.3)	7
II — Modified dependence	1 (9)	9 (81.9)	1 (9)	11
III — Modified independence	4 (21)	14 (73.7)	1 (5.3)	19
IV — Complete independence	31 (35.6)	39 (44.8)	17 (19.5)	87
Final dependence level				
I — Complete dependence	2 (20)	7 (70)	1 (10)	10
II — Modified dependence	2 (50)	2 (50)	0 (0)	4
III — Modified independence	3 (15)	14 (70)	3 (15)	20
IV — Complete independence	30 (33.3)	44 (48.9)	16 (17.8)	90
Final status of patients				
Living free of disease	24 (29)	44 (53)	15 (18)	83
Living with recurrence	6 (30)	10 (50)	4 (20)	20
Perioperative death	0 (0)	1 (100)	0 (0)	1
Death due to tumor progression	1 (50)	1 (50)	0 (0)	2
Death due to another reason	3 (30)	6 (60)	1 (10)	10

WHO, World Health Organization.

completely invaded and obstructed in 19 patients (15.4%), partially invaded in 30 patients (24.2%), and not invaded in 75 patients (60.5%). Angiography was undertaken in 74 (59.2%) meningiomas, and 10 (8%) of them were embolized.

There were 16 patients (12.8%) who underwent a total resection of the SSS at the site of tumor implantation; in 97 cases (77.6%), a total tumor resection was done by coagulating the area of tumor implantation in the SSS. Total tumor resection without coagulating the implantation site was performed in 5 patients (4%). In 6 patients (4.8%) in whom total removal of tumor would have required sacrificing the SSS, we decided to partially resect the tumor, obtaining a Simpson Grade IV resection.

Patient Outcomes

In general, functional results were satisfactory. During the preoperative evaluation, there were 11 (8.9%) patients listed as completely dependent and 23 (18.5%) patients with modified dependence. After surgery, there were 7 (5.6%) patients with complete dependence and 11 (8.9%) patients with modified dependence. At the end of follow-up there were 10 patients (8.1%) with total dependence and 4 patients (3.2%) with moderate dependence.

At the final status stage of the patients, at the end of follow-up, there were 83 (71.6%) patients alive without tumor presence or with a stable rest of the tumor, 20 (17.2%) patients with progression or tumor recurrence, 1 (0.9%) patient died 1 month later of meningitis, 2 (1.7%) patients died secondary to tumor progression, and 10 (8.6%) patients died from other pathologies (2 pulmonary edema, 1 colon carcinoma, 1 bladder carcinoma, 1 heart attack, 1 primary dementia, 1 urinary sepsis, 1 pancreatitis, and 2 natural death).

Complications

The following complications were reported: 1 patient developed hematoma after surgery that didn't require surgical evacuation, 2 patients with brain edema required a decompressive craniectomy, 1 cerebrospinal fluid fistula, 1 surgical infection which required reoperation, 14 deep vein thrombosis, and 1 of them required a cava vein filter.

Recurrence and Progression

Tumor recurrence was detected in 34 of 125 cases, of whom 18 were reoperated. Time for recurrence was 9 to 336 months (mean 84.44 months). The histology in these reoperated meningiomas were WHO grade I in 10 patients, grade II in 6 patients, and grade III in 2 patients. In 6 patients a total resection of SSS were performed, as it was totally obliterated; tumor resection in the rest of the cases were WHO grade II on the Simpson score scale.

Time of Recurrence

Kaplan–Meier's survival curves for tumor recurrence were different, with statistical significance (Mantel-Cox) for these variables: sex, age (≤60 years vs. >60 years), histologic types, and WHO histologic grades (Figures 1–4). There were no statistical differences in proportion recurrence-free areas depending on Simpson removal grade and tumor size, this result is significant in others published studies as DiMeco et al.[5], who reported lower area under the curves of tumors larger than 4 cm and Simpson Grade IV. This different result is probably explained by our low number of Simpson Grades I and IV.

Statistical Associations

There was a statistical association between male sex and greater risk of recurrence $P = 0.013$ and relative risk (RR) 2.7 (95% confidence interval [CI] 1.21–6.15); an association also was found between female sex and the status of patients at the end of the follow-up, with a greater number of women with total independence ($P = 0.039$); there was an association between male sex and RT ($P = 0.037$) but without RR. The frequency of total infiltration of the venous sinus versus partial and no infiltration was greater in men (11 of 44 cases in men vs. 8 of 80 in women, $P = 0.026$).

There was a statistical association between recurrence and patient status at the end of follow-up, with a greater number of total dependent classifications in patients with recurrence (6 total dependent patients with recurrence vs. 3 patients without recurrence; $P = 0.026$). Recurrence was associated with histologic type, with a greater rate of recurrences observed in atypical, anaplastic, and malignant types ($P = 0.026$).

Histologic grade II/III of the WHO was associated to a greater level of SSS invasion ($P = 0.019$ and RR 3.24 [95% CI 1.17–8.94]). WHO grade I was also associated with a greater probability of tumor-free resection or with a stable tumor rest at the end of the follow-up ($P = 0.003$).

There were statistical associations between dependent levels in all patients' time points (preoperative, postoperative, and at the end of the follow-up, with $P < 0.05$ in all of them). Patients older than 60 years and tumor location were another association in our study, with a lower number of tumors in the posterior third (3 cases vs. 17 cases, $P = 0.005$).

Binary Logistic Regression Model

We conducted a binary logistic regression model to know the RR of this kind of tumor. We have excluded the rarest histologic type of tumors because the statistic program excluded automatically these categories because of their low number of cases. Therefore, this model was made for meningothelial, fibroblastic, and transitional types of parasagittal meningiomas.

This is a significant model, it makes clear between 0.20 (R^2 of Cox and Snell) and 0.29 (R^2 of Nagelkerke) of the dependent variable, and it classifies correctly 74.4% of the cases. Hosmer–Lemeshow test had a $P > 0.05$; therefore, this model is accepted.

On the basis of the results, the equation of regression would stay according to the following formula:

$$\text{Risk of recurrence} = -4.88 + \text{Exp}\,\beta 1\ (\text{sex}) + \text{Exp}\,\beta 2\ (\text{size}) + \text{Exp}\,\beta 3\ (\text{if fibroblastic}) \text{ or } + \text{Exp}\,\beta 4\ (\text{if transitional})$$

$$\text{Risk of recurrence} = -4.88 + 2.93\ (\text{sex}) + 1.46\ (\text{size}) + 10.27\ (\text{if fibroblastic}) \text{ or } + 7.38\ (\text{if transitional})$$

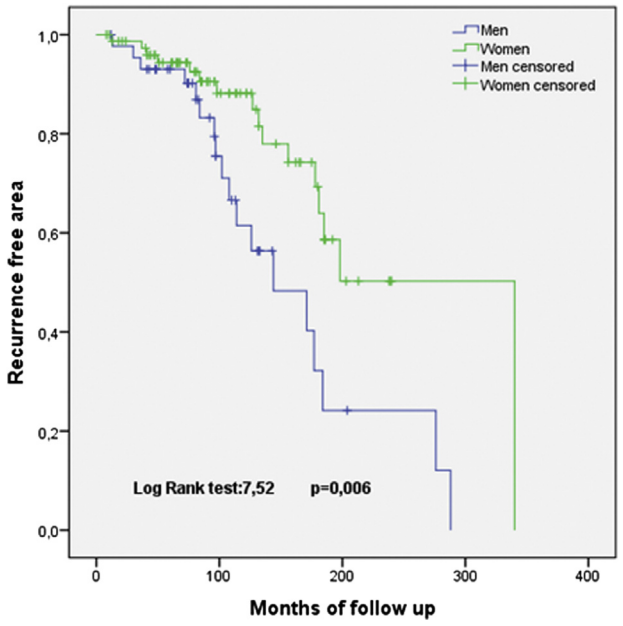

Figure 1. Sex and recurrence.

