Long term follow up in 183 high grade meningioma: A single institutional experience

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ARTICLE INFO

Keywords:
High grade meningioma
Atypical meningioma
Anaplastic meningioma
Radiotherapy
Chemotherapy

ABSTRACT

Introduction: Meningiomas are usually considered benign lesions, however a proportion of them shows a more aggressive behavior, defined high-grade meningiomas (HGM). Effective medical treatments are lacking, especially at the time of recurrence.

Methods: Through a retrospective analysis, we examined epidemiological, diagnostic, therapeutic, recurrence information and survival data of HGM treated at our institution between 2010 and 2018.

Results: 183 patients (105 females and 78 males), with median age of 58 years (25–88), were included; 168 were atypical, 12 anaplastic, 3 rhabdoid. Overall, m-PFS was 4.2 years, and m-OS was 10.3 years. Gross-total resection had a 5-year survival rate of 95% compared with subtotal/partial resection (86% and 67%) (p = 0.002). Higher expression of Ki-67/MIB-1 seems associated with higher risk of death (HR:1.06 with 95% CI, 1.00–1.12, p = 0.03). No statistically significant differences were seen in survival between the group managed with a wait-and-see strategy vs the group treated with RT while a difference on PFS was seen (4.1 years vs 5.2 years p = 0.03). After second recurrence, the most employed treatments were systemic therapies with a very limited effect on disease control.

Conclusions: Data confirmed the aggressive behavior of HGM. The extent of resection seems to correlate with a favorable outcome regardless histological subtypes. The role of RT remains controversial, with no statistically significant impact on OS but a possible role on PFS. Recurrent HGM remains the real challenge, to date no chemotherapies are able to achieve disease control. Future research should focus on biological/molecular predictors in order to achieve a patient-tailored treatment.

1. Introduction

Meningioma is one of the most common tumors of the central nervous system (CNS), accounting for 36.8% of tumors overall, according to the US Central Brain Tumor Registry in the United States [1]. Meningiomas most likely arise from arachnoid cap cells, and they exhibit a broad and heterogeneous spectrum of histological features and clinical characteristics [2]. The World Health Organization (WHO) classifies meningiomas into the following three grades: benign meningiomas (WHO grade I; 81.3% of meningiomas) with a benign course and a 5-year recurrence rate of 10.3%; high-grade meningioma (HGM) including atypical (WHO grade II); and anaplastic meningioma (WHO grade III). In particular meningiomas are classified as grade II if lesions contain 4–19 mitoses per ten consecutive high power fields or brain invasion, while they are classified as grade III in presence of presence of >20+ mitoses per ten consecutive high-power fields. Rhabdoid and papillary morphologic variants are also considered to be grade III [3]. Their incidence varies widely from 1.5% to 35% of all meningiomas,
with atypical outnumbering anaplastic in a rough proportion of six to one. From a prognostic point of view, atypical meningiomas usually present an intermediate clinical course with a recurrence rate of 30–40%. Conversely, anaplastic meningiomas show a particularly dismal clinical course, with recurrence in nearly 100% of patients and a 5-year survival rate of 32–64%. In particular, WHO grade III meningiomas can arise either de novo or progress from lower-grade tumors, and they are associated with an aggressive and malignant growth pattern, even with metastatic dissemination [4–7].

Surgery remains a mainstay of meningioma treatment and several retrospective studies have reported the importance of gross total resection (GTR) and its association with better survival. There is a consensus about the relevance of adjuvant radiotherapy (RT) for WHO grade III meningiomas, while the role of RT in treating WHO grade II meningiomas remains controversial.

Unfortunately, when patients fail to respond to standard surgical and radiation therapies, current treatment options are extremely limited, and they mainly consist of a second surgical procedure, re-irradiation, or proton therapy, when feasible. Thus, interest in chemotherapy (CHT) and targeted therapies has emerged in an effort to treat this group of patients. However, none of the current CHT agents has been effective in treating these tumors.

The primary aim of this study was to describe the clinical (including surgical procedure, RT, and CHT), radiological, and molecular features of a large population of patients who are diagnosed with HGM between 2010 and 2018. These data were retrospectively acquired in a “real-life” setting to identify relevant outcome measures for future prospective studies. The secondary aims were to evaluate progression-free survival (PFS) and overall survival (OS).

2. Methods

In this study, we retrospectively reviewed clinical records on WHO grade II and III meningioma patients who were consecutively treated at Fondazione IRCCS Istituto Neurologico Carlo Besta from January 2010 to December 2018. Epidemiology, radiology, pathology, and treatment data were obtained from the Cancer Registry of the Fondazione IRCCS Istituto Neurologico Carlo Besta (Microsoft Access Database, [Microsoft Office Professional Plus 2010®], Redmond, US)).

The extent of surgical resection was described according to the Simpson grade, as follows: GTR was defined as Simpson grades I–II, subtotal resection as Simpson grades III, and partial resection as Simpson grade IV.

Histological diagnosis of atypical, anaplastic, and rhabdoid meningioma was made by our neuropathologist who assessed the mitotic index, brain invasion, and increased cellularity according to the WHO grading system before 2016 based on the new WHO grading system [8].

Time from surgery to progression, death, or the last date of follow-up was measured and estimated using the Kaplan–Meier method [9]. Additionally, 95% confidence intervals (CIs) were calculated using the associated estimated standard errors. The log-rank test was used to compare the significance of the following prognostic variables: type of surgery (GTR vs. partial resection/biopsy), histological subtype, and post-surgical treatments (no RT nor stereotactic radiosurgery [SRS] vs RT and/or SRS). A Cox proportional hazard model was used to provide hazard ratios (HRs) with the corresponding 95% CI as relative risk estimates of survival to the increasing MIB-1 value and age.

STATA statistical software, version 16 (StataCorp., College Station, TX, USA) was used for the statistical analysis and p values <0.05 were considered significant.

Treatment toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The study was conducted according to the ethical rules for retrospective observational studies. Because the data were analyzed anonymously and the patients privacy was protected, the Institutional Ethical Committee waived the requirement for informed consent.

3. Results

Overall, 291 adult patients who underwent surgery for a newly diagnosed intracranial WHO grade II and III meningioma at our Department of Neurosurgery between 2010 and 2018 were evaluated for the present study. These patients were extrapolated from a pool of 1936 patients with a newly diagnosis of meningiomas (grade I–III) treated by our Institution from 2010 and 2018, equal to 15% of the total.

One hundred eight patients were excluded from the analysis due to the lack of data about post-surgery treatments and follow up because of about 80% were out of the geographical referred region of our hospital.

One hundred eighty-three patients (105 females and 78 males), with a median age at diagnosis of 58 years (range, 25–88 years), were included. The pre-operative median Karnofsky Performance Status (KPS) was 80 (range, 60–100). The more frequent onset symptoms were headache (38%), dysesthesia (19%), gait disturbance (15%), aphasia (13%), and ataxia (13%).

One hundred sixty-eight patients were diagnosed with grade II (atypical) and 15 were diagnosed with grade III meningioma (three rhabdoid and 12 anaplastic). Among the 168 atypical meningiomas, seven were radiation-induced. The primary lesions, which occurred on average 37 years (range, 21–42 years) before the diagnosis of meningioma, were brainstem glioma (n = 2), ependymoma (n = 2), astrocytoma (n = 2), and chronic myeloid leukemia, and all of these patients were treated with median-high dose of RT that ranged between 30 and 50 Gy.

Moreover, four patients with a diagnosis of atypical meningioma were affected by neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2). Meningiomas were localized mainly in the cerebral convexity (59%), parasagittal/falx (15.8%), petrous apex (6.5%), sphenoid (5.4%), and olfactory groove (4.9%). A detailed overview is presented in Table 1.

At the time of diagnosis, all patients underwent surgery, as follows: GTR was performed in 99/183 patients, with subtotal resection in 32/183 and partial resection in 52/183 patients, on the basis of Simpson grade I–IV.

There were 18/183 patients who experienced complications after surgery. In particular, after the GTR, 11 patients developed hemiparesis,

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hematoma, and aphasia, and after subtotal resection, two patients had cerebral hemorrhage and five patients showed hemiparesis, aphasia, and hematoma after partial resection.

For immediate post-surgery treatments, 46/183 patients were treated with adjuvant RT (20 GTR and 26 partial/subtotal resection) and 22/183 were treated with SRS. Among these patients, four underwent both RT and SRS as a result of multifocal lesions. Only two patients were treated with proton therapy. All grade III meningiomas underwent adjuvant radiotherapy with a total dose of 60 Gy delivered in 30 daily fractions. Grade II meningiomas received postoperative radiotherapy in case of Simpson grade resection III–IV. SRS was delivered as exclusive therapy for new or relapsed lesions. Among these patients, four underwent both RT and SRS as a result of multifocal lesions. Only two patients were treated with proton therapy. Adjuvant RT was started between 4 and 12 weeks after surgery. Most patients (10/15) received standard fractionated radiotherapy with a daily fraction of 2 Gy up to a total dose of 60 Gy. Five out 15 underwent adjuvant or salvage RT.

Additionally, 39/183 patients with subtotal or partial resection with a small residual tumor (<2.5 cm) and without neurological impairment were managed using a wait-and-see strategy on the basis of a medical decision or patient refusal. Thirty-two patients were lost to follow-up. Among the evaluable patients, 49% had a first recurrence (median PFS, 4.2 years). Therapeutic options consisted of SRS re-irradiation (47.2%), repeat surgery (35.1%), CHT with hydroxyurea, and other cytotoxic chemotherapeutic agents as somatostatin (6.7%), RT (5.4%), proton-therapy (1.3%), and bevacizumab (1.3%). The median duration of therapy was 7 months (range, 1–16 months).

For subsequent local recurrences, a re-surgery was performed in 4.6% of patients, and re-irradiation, mainly consisting of radiosurgery and adrotherapy, was performed in 13.9% of patients. Another subgroup of patients (15.2%) was retreated with the following systemic chemotherapies: hydroxyurea and somatostatin, experimental treatment with trabectedin, cyclophosphamide-adriamycin-vincristine, and temozolomide.

In this subgroup of patients who were treated with CHT, 30.4% achieved stable disease at 6 months, while 39.1% had disease

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**Fig. 1.** Meningiomatosis (a.) and extra CNS metastasis of high grade meningioma (b. and c.).
progression without any clinical benefit. Overall, the median time between diagnosis and the start of CHT treatments was 7 years (range, 1–23 years).

Among all patients who received CHT, 11% reported grade 3–4 myelotoxicity, including cases of leukopenia, neutropenia, thrombocytopenia, and hepatic disease with jaundice.

Overall, eight meningioma (six atypical, two anaplastic) patients became metastatic in the course of the disease. In particular, five patients developed cutaneous metastasis, two patients had pulmonary localizations, and one patient had leptomeningeal dissemination (Fig. 1).

Among 183 analyzed patients, median follow up was 3.7 (interquartile range [IQR], 2.3–7.4 years). Median PFS was 4.2 years (95% CI, 3.6–5.7%), with a 5-year PFS of 46%. Median OS for the whole group of patients was 10.3 years (Fig. 2) with an OS rate at 5 and 10 years of 83% (95% CI, 73–88%) and 57% (95% CI, 40–71%), respectively.

For tumor resection, patients who received GTR had a 5-year survival rate of 95%, while those who received subtotal and partial resection had a survival rate of 86% and 67%, respectively (p = 0.002). For PFS, patients who received GTR had a median PFS of 5.3 years compared to 5 years and 2.5 years for patients with subtotal and partial resection, respectively (p = 0.003) (Fig. 3).

When patients were grouped by the histological type, atypical vs. anaplastic/rhabdoid, the median OS was 10.3 vs. 5 years, respectively (p = 0.03). Grade II meningioma had an overall 5-year survival rate of 86%, whereas the overall 5-year survival rate for anaplastic/rhabdoid meningiomas was 50%.

Median PFS was 4.5 years for atypical meningioma and 2.2 years for anaplastic/rhabdoid meningioma (p = 0.11). The recurrence rate was 0.16 for the atypical and 0.23 for the anaplastic/rhabdoid group (Fig. 4).

We also investigated the effect of Ki-67/MIB-1 on OS. A higher expression of Ki-67/MIB-1 was associated association with higher risk of death (HR, 1.06 95% CI, 1.00–1.12, p = 0.03).

For post-surgical treatments, no statistically significant differences were observed between the group that was managed using a wait-and-see strategy and the group that was treated with RT and/or SRS in terms of OS (5-year survival rate of 86% vs. 78%; p = 0.42). For PFS, there was a difference between the first and second groups (4.1 years vs. 5.2 years; p = 0.03).

Sex did not affect OS nor PFS. However, the risk of death increased with age, which influenced OS without affecting PFS (HR: 1.04 with 95% CI, 1.01–1.06, p = 0.01).

4. Discussion

In this retrospective review, we analyzed 183 patients with a WHO grade II–III who underwent surgery at our institution between 2010 and 2018. Although the disease is rare, the study collected the largest recent national series of aggressive meningiomas.
21 and 42 years of age) for primary malignant brain tumors and leukemia with a medium-high radiation dose (\(\geq 30\) Gy).

A close relationship exists between hormones, particularly progesterone, and meningiomas. There are various levels of evidence suggesting the association between sex hormones, mainly progesterone, and the growth of meningiomas. Progesterone receptors have been discovered in up to 80% of meningiomas, and an inverse correlation was detected between progesterone receptor expression and Ki-67 labeling [4]. Meningiomas are marked predominant in females and increased tumor growth was observed when the highest progesterone levels were reached (pregnancy and menstrual cycle luteal phase). However, the mechanism of this association with pregnancy and probably progesterone-stimulated tumor growth has not been clearly defined [11].

Nearly all meningiomas (70–100%) express somatostatin receptors. These receptors exert an antiproliferative role when activated. Treatment with progesterone inhibitors or somatostatin analogs showed unclear results [12,13]. According to literature data, in our series, the higher meningioma incidence was in women with a male-to-female ratio of 1:3.3, and a trend toward earlier recurrence in men compared to women (5-year PFS, 37% vs. 52%, \(p = 0.2\)).

For other risk factors, in patients with NF2, Neurofibromin 2 gene mutations are the first genetic alterations that are implicated in the tumorogenesis, although other genes are also likely involved in the complex growth of meningiomas [14]. Although NF is a rare autosomal dominant tumor syndrome with an estimated birth incidence of 1 in 33,000 [15], in our cohort, 2.2% of patients were affected by NF1 or NF2 with the presence of multiple meningioma. To date, these patients are in good clinical conditions with stable disease.

Older age was not found to be a good prognostic factor in several series [16–20]. Durand et al. found that patients over than 60 years of age had a worse prognosis. Colli et al. concluded that age \(< 60\) years at diagnosis seemed to correlate positively with OS but not to PFS [21,22]. In our series, age did not influence PFS, but HR suggested a significantly increased risk of death with increasing age (HR 1.04, 95% CI, 1.01–1.06, \(p = 0.01\)). Because of the lack of literature data and clinical evidence, the current treatment management is mainly based on institutional experience. However, numerous prospective clinical trials are ongoing, and they will provide more defined clinical practice guidelines. Generally, the first approach consists in the maximum amount of safe surgical resection, which is especially recommended for all aggressive meningioma causing neurological symptoms [4].

Surgical removal of HGM is challenging, and it is not always completely successful because of the absence of clear cleavage planes between the tumor and surrounding vessels, brain parenchyma, or neurological structures, which could be caused by scars and/or irradiated tissue. This scenario is more common in patients who are undergoing repeat surgeries and in older patients who also have a higher risk of post-operative neurological deficits [23,24]. However, surgery remains the cornerstone of HGM patient management. Because of the abovementioned drawbacks, it is imperative that surgical decisions are made on a case-by-case basis. In the context of HGM, a case-by-case approach means tailoring ad hoc solutions to the specifics of each recurrence and for each patient. Research on the prognostic characteristics of recurrent HGMs is still ongoing, but many factors are already integral to the standard decision-making and risk-benefit analysis that was conducted at the time of each recurrence. The most important among these factors are patient-related factors, such as sex and age of tumor onset, and tumor-related factors, such as size, edema, location, and other features that have a direct impact on the extent of tumor resection [23].

Zaher et al. reported that age (\(< 50\) years) and total surgical excision are independent prognostic factors for survival [25], while independent prognostic factors for clinical outcome reportedly include skull-based HGM, male sex, age of disease onset, and the MIB-1 index [40]. In terms of pathological parