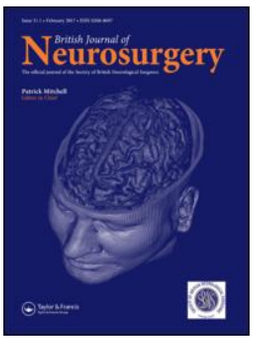

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ORIGINAL ARTICLE

Multicentric and diffuse recurrences of meningiomas

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ABSTRACT

Background: Meningiomas recur with a rate of 10–32% at 10 years. Several features influence the risk of recurrence.

Objective: To define the pathological and surgical features at risk of multicentric-diffuse versus local–peripheral recurrence.

Methods: Thirty-three patients operated on for intracranial meningiomas who experienced multicentric-diffuse recurrence were retrospectively analyzed. The data of these patients were compared to those of 50 patients who experienced local–peripheral recurrence. The analyzed factors included age and sex, tumor location and shape, brain-tumor interface, entity of resection, WHO grade, Ki67 MIB1, progesterone receptor (PR) expression, number of reoperations, progression of WHO grade, and outcome.

Results: Meningiomas which recurred in multicentric-diffuse pattern showed at initial surgery a significantly higher rate of flat-shaped tumors ($p = .0008$) and of cases with Ki67 Li $\geq$ 4% ($p = .037$) than those which recurred in localized-peripheral pattern, whereas other factors did not significantly differ. Among patients with multicentric-diffuse recurrences, 25 underwent one to three reoperations; 17 among them (66%) are alive with local tumor control or slow progression 2–25 years after the initial surgery versus only 2 out of 8 who did not undergo surgery.

Conclusions: Flat-shaped meningiomas and those with Ki67 Li $\geq$ 4% are at higher risk of multicentric-diffuse recurrence. Multiple reoperations over a period of several years may obtain rather long survivals in selected patients with prevalent intradural, not anaplastic tumors and not too extensive dural infiltration.

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Meningioma; recurrence; proliferation index

Introduction

Intracranial meningiomas are estimated to recur in 10–32% of the cases at 10 years.[1–3] The main risk factors include the WHO grade,[4–7] Simpson grade of surgical resection,[8,9] proliferation index Ki67-MIB1,[10–13] mitotic index,[14] and postoperative adjuvant treatments.[1,15,16] Other factors have also been suggested, such as patient age and sex,[4,17] tumor size,[18–20] location[21,22] morphology,[18,21,23] brain invasion[9,13] and progesterone receptor (PR) expression.[7,24–26] However, all published studies consider the overall recurrences, with no focus on their topography and extension.

The aim of this study is to discuss the different morphologies of recurrent meningiomas, the factors correlated with their different extension and the therapeutic implications. No previous studies have focused on these factors.

Materials and methods

Classification of recurrences

According to their topography on post-contrast magnetic resonance imaging (MRI) and surgical descriptions, recurrent meningiomas were classified in four types:

- type 1: local, confined to the previous dural site;
- type 2: peripheral, at the surrounding dura, contiguous to the previous site;
- type 3: multicentric, with multiple nodules both at the dural site and distant, with seemly normal interposed dura mater;
- type 4: diffuse, with multiple nodules with interposed dural infiltration, or diffuse extradural infiltration.

Patient population

Eight hundred-five patients surgically treated with the histological diagnosis of meningioma at the neurosurgical clinic of the 'Federico II' University School of Medicine of Naples between 1993 and 2015 were reviewed. Among them, 33 multicentric and diffuse recurrences were identified (group 1). A control group of 50 consecutive patients with local–peripheral recurrence treated between 2006 and 2016 was also identified (group 2). The data of these 83 patients, both at initial diagnosis and at recurrence, were analyzed. The inclusion criteria at initial diagnosis were a single meningioma, no diffuse dural infiltration, resection of Simpson grades 1–3, WHO grades 1 and 2. Cases with neurofibromatosis and other conditions influencing the tumor progression, patients with history of other intracranial tumors, post-irradiation, multiple and malignant meningiomas and those lost to follow-up were excluded.

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Analyzed factors

The case histories, preoperative and follow-up MRI studies, surgical descriptions and pathological findings were re-examinated both at initial diagnosis and at recurrence. The analyzed factors at initial diagnosis include patient age and sex, tumor location and shape, brain–tumor interface, entity of surgical resection, adjuvant treatments, WHO grades (I versus II), Ki67 MIB1, PR expression.