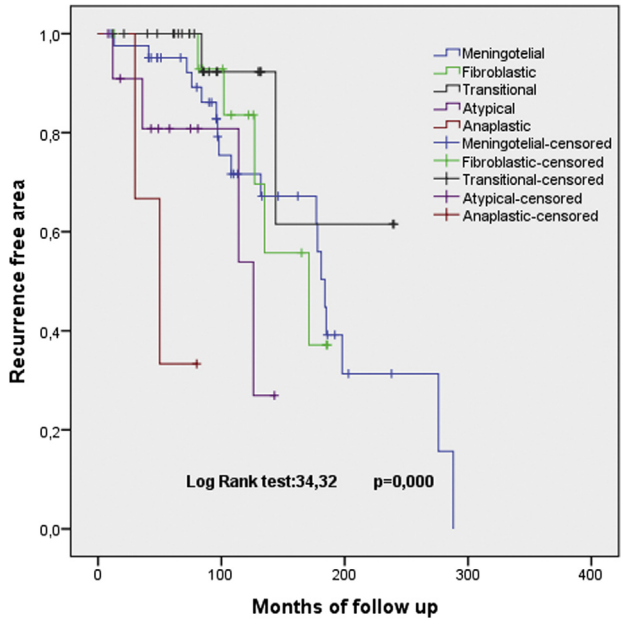

Figure 3. Histologic type and recurrence.

DISCUSSION

To have a complete view of these type of tumors, it is necessary to take into account the aspects relative to the morbidity and mortality of the surgery, risk factors for recurrence, and the outcome of the patients during follow-up. On the first point, in older series such as those of Hoessly and Olivecrona[6] in 1953, the mortality of operated parasagittal meningiomas was 12.3% and in more recent series mortality is approximately 1.9%–1.7%; the decrease in

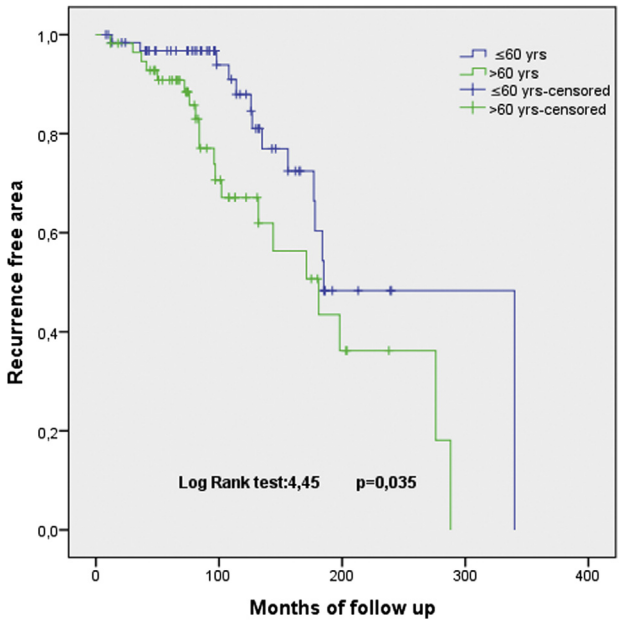

Figure 2. Age and recurrence.

