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Chapter

Topographic Distribution of Intracranial Meningioma's Recurrences: Localized Versus Diffuse-Multicentric

Francesco Maiuri, Sergio Corvino, Elia Guadagno and Marialaura Del Basso De Caro

Abstract

Meningiomas recur with a rate of 10–32% at ten years. Several features influence the risk of recurrence. Our aim is to define the pathological and surgical features at risk of diffuse-multicentric versus local-peripheral recurrence. Thirty-three cases of multicentric-diffuse recurrence of intracranial meningiomas were retrospectively analyzed and compared with 50 cases 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. The multicentric-diffuse recurrences were mainly related to flat-shaped and Ki67 Li greater than 4% features at first surgery. Among patients with multicentric-diffuse recurrences, 25 underwent one to three reoperations; among them, 17 are alive with local tumor control or slow progression 2 to 25 years after the initial surgery versus only 2 out of 8 who did not undergo surgery. We conclude that flat-shaped meningiomas and those with Ki67 Li greater than 4% are at higher risk to recur in multicentric-diffuse pattern. Even 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.

Keywords: meningioma recurrence, diffuse recurrence, proliferation index, meningioma shape

1. Introduction

The recurrence's rate of intracranial meningiomas ranges from 10–32% at 10 years [1–3] .The main risk factors include the WHO grade [4–7], the extent of resection according to Simpson [8–10], the proliferation index Ki67-MIB1 [11–14] and mitotic index [15] and the postoperative adjuvant treatments [1, 16, 17]. Other factors have also been suggested, such as patient age and sex [4, 18], tumor size [19–21], location [22, 23] and morphology [19, 22, 24], brain invasion [10, 14], progesterone receptor (PR) expression [25–27].

Meningiomas may recur with different patterns of growth, from more localized to more extensive and sometimes diffuse forms. This carries several diagnostic and therapeutic implications. However, all published studies consider the overall

recurrences, with no focusing on their topography and extension, which were first discussed only in our recent report [28].

2. Classification of the recurrences

According to their topography on the post-contrast magnetic resonance imaging (MRI) and surgical findings, the recurrences of meningiomas may be classified in 4 types [28]:

- type 1, local, at 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 dural and extradural infiltration.

Local type 1 is the most frequent regrowth pattern. It may occur after resection of Simpson grades 2 to 4; the tumor may growth both intradurally and at the bone. The recurrence may involve from a variable portion to the whole initial dural attachment and may extend to the contiguous previously normal dura.

Peripheral type 2 recurrences may be observed after initial resection of grade 1, but also of grade II when the dural attachment was carefully and extensively coagulated. The recurrence may involve a variable dural portion contiguous to the initial attachment and may often extend to it. In cases with larger recurrences the site of regrowth (local versus peripheral) is difficult to be defined.

Multicentric type 3 recurrences are characterized by tumor nodules or mass both at initial dural attachment or contiguous dura and in distal dural regions where no tumor nodules nor dural enhancement were visible on the magnetic resonance imaging at initial surgery. In this type the dura mater between local-peripheral and distal recurrent nodules seems to be normal.

Diffuse type 4 recurrences show multiple nodules of tumor regrowth even in very distal regions, with variable infiltration of the interposed dura and bone.

The above discussed patterns of recurrence suggest that multicentric and diffuse recurrences are two phases of the same pathological conditions.

3. Pathological origin of the multicentric-diffuse recurrences

The pathological mechanisms responsible for meningioma recurrence in distal dural regions are not well defined and deserve to be discussed.

The concept of regional multicentricity of meningiomas is known since about 35 years. Borovich and Doron [29] demonstrated in convexity meningiomas small tumor nodules as well as intradural clusters of tumor cells in the dural specimens taken up to 3 cm from the tumor. Qi et al. [30] found tumor invasion in 88% of dura adjacent to convexity meningioma up to 2,5 cm from the tumor origin. These observations may explain some “unexpected relapses” after an apparent complete resection (Simpson grade 1) of convexity meningiomas [29] and the frequent peripheral recurrences at the dura surrounding the initial attachment after resection od Simpson grades 1 and 2 in all locations.