The analyzed factors at recurrence include interval time between initial surgery and recurrence, management (conservative, surgery, radiotherapy), WHO grade, Ki67 MIB1 and PR expression of the recurrent tumor, and outcome.

The tumor location was defined from review of the surgical description. Three groups were identified. Group A, or medial skull base, includes olfactory groove, planum ethmoidale, tuberculum sellae, anterior clinoid, clival-petroclival and foramen magnum meningiomas. Group B, or lateral skull base, includes middle-lateral sphenoid wing, temporal fossa, spheno-orbital, petrous bone and occipital fossa meningiomas. Group C, or non-skull base, includes brain convexity, parasagittal and falx meningiomas and those of the lateral tentorium, cerebellar convexity and lateral ventricle.

The tumor shape was defined on MRI and classified as round (tumor diameter/dural base ratio > 1) and flat (tumor diameter/dural base ratio ≤ 1). The brain–tumor interface was defined on the surgical descriptions and classified as preserved or lost.

The extent of surgical resection was defined according to the Simpson classification[27] on the postoperative post-contrast MR studies.

All pathological specimens, both at initial surgery and reoperations, were separately reviewed by two pathologists (MLDC and EG) unaware of the type of recurrence. They were classified according to WHO 2000[28] and 2007[29] classifications, in relation to the observation period. Immunohistochemical studies were performed to evaluate the Ki67 MIB1 and the PR expression.

The expression of Ki67 MIB1 was evaluated in all cases by monoclonal antibody MIB1 Immunotech (dilution 1:1000, overnight incubation). The streptavidin–biotin system and the diaminobenzidine (DAB) were used for antigen detection and visualization. A specimen of breast carcinoma was used as positive control. The values of Ki67 Li were graded as <4 and $\geq 4\%$.

PR expression was determined in all specimens by monoclonal antibody against the progesterone (Dako 1:400 overnight incubation). The quantitative evaluation was expressed as number positive per 100 cells for HPF for a total of 500 cells. The following score was used: 1. negative or weakly positive (up to 15%); 2. moderately positive (16–50%); 3. significantly positive (51–79%); 4. markedly positive ($\geq 80\%$).

Follow-up ranges from 2 to 25 years. The presence and extension of the recurrence was defined on the control MR studies.

Statistical analysis

Student *t* test and Fisher exact tests were used for individual variables. Kaplan–Meier curves were used to show time to progression-free survival and recurrence. Two-sided *p* values smaller than .05 were considered to be significant. Statistical analyses were performed using Fisher Exact Test Calculator.

Ethical considerations

The study was reviewed and approved by the Institutional Review Board of our hospital. All methods were performed in accordance with the relevant guidelines and regulations. All patients provided written informed consent prior to participation.

Results

Findings at initial diagnosis

Clinical-radiological findings

No differences in patient sex and age at diagnosis were evidenced between the two groups (Table 1). Meningioma location was not significantly different. The rate of the spheno-orbital and parasagittal meningiomas was higher in the group of diffuse recurrences but this finding did not reach significance. The analysis of the tumor shape on MRI studies showed significantly a higher rate of flat-shaped tumors in group 1 (76%) than in group 2 (38%) ($p = .0008$).

Table 1. Clinical, radiological and surgical findings at initial diagnosis.

Covariates	Group 1 multicentric-diffuse recurrences (33 pts)	Group 2 localized-peripheral recurrences (50 pts)	Statistical analysis
Age (mean)	52 years	57 years	$p = 0.08$
Sex	F 22 (67%)	F 31 (62%)	$p = 0.81$
	M 11 (33%)	M 19 (38%)	
Tumor location			$p = 0.55$
Medial skull base	3 (9%)	8 (16%)	
Lateral skull base	12 (36%)	14 (28%)	
Non skull base	18 (55%)	28 (56%)	
Tumor shape			$p = 0.0008$
Flat	25 (76%)	19 (38%)	
Round	8 (24%)	31 (62%)	
Brain–tumor interface			$p = 0.11$
Preserved	15 (45%)	32 (64%)	
Unclear lost	18 (55%)	18 (36%)	
Extent of resection (Simpson grade)			$p = 0.67$
I	9 (28%)	18 (36%)	
II	14 (42%)	20 (40%)	
III	10 (30%)	12 (24%)	
Interval between initial surgery and recurrence (median)	4.7 years	5.3 years	$p = 0.07$

Table 2. Pathological findings at initial diagnosis.