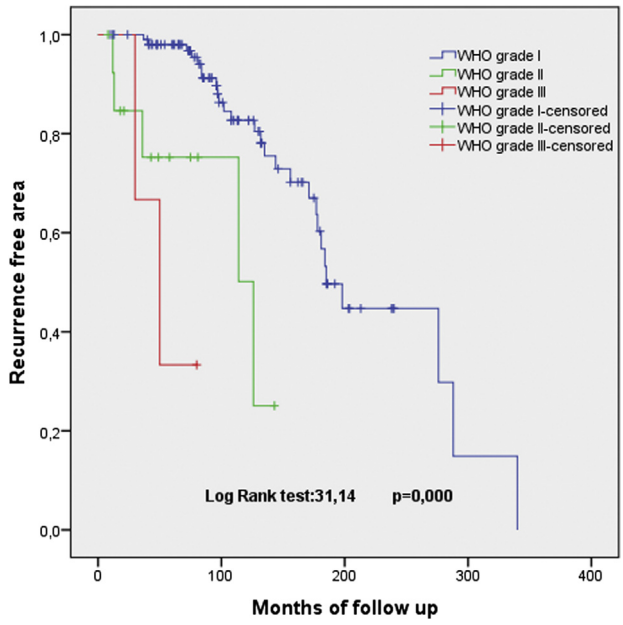

Figure 4. World Health Organization (WHO) grade and recurrence.

percentages is due to improvements in microsurgical techniques and advances in perioperative care.[6] Morbidity is another factor that depends on the aggressiveness of surgery performed in patients, in our series, morbidity was 15.2% fundamentally secondary to deep-vein thrombosis, but in other studies morbidity can increase up to 28.7%, including in this percentage the number of brain swelling and postoperative hematomas.[1,7-9]

The majority of these complications have a relationship with the damage of cortical veins around the tumors or in the SSS. The authors generally agree that the anterior third of the SSS can be sacrificed by removing it with the tumor during surgery without major complications.[1,2,6-8,10-19] The classic paradigm that says that the cortical veins anterior to the vein of Trolard are not important and can be coagulated is not totally clear and not always accepted; we are not sure of that affirmation according to our experience.

The rupture and coagulation of these hypertrophic bridging veins, especially the ones located in the middle third of the SSS, can produce venous infarction, with hyperemia, brain edema and the corresponding associated deficits.[1,2,5,7,15] In series like those of DiMeco et al.,[5] the reconstruction of SSS using other corporal veins and synthetic materials such as Gore-Tex creates good results in patients, presenting no complications even though there is a greater risk of venous infarction or sinus thrombosis. A valid strategy to avoid the risk of complications is to remove the tumor to a safe area around the SSS and wait for its total occlusion and development of collateral blood flow, this is the strategy used by our surgical team. All these considerations translate into the risk of morbidity and mortality.

The second point to keep in mind is the probability of recurrence of these tumors. The factors that may influence greater recurrence are not completely clear. In our series, only male sex was a prognostic factor of recurrence, with a greater RR for men. Male sex also was associated with increased SSS invasion. This invasion is not associated directly with a greater recurrence, so it is not a confusion factor. The association "SSS invasion and recurrence" has a $P = 0.594$ on the χ^2 test; therefore, it does not make us suspect that it's because of a low number of cases. A possible explanation for this association may be the presence of progesterone receptors (PRs) in these type of tumors, affecting of negative form the growth of the tumors when women reach an advanced age. The majority of published studies, using a monoclonal antibody fixed to the tumors, report the presence of PR in 90% of tested meningiomas in female subjects. A lower presence of PR was noted in anaplastic meningiomas, and PR expression was inversely correlated with ki67 expression and WHO grading.[20]

The mean age in operated women in this study was 58.14 years, which corresponds to the postmenopausal period and therefore to a low progesterone activity; because the tumor growth is hormone dependent, recurrence is less likely. In contrast, in the male sex tumor growth is progesterone independent and more constant through time and so the age of the patient doesn't influence the appearance of recurrence; this is a possible explanation because in our cohort the Kaplan–Meier curves are different, with a lower area under the curve for men. However, this is only a hypothesis that requires a complementary analysis of hormonal receptors that we did not perform in our study.

Historically, an incomplete resection of the tumor has been considered the most important factor for recurrence, based on studies performed in the middle of the last century like those Hoessly and Olivecrona[6] or Simpson.[18] These classical studies were performed with a large number of cases but used older surgical techniques, before the arrival of the surgical microscope, bipolar coagulation, ultrasonic suction, and in tumors from many locations, extrapolating the results to parasagittal tumors. In the same way, the criteria of histologic classification have been examined and modified in several occasions during the years and that's why there is a great probability that some parasagittal meningiomas classified as WHO grade II are actually WHO grade III tumors.[6,18] More recently, the study of DiMeco et al.,[5] which included 108 meningiomas invading the SSS, identified Simpson Grade IV as a risk factor for recurrence, but the univariate analysis (Cox model) was made with 85% confidence interval.

In a later study with 25 years of follow-up, Petterson-Segerlind et al.[21] identified that an incomplete resection of the tumor was a risk factor for recurrence by comparing Simpson Grades IV versus I-III Grades groups (RR 1.78; 95% CI 1.03–2.12). The results are very evident, thanks to this long period of patient follow-up, facilitating the appearance of tumors recurrence and therefore increasing the statistical power.[21]

In a recent study, Otero et al.[3] reviewed recurrence in 208 WHO grade I meningiomas, located in convexity, falx/parasagittal, and skull base. They concluded that there is no significant difference in recurrence rates between the different Simpson grades in any of the location groups. Patient follow-up in this study had a median of 5 years, which we consider a short time for most WHO grade I meningioma to recur.

Data suggest that with the use of modern surgical techniques, small residual portions of WHO Grade I meningiomas left in and around the SSS generally do not grow for several years after surgery. In our study, no significant statistical differences were found between the Simpson Grade IV and I-III groups; however, as we have stated, the time of follow-up was not as longer as others published studies. We found differences in Kaplan–Meier's curves with shorter recurrence time for male sex, patients older than 60 years, and meningiomas WHO grade II-III compared with grade I. In combination, sex, tumor size, and histologic type can explain 74.4% of the cases by an equation of logistic regression. Using this formula, we can calculate the individual risk of recurrence for each patient.

Regarding patients' functional development, we can affirm that the initial condition determines the postoperative and final condition of patients. There is a strong statistical association between all these functional conditions, as if they were links of a chain. Therefore, when we speak to the patient about their possible functional deficits after surgery, we will have to bear the previous condition in mind as the principal prognostic factor.

It's very important to keep in mind the possibility of a complementary treatment with RT or radiosurgery (Rs), depending on the size and location of the rest of the tumor. The need to administer radiation after surgery in tumors with WHO grade II or III is commonly accepted, but there isn't a general consensus on

WHO grade I tumors with remnants on the SSS; some surgeons prefer waiting to see the growth of the rest of the tumors and reoperate if it reaches a suitable size, and others prefer administering radiation.[13,16]

With the use of the RT in its diverse types, control of recurrence has been obtained between 71% and 98% in WHO grade I meningiomas, depending on the series. A review done by Alkemade et al. demonstrated how the rate of recurrence during 5 years' follow-up decreased from 45% to 10% after RT. Rogers et al. demonstrated how a subtotal resection and RT as adjuvant treatment increases the rate of progression-free survival in a period of 5 years from 38%–63% to 80%–100%. Regarding the use of Rs, Kondziolka et al. obtained a global control rate of 9% in 5 years.[22-26]

CONCLUSIONS

Parasagittal meningiomas are tumors of benign behavior but sometimes are difficult to manage medically and surgically because of their trend to reappear (27.2% cases) and to invade the SSS (39.2% cases). Times of recurrence range from 9 to 336 months (mean 84.44 months). Male sex is an independent risk factor of tumor recurrence that combined with tumor size and histologic type (meningothelial, fibroblastic, and transitional) can explain the 74.4% of the cases in our series in a logistic regression equation. The most important factor for the level of dependence of the patients after surgery is their level of dependence before it. RT or Rs are useful tools after surgery on high-grade meningiomas and in WHO I tumors with subtotal resection.

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