These pathological findings support the concept of a wide dural excision 2-3 cm beyond the tumor base (grade zero resection), which was suggested for convexity [31] and falx meningiomas [32].

Mooney et al. [32] suggest that in the falcine meningiomas the tumor cells may spread from the site of origin to other falx regions between the two dural leaflets of the falx. However, this pattern of diffusion of the tumor cells cannot explain the very distant recurrences from other locations. For multiple meningiomas some studies [33, 34] have suggested that they may arise from a single progenitor cell and could then spread through the subarachnoid space. A similar mechanism may also be advocated for distant recurrences.

However, it is more like that multicentric-diffuse recurrences represent the progressive growth of multiple distant dural nodules with different growth potential. In this way the meningioma may be considered, at least in several cases, a diffuse disease of the meninges than a localized tumor.

4. Data of the personal series

Thirty-three patients with multicentric-diffuse recurrences of meningiomas are included in our series [28] (**Tables 1-3** and **Figures 1-3**). They are 22 females (67%) and 11 males (33%), with a median age of 52 years. The findings at initial surgery were as follows (**Table 1**). The most frequent location was non skull-base (55%), followed by lateral (36%) and medial skull-base (9%). The tumor was mostly flat-shaped (76%) and less frequently round (24%). Complete resection (Simpson grades 1 and 2) at initial surgery was obtained in 23 among 33 patients (70%).

The pathological findings at initial diagnosis (**Table 1**) showed 52% of WHO [35] grade I and 48% of grade II tumors; the Ki67-Li was <4% in 20% and ≥ 4%in 80%. The PR expression was ≤50% in 82% of specimens and > 50% in 9%.

When compared to the findings of meningiomas which showed localized-peripheral recurrences, only the higher rates of flat-shaped tumors ($p = 0.0008$) and tumors with Ki67-Li ≥4% ($p = 0.037$) were significant [28].

The management and outcome of the recurrences were as follows (**Table 2**). Twenty-five out of 33 patients (76%) were reoperated on and underwent one (48%) or two or three reoperations (52%) (**Figures 1** and **2**). The complete resection (Simpson grades I and II) was possible only in 5 among the 25 patients (20%). The histological WHO grade at first reoperation was similar to that of the initial surgery in 15 out of 25 patients (60%); progression to a higher grade was observed in 10 cases (40%).

Adjuvant treatments included external radiotherapy in 20 patients, stereotactic radiosurgery in 9 and chemotherapy in 5.

When compared to patients with localized-peripheral recurrences, those with multicentric-diffuse recurrences showed significantly higher number of reoperations ($p = 0.0034$), lower rate of gross total resection ($p = 0.00001$) and higher but not significant rate of cases with progression of the WHO grade ($p = 0.09$) [28].

The actual follow-up ranges from 2 to 25 years. One patient died postoperatively for respiratory failure. Among the other 24 patients operated on, eleven (34%) are alive with local tumor control versus none out of eight patients who did not undergo surgery ($p = 0.029$). Six (25%) show slow tumor progression with no symptoms in spite the surgery. Seven patients of the surgical group (29%) died during the follow-up (5 for tumor progression) versus 6 (for tumor progression) out of 8 (75%) of the non-surgical group ($p = 0.038$). Thus, among 25 patients reoperated on 17 (68%) are alive after one or more reoperations versus only 2 out of 8 (25%) who did not undergo surgery.