Covariates	Group 1 multicentric-diffuse recurrences (33 pts)	Group 2 localized-peripheral recurrences (50 pts)	Statistical analysis
WHO grade			$p = 0.36$
I	17 (52%)	32 (64%)	
II	16 (48%)	18 (36%)	
Ki67 Li			$p = 0.037$
<4%	7 (20%)	22 (44%)	
≥4%	26 (80%)	28 (56%)	
P.R. expression			$p = 0.31$
≤15%	11 (33%)	14 (28%)	
16–50%	16 (49%)	18 (36%)	
51–79%	3 (9%)	12 (24%)	
≥80%	3 (9%)	6 (12%)	

Management

At surgery, no significant differences of type of brain–tumor interface were evidenced between the two groups. The extent of resection (Sinpson grades I versus II versus III) was also not significantly different.

The adjuvant treatments included radiotherapy in nine patients of group 1 (atypical meningiomas with resection of Simpson grades II or III). Among patients of group 2, four were treated by radiosurgery and two by external radiotherapy.

Pathological findings

Group 1 meningiomas showed at initial diagnosis slightly higher rate of atypical WHO cases (48%) than group 2 cases (36%), with no statistically significant difference. On the other hand, tumors with values of Ki67 Li >4% were significantly more numerous in group 1 (80%) than in group 2 (56%) ($p = 0.037$). Finally, the rates of PR expression were not significantly different (Table 2).

Findings at recurrence

Management

The interval between initial surgery and recurrence was not significantly different between group 1 (4.7 years) and group 2 (5.3 years) ($p = 0.07$).

All 50 patients of group 2 with localized-peripheral recurrence were reoperated on. In group 1, 25 out of 33 patients underwent surgery (Figures 1 and 2); all had intradural tumor ≥3 cm and no extensive "en plaque" dural involvement. In eight surgery was not performed because of the extensive en plaque dural infiltration and small intradural mass. Gross total resection (Simpson grades I and II) was obtained in only 5 (20%) of multicentric diffuse recurrences and in 38 (76%) of local-peripheral ones ($p = 0.00001$).

The number of operations is given in Table 3. In group 1, 12 (48%) patients had one reoperation, 10 had two, and 3 had three reoperations. In group 2, 41 (82%) patients had one reoperation, and 9 (18%) had two. Thus, more than one reoperation was necessary in 13 patients of group 1 (52%) versus 9 of group 2 (18%) ($p = 0.0034$). External radiotherapy was administered in 20 not previously irradiated patients of group 1 and in 12 of group 2. Stereotactic radiosurgery of residual nodules was administered in nine patients of group 1 and in two of group 2. Chemotherapy with hydroxyurea was administered in five aggressive cases of multicentric-diffuse recurrences (2 atypical and 3 anaplastic), with scarce clinical results.

Pathology

Progression of the WHO grade from the initial operation to the first recurrence was observed in 10 among 25 meningiomas reoperated on of group 1 (40%), 7 among them progressed from WHO grades I–II and 3 from WHO grades II to III. In group 2, 11 among 50 tumors (22%) progressed from grades I–II. The difference between the two groups was not significant. However, all three cases which recurred as anaplastic WHO III forms belonged to the group 1 of multicentric-diffuse meningiomas.

Outcome

In group 1 with multicentric-diffuse recurrences, one patient died in the postoperative course for respiratory failure. Among the other 24 patients operated on (group 1A) (Table 4), 11 (46%) are still alive with tumor control versus none out of eight patients who did not undergo surgery (group 1B) ($p = 0.029$). Six (25%) show slow tumor progression with no symptoms, in spite of surgery. Seven patients of group 1A (29%) died during the follow-up (5 for tumor progression and 2 for unrelated causes) versus 6 (for tumor progression) out of 8 (75%) of group 1B ($p = 0.038$).

Thus, among 25 patients reoperated on for multicentric-diffuse recurrences, 17 (68%) are alive after one or more reoperations versus only 2 out of 8 patients (25%) who did not undergo surgery ($p = 0.038$).

In group 2, local tumor control was achieved in 41 patients (82%) and tumor progression was observed in 4 (8%); five patients (10%) died during the follow-up for unrelated causes.

Thus, as expected, patients reoperated on for multicentric-diffuse recurrences show significantly lower rate of tumor control ($p = 0.0025$) and higher rates of tumor progression and death ($p = 0.068$) than those reoperated on for local–peripheral recurrences.

Discussion

Recurrence or regrowth of intracranial meningiomas most often occur at the initial dural site or at the contiguous dura, sometimes with invasion of an underlying venous sinus or bone. However, some patients show variably diffuse recurrences, with nodules distant from the initial site, with or without local recurrence and with seemly normal or infiltrated interposed dura mater. This study compares the data of two groups of patients with different patterns of recurrences (localized-peripheral versus multicentric-diffuse), with the aim to define whether there are

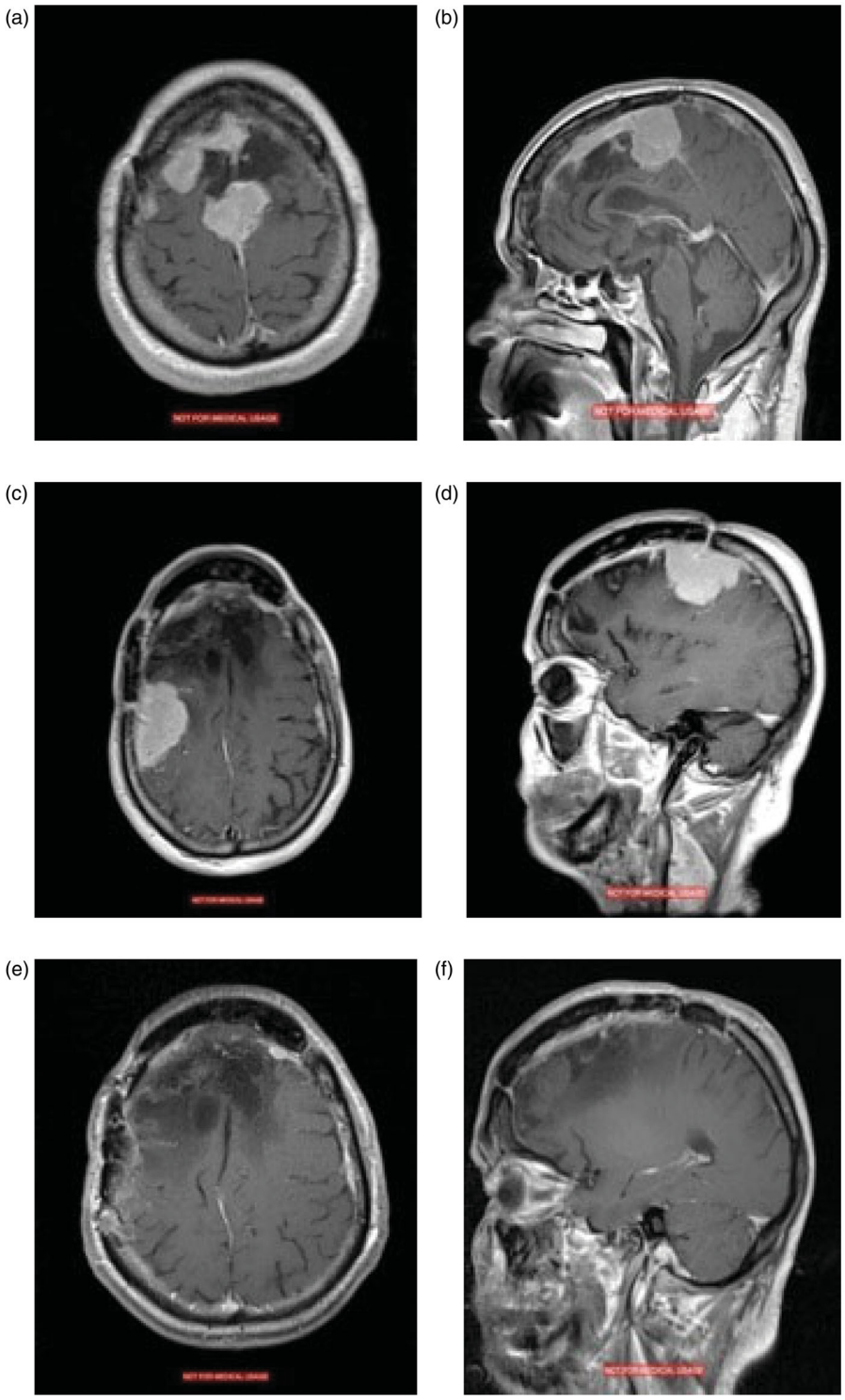

Figure 1. Post-contrast MRI of a patient who underwent resection of a 3-cm anterior parasagittal meningioma and stereotactic radiosurgery in 2006. (a, b) MRI at 3 years: diffuse recurrence involving both the falx and the convexity treated by gross total resection; (c, d) MRI in 2014: second recurrence involving the right temporo-parietal region and the middle parasagittal region; (e, f) MRI in 2015: complete tumor resection with diffuse linear dural enhancement.

different features at both initial surgery and recurrence. No previous studies have discussed this peculiar aspect of the meningioma recurrences.

We have included in group 1 only meningiomas with localized dural attachment at initial surgery and multicentric-diffuse regrowth at first recurrence; patients who already had diffuse dural infiltration at initial diagnosis and those who experienced diffuse regrowth only at second or later recurrences were excluded. For this reason, the number of cases of meningiomas with diffuse-multicentric recurrence is rather small, in spite of the long observation period (24 years). However, this selection is necessary to define why an initially localized meningioma may recur in a localized-peripheral or in a multicentric-diffuse pattern.

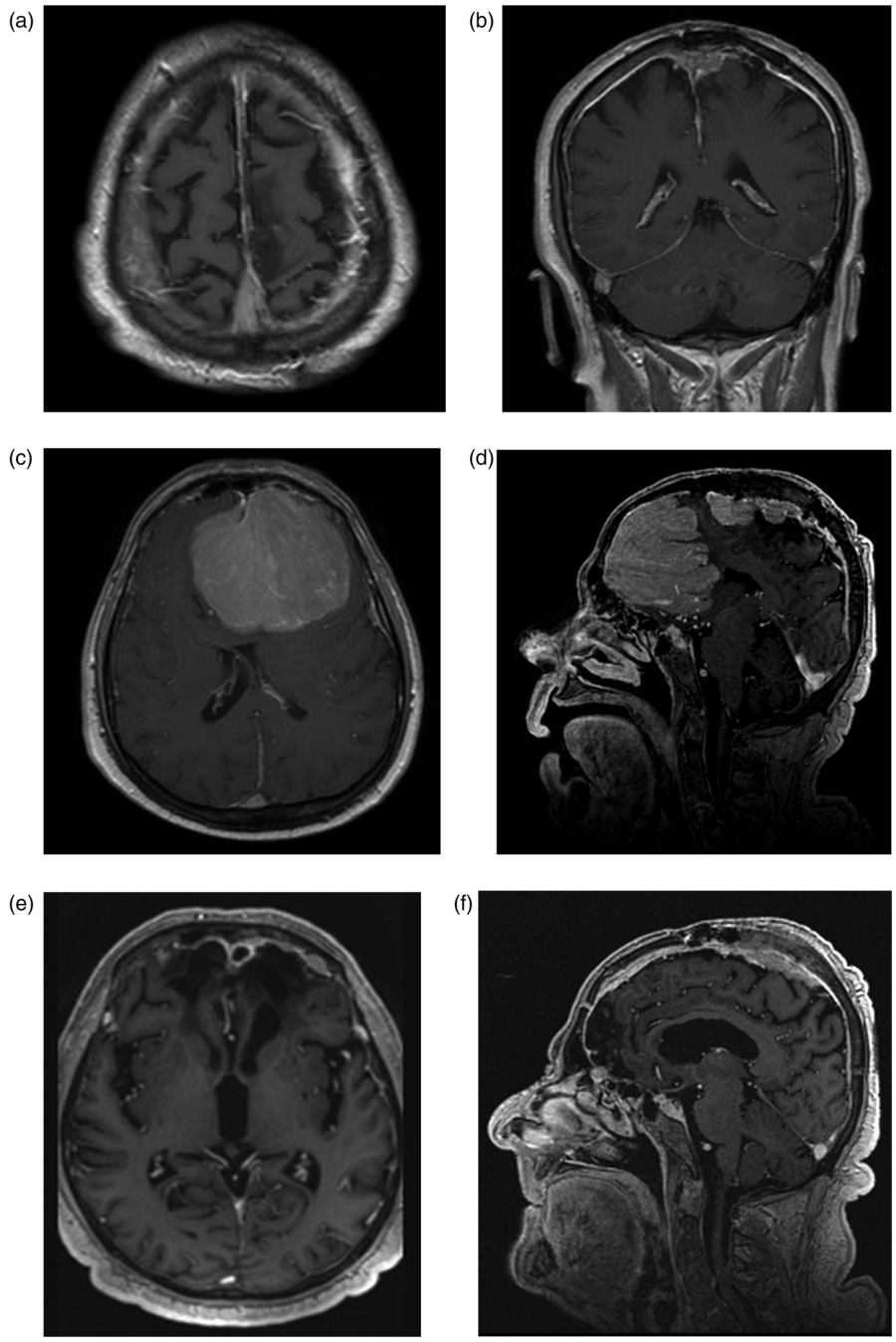

Figure 2. Post-contrast MRI of a 72-year-old man who underwent resection of the 2.5 cm WHO II meningioma of the left middle parasagittal region and stereotactic radiosurgery in 2012. (a, b) MRI in 2015: residual tumor in the middle third of the superior sagittal sinus; (c, d) Post-contrast MRI in May 2018: very diffuse recurrence with a large tumor of the anterior third of the falx and smaller nodules of the left side of the falx anterior to the previous surgical field; (e, f) Post-contrast MRI in December 2018: gross total resection of both intradural meningiomas; residual extensive infiltration of the superior sagittal sinus and falx.

Table 3. Surgical and pathological data on meningioma recurrences operated on.

Covariates	Group 1 multicentric-diffuse recurrences (25 pts)	Group 2 localized-peripheral recurrences (50 pts)	Statistical analysis
Number of surgeries			$p = 0.0034$
One reoperation	12 (48%)	41 (82%)	
Two or three reoperations	13 (52%)	9 (18%)	
Entity of resection			$p = 0.00001$
Gross total	5 (20%)	38 (76%)	
Subtotal or partial	20 (80%)	12 (24%)	
Progression of the WHO grade at first reoperation	10 (40%)	11 (22%)	$p = 0.09$
From I to II	7	11	
From II to III	3	—	
Postoperative death	1 (4%)	—	$p = 0.33$

Table 4. Outcome of patients with meningioma recurrence.

Covariates	Group 1A surgery (24 pts)	Group 1B conservative treatments (8 pts)	Statistical analysis (group 1A versus group 1B)	Group 2 Surgery (50 pts)	Statistical analysis (group 1A versus group 2)
Local control	11 (46%)	—	$p = 0.029$	41 (82%)	$p = 0.0025$