Covariates	Number of cases (rate)
Age (mean)	52 y
Sex	F 22 (67%) M 11 (33%)
Tumor location	
medial skull base	3 (9%)
lateral skull base	12 (36%)
non skull base	18 (55%)
Tumor shape	
flat	25 (76%)
round	8 (24%)
Brain-tumor interface	
preserved	15 (45%)
unclear- lost	18 (55%)
Extent of resection (Simpson grade)	
I	9 (28%)
II	14 (42%)
III	10 (30%)
Interval between initial surgery and recurrence (median)	4.7 y
WHO grade	
I	17 (52%)
II	16 (48%)
Ki67 Li	
< 4%	7 (20%)
≥ 4%	26 (80%)
P.R. expression	
≤ 15%	11 (33%)
16–50% 51–79%	16 (49%) 3 (9%)
≥ 80%	3 (9%)

Table 1.
Clinico-radiological, surgical and pathological findings at initial diagnosis (33 patients).

Covariates	Number of cases (rate)
• Surgery	25(76%)
• Number of surgeries	
One reoperation	12 (48%)
Two or three reoperations	13 (52%)
• Extent of resection	
Gross total	5 (20%)
Subtotal	20 (80%)
• WHO grade at the first reoperation	
Similar to the first surgery	15 (60%)
Progression from I to II	7 (28%)

Covariates	Number of cases (rate)
• Progression from II to III	3 (12%)
• Postoperative death	1 (4%)
• External radiotherapy	20 (60%)
• Stereotactic radiosurgery	9 (27%)
• Chemotherapy	5 (15%)

Table 2.
Management of 33 patients with multicentric-diffuse recurrences.

Covariates	Group 1-Surgery (24 pts)	Group 2-No-surgery (8 pts)	Statistical significance (Group 1 Vs Group 2)
Local control	11 (46%)	—	p = 0.029
Tumor progression	6 (25%)	2 (25%)	n.s.
Death during the follow-up	7 (29%)	6 (75%)	p = 0.038

Table 3.
Outcome of 33 patients with multicentric-diffuse meningioma recurrence.

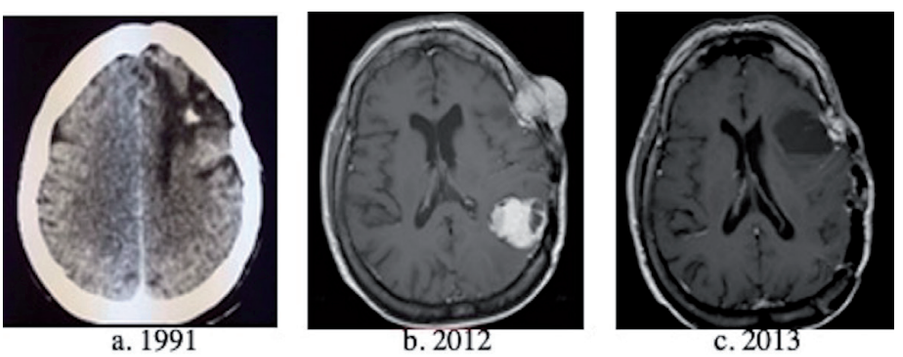

Figure 1.
58 years old woman with history of previous resection of a WHO I grade meningioma of the left frontal convexity in 1991. (a) Postoperative CT after the initial surgery: no residual tumor; (b) Post-contrast MRI 21 years later: local multicentric recurrence at the previous dural site and distal recurrence at the left parietal region; (c) Postoperative MRI showing resection of both nodules (WHO grade I) and interposed dura.