Tumor progression	6 (25%)	2 (25%)	$p = 1$	4 (8%)	$p = 0.068$
Death during the follow-up	7 (29%)	6 (75%)	$p = 0.038$	5 (10%)	$p = 0.048$

Clinical–surgical findings

The flat-shaped morphology of meningiomas at initial diagnosis is the only radiological finding with a significantly higher risk of multicentric-diffuse recurrence in this study ($p = 0.0008$). This has not previously been reported. Flat-shaped meningiomas are characterized by prevalent dural involvement as compared to the round-shaped ones. Thus, it is likely that they may be associated to various degree of even distant microscopic dural infiltration,[30] sometimes resulting in multicentric and more diffuse recurrence. On the other hand, the dural tail on MRI does not seem to reflect dural infiltration and is not correlated to the recurrence in most studies.[8,18,21] We did not investigate this finding. The lost or unclear brain–tumor interface, although at risk of recurrence,[9,13] does not correlate with the diffuse pattern of regrowth. Infact, the presence of residual cells nests at the not preserved brain-tumor interface does not explain the recurrences in distal dural regions and the diffuse regrowth.

A role of tumor location in meningioma recurrence has long been suggested.[2,21] Several reports have found significantly higher rate of atypical meningiomas[22,31–35] and higher risk of aggressive behavior and recurrence[22,32] in non-skull base versus skull base meningiomas. However, in this study, the tumor location does not significantly correlate with the different patterns of recurrence.

The degree of resection at initial surgery is mostly considered a major risk factor of recurrence.[8,36] However, some studies found no statistically significant differences in progression-free survival between Simpson grades 1 to 4[37] and 1 to 3[12,38] resections for benign WHO I meningiomas. The authors speculate that the discrepancy may reflect the technical surgical improvement and the small tumor remnants in incomplete resections. These data agree with the lack of significant correlation between entity of resection according to the Simpson grade at initial surgery and growth pattern of recurrence in this study.

Pathological findings

In this study, only values of Ki67 Li $\geq$4% resulted at risk of multicentric-diffuse recurrence, whereas the WHO grade (I versus II) did not significantly. Several reports[24–26] including our previous own, 7 found higher recurrence risk for intracranial meningiomas with higher Ki values and lower PR expression. However, in this study the PR expression is not correlated with the pattern of diffuse regrowth. Both these findings have not previously been reported.

The higher initial values of Ki67 LI of meningiomas recurring as diffuse forms suggest that small tumor foci in the surrounding dura, even distant from the initial attachment, may diffusely regrow, if their growth potential is higher.

Several studies have shown that different gene expression profiles and chromosomal abnormalities correspond to meningioma subtypes with different aggressiveness and different risk of recurrence.[39–43] It is likely that meningiomas which recur in multicentric-diffuse pattern have different biomolecular profiles as compared to other ones.

Management of multicentric-diffuse recurrences

No studies defining the guidelines for reoperation of multicentric and diffuse recurrences of intracranial meningiomas have been published. Thus, the decision on surgical versus conservative management is based on several factors, including KPS, tumor location (critical versus noncritical), significant intradural mass versus prevalent dural infiltration, entity of extradural extension, WHO grade of the initial tumor, time to recurrence, surgeon's opinion. We have reoperated on only patients with significant intradural tumor ($\geq$3 cm) and no extensive en plaque dural infiltration. However, a gross total resection (Simpson grades I and II) was obtained only in 20% of the cases versus 76% of local–-peripheral recurrence.

Further recurrences may be reoperated on following the same criteria, if they occur after several years and if the tumor does not progress to anaplastic WHO III form.

Radiation therapy of diffuse-multicentric recurrences of meningiomas is recommended, if not already administered after the initial operation, both because of the more often partial resection at reoperation (80% of our cases) and the WHO II and III histology in most cases (21/25 or 84% in our series).

The need for radiation therapy in patients with WHO II grade recurrent meningiomas is well recognized, particularly for incompletely resected tumors.[44–47] Stereotactic radiosurgery is reported for tumors $\leq$ 3 cm, with a local control at 2 years from 50 to 80% and not infrequent recurrence outside the radiosurgical target.[45,48] Besides, even reradiosurgery for recurrent meningiomas has been recommended if the first radiosurgical treatment was unsatisfactory.[49] However, all studies include the overall group of recurrences; on the other hand, there are not studies concerning the diffuse recurrences and the best radiation modality. We have performed external brain radiation therapy in our patients. It is necessary for diffuse-multicentric recurrences, due to their extensive growth. We have reserved stereotactic radiosurgery to nine selected cases in association with the external radiotherapy to further control smaller nodules.

Many clinical trials concerning the medical therapy have studied the effects of cytotoxic chemotherapy,[50,51] hormone-directed therapy,[52,53] other targeted therapies[54–56] and molecular therapies[57] in multiple recurrences and anaplastic meningiomas. We have treated five patients with hydroxyurea with scarce results. We suggest that targeted and molecular therapies chosen on the basis of their biomolecular profile may be useful in diffuse-multicentric recurrences showing progression after surgery and radiotherapy.

Conclusion

The flat-shaped meningiomas and those with Ki67 Li $\geq$4% at initial diagnosis are at higher risk of recurring in a multicentric-diffuse pattern. Other factors are not relevant.

Even multiple reoperations over a period of several years in selected patients with prevalent intradural tumor and not

extensive "en plaque" dural infiltration may obtain long survivals in non-anaplastic and less aggressive forms.

Limitation of the study

The study is retrospective. Because of the unusual occurrence of multicentric-diffuse recurrences, the number of cases is limited, although the study covers a rather long period (24 years).

Disclosure of interest

No potential conflict of interest was reported by the author(s).

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