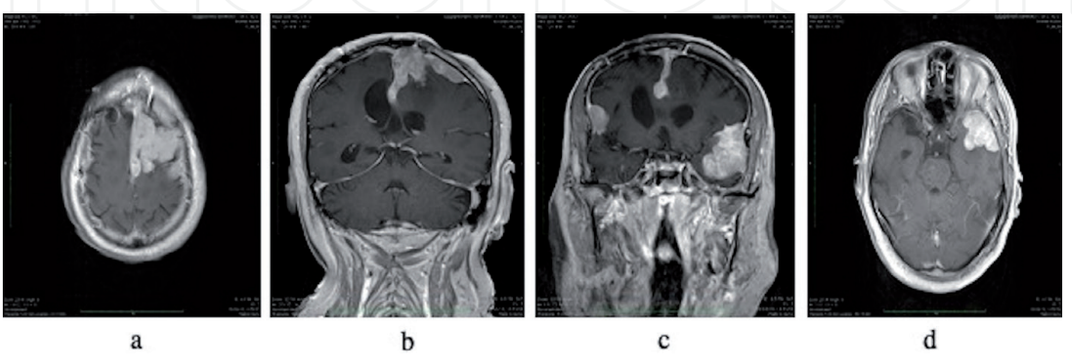

Figure 2.
68 years old man who underwent resection of an anterior parasagittal WHO grade II meningioma in 2010. (a-d) Post-contrast MRI, T1 axial (a, d) and coronal (b, c) sequences: diffuse recurrences of the parasagittal and both convexity regions with significant tumor masses, at the left parasagittal and convexity and at the anterior temporal convexity. Two-stage resection of the masses and irradiation.

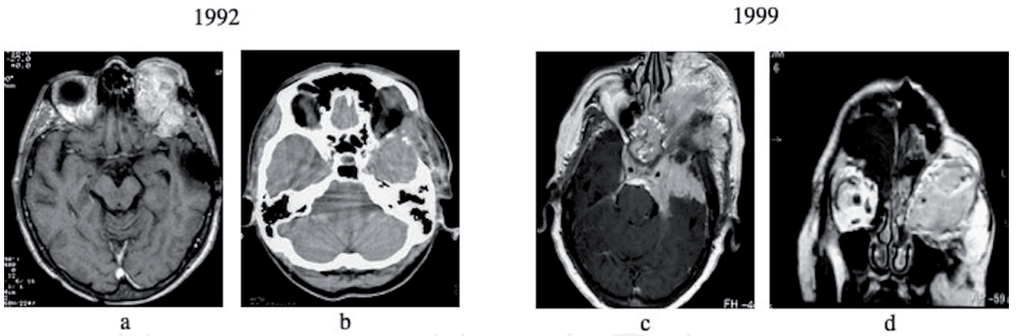

Figure 3.
(a-b) 72 years old man with history of a left spheno-orbital WHO grade II meningioma: a) preoperative T1 axial post-contrast MRI and (b) postoperative CT scan: complete resection. (c-d) Post-contrast T1 axial (c) and coronal (d) MRI sequences seven years after the initial surgery: large tumor recurrence involving the left orbital cavity and extending diffusely in the intracranial compartment at the suprasellar, left parasellar region and temporal fossa. Management by external radiotherapy.

5. Risk factors at initial diagnosis

Several pathological, neuroradiological and surgical findings at initial diagnosis are correlated to the meningioma recurrence. However, which factors may be considered at risk of multicentric-diffuse recurrence are not defined.

5.1 Location

The meningioma location is a significant risk factor of recurrence. Medial skull-base meningiomas include locations, such as olfactory groove, tuberculum sellae, anterior clinoid, foramen magnum, with low recurrence rates (0–15%) [36–38]. Besides, the low recurrence rate of spinal meningiomas is well known (0–10% in 15 among 19 reviewed series in our recent study [39]). On the other hand, the reported recurrence rates are higher for lateral skull-base (35–40% for lateral sphenoid wing and mainly spheno-orbital [38–40]) and for non-skull base meningiomas (16 to 24% for parasagittal and falcine) [23, 41].

However, when the rates of multicentric-diffuse recurrences are considered, the differences for intracranial tumor locations are not relevant. Although in our study [28] spheno-orbital and parasagittal meningiomas show higher rates of multicentric and diffuse recurrences, this finding does not reach significance. Our series does not include diffuse recurrences of spinal meningiomas; this agrees with the well known better biological behavior of this location.

Thus, the meningioma location is correlated with the rate but not with the growth pattern of the recurrences.

5.2 Shape

The shape of meningiomas may be variable. According to the rate height/base on magnetic resonance imaging, the meningiomas may be classified as round (rate > 1) and flat-shaped (rate ≤ 1). Flat-shaped meningiomas are characterized by prevalent and often extensive dural involvement as compared to round-shaped ones. Thus, it has been shown that flat-shaped meningiomas are more likely to recur than round ones [22, 24].

The flat-shaped morphology at initial diagnosis was the only radiological finding at significantly higher risk of multicentric diffuse recurrence as compared to local-peripheral recurrence in our study ($p = 0.0008$) [28]. Thus, it is like that flat-shaped meningiomas are associated to various degree of even distant microscopic dural infiltration.

5.3 Dural tail

The change of the peritumoral dura mater depicted on the postcontrast magnetic resonance studies and defined as "dural tail" is known since its description in 1989 [42]. It may correspond to various histopathological patterns, including increased loose connective tissue, angiogenesis, dilated vessels, reactive hyperplasia, tumor invasion [42, 43]. Qi et al. [30], in a large series of convexity meningiomas, described several types of dural tail with different histological aspects: smooth (uniformly extended) with tumor extension up to 1,5 cm; nodular, with nodular hyperplasia corresponding to tumor nodules and tumor extension to the distal dura up to 2,5 cm; mixed, with nodular enhancement proximal to the dural attachment and distal smooth enhancement. In spite of the presence of tumor cells nodules, the finding of dural tail was found to be not correlated to the meningioma recurrence in most studies [9, 19, 22]. We did not investigate this finding in our series of multicentric-diffuse recurrences; however, we suggest that further studies will define this aspect.

5.4 Brain-tumor interface

The brain-tumor interface, more often well preserved during meningioma surgery, may be unclear or lost, often with variable pial invasion, as in WHO grade II tumors. In such cases the tumor resection may be incomplete, with residual nodules mainly in critical regions. This may increase the risk of recurrence at the initial site or at the surrounding region [10, 14, 22]. On the other hand, the presence of the residual cell nests at the brain-tumor interface does not explain the recurrences in distal dural regions and the diffuse regrowths.

5.5 Extent of surgical resection

The entity of the resection at initial surgery is mostly considered a major risk factor for recurrence [23, 44, 45]. However, the clinical usefulness of the Simpson grading in general has been questioned, at least for benign meningiomas. Some studies found no statistically significant differences in progression-free survival between Simpson grades 1 to 4[46] and 1 to 3 [13, 47] resections for WHO I grade meningiomas. This discrepancy may reflect the technical surgical improvement and the smaller tumor remnants in incomplete resections. In a recent report Haddad et al. [48]. found that patients with WHO grade I meningiomas and Ki67-MIB1 > 4,5% treated by gross total resection had similar risk of recurrence as those patients with subtotal resection. In this study, early recurrences were more significantly impacted by extent of resection, whereas the Ki67-MIB1 was more significant for later recurrences.

In our study on multicentric-diffuse recurrences [28], their rate is not impacted by the extent of resection at initial surgery.

5.6 Multiple meningiomas

Multiple meningiomas account for 2 to 8% of all meningiomas [49]. They may be diagnosed either initially or during the neuroradiological follow-up.

In a large metanalysis of the literature on multiple meningiomas, Pereira et al. [49] found recurrence rate of 8.07% and no higher with respect to single ones. On the other hand, in the study by Gousias et al. [45] multiple meningiomas showed higher recurrence rate and significantly lower progression-free survival than single ones.

Multiple meningiomas likely develop from multicentric dural tumor foci according to the Borovich [29] theory. A similar mechanism is suggested for multicentric recurrences. In our study on multicentric-diffuse recurrences two patients had multiple meningiomas (two lesions) at initial diagnosis, with no significant differences with local-peripheral ones. We think that further studies on the long-term follow-up of patients operated on for multiple meningiomas will defined the recurrence rates and patterns of these cases.

5.7 Pathological findings

In our study [28] meningiomas with values of Ki67 Li ≥ 4% are related to major risk of multicentric-diffuse recurrence, while the WHO grade (I versus II) is not significant. Several reports [7, 25–27] confirmed the relationship between higher Ki67-Li values and lower PR expression, and higher recurrence risk for intracranial meningiomas. 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 even small dural tumor foci, even distant from the primary tumor site, may diffusely regrow.

Several studies have found that different genetic profiles and chromosomal abnormalities correspond to different meningioma subtypes with different aggressiveness and recurrence's rate [50–54], making speculate the existence of characteristic biomolecular profiles for meningiomas which recur in multicentric-diffuse pattern.

6. Management

The management of multicentric-diffuse recurrences of intracranial meningiomas is often difficult to be defined; there are not studies defining the guidelines. The management options include a second surgery, external radiotherapy, stereotactic radiosurgery, medical therapy.

The decision is based on several factors, including tumor location (non-skull base versus skull base; critical versus not critical), significant intradural mass versus prevalent dural infiltration (**Figures 4** and **5**), entity of bone extension, time to recurrence, WHO grade of the initial tumor, patient age and KPS, neurological symptoms and signs.

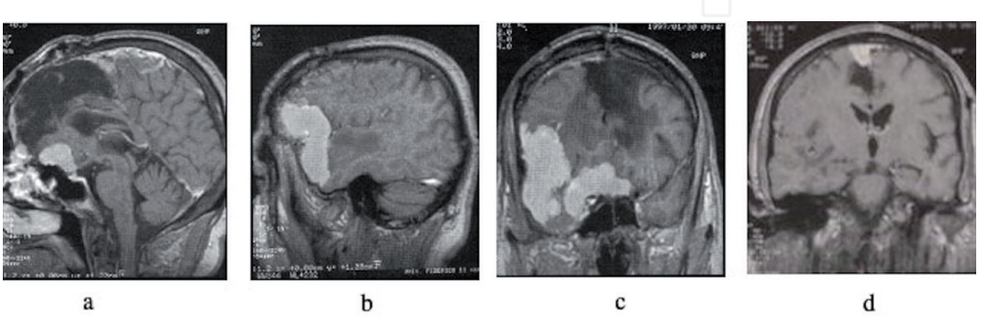

Figure 4.
Post-contrast MRI of a 58 years old man with history of previous surgery (5 years before) of gross-total resection of a bilateral meningioma of the anterior third of the falx (WHO grade II). Sagittal (a-b) and coronal (c-d) T1 sequences: distant and diffuse recurrence at the right fronto-temporal bone and suprasellar regions, with no recurrence at the initial tumor site. Reoperation and resection of the recurrent tumor (WHO grade II). Postoperative death for respiratory failure.

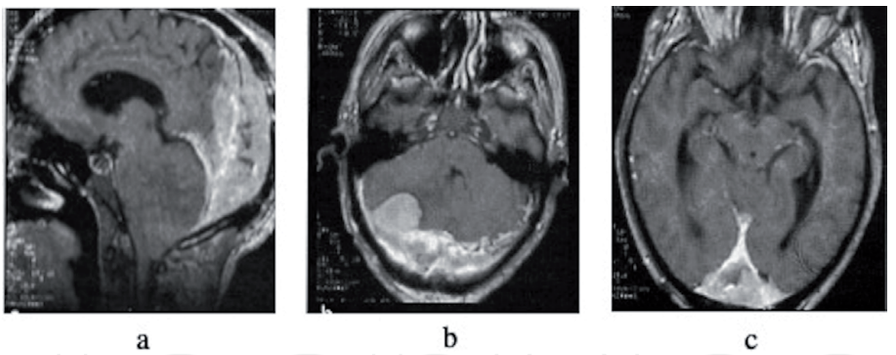

Figure 5.
Post-contrast MRI of a 70 years old woman with history of previous (7 year before) surgical resection (Simpson 3) of a WHO grade II meningioma of the posterior parasagittal region: sagittal (a) and coronal (b-c) sequences: diffuse recurrence with extensive dural and superior sagittal sinus involvement and tumor nodules at the posterior fossa. No reoperation was decided.

6.1 Surgery

The indication to reoperation is mainly posed for younger and middle-aged patients with symptomatic recurrences. According to the location and pattern of regrowth, surgery should be reserved to cases with prevalent intradural tumor growth, tumor nodules ≥3 cm and not extensive dural infiltration (**Figures 1**). Non skull-base meningiomas, mainly if limited to the brain convexity, are usually more favorable to surgery, because of the chance of more wide resection of the involved dura mater. For skull-base meningiomas a more wide resection is possible at the anterior cranial fossa and external sphenoid wing; on the other hand, diffuse recurrences at the suprasellar, parasellar and spheno-orbital regions (**Figure 3**), as well as clival and petroclival regions, are difficult to treat, because of the involvement of the cranial nerves and vessels; for such locations a second surgery is only justified for the resection of a large symptomatic intradural mass.

Elderly patients with comorbidities, particularly if with no or trivial neurological symptoms, must be treated conservatively with periodical radiological follow-up.

The WHO grade at initial diagnosis is obviously important. Only WHO grades I and II meningiomas are suitable for reoperation. On the other hand, anaplastic WHO grade III tumors at initial diagnosis must not be reoperated on.

In selected patients according to the above discussed criteria the reoperation results is satisfactory resection of the intradural tumor and involved dura. However, a really complete resection with no residual contrast enhancement on MRI (Simpson grades 1 and 2) is obtained only in some cases (20% in our series versus 76% of local-peripheral recurrences) [28].

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.

6.2 Radiotherapy

All studies focusing on the irradiation of recurrent meningiomas include all recurrences; thus guidelines of radiotherapy management of diffuse recurrences are not available.

The external radiotherapy of multicentric-diffuse recurrences of meningiomas is in our opinion mandatory, independently from the entity of resection and the WHO grade, but mainly in subtotally or partially resected WHO grade II recurrences [55, 56].

The stereotactic radiosurgery is scarcely indicated, because of the extensive and diffuse tumor growth. It may sometimes be performed in association to the external radiotherapy to increase the control of smaller nodules and to treat the not infrequent second recurrences outside the radiotherapic field [57]. Besides, re-radiosurgery for recurrent meningiomas is advisable if the previous radiosurgical treatment was unsatisfactory [58].

6.3 Medical therapy

The medical therapy is reserved to recurrent meningiomas which show growth progression after surgery and irradiation and to malignant WHO III forms. Many clinical trials have studied the effects of cytotoxic chemotherapy [59, 60], hormone-directed therapy [61, 62], other targeted therapies [63–65] and molecular therapies [66]. Targeted and molecular therapies defined on the basis of the biomolecular profile of the meningioma may be useful in diffuse-multicentric recurrences showing progression after surgery and radiotherapy.

7. Conclusions

Meningiomas may sometimes recur as multicentric-diffuse forms, with dural infiltration and recurrent tumor mass distal to the initial site. These may result from the progressive growth of multiple tumor nodules with different growth potential.

Flat-shaped radiological aspect and Ki67 Li ≥4% at initial diagnosis are related to higher risk of recurrence in multicentric-diffuse pattern.

Patients with not anaplastic intracranial meningioma with prevalent intradural component and not extensive dural infiltration may undergone multiple surgical operations during years experimenting good postoperative quality of life.

Further studies will investigate whether the different patterns of regrowth and recurrence correspond to different biomolecular and genetic expression of the meningioma. This will aid to predict the tumor behavior and to detect the most appropriate molecular therapies.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

WHO	World Health Organization
MRI	Magnetic Resonance Imaging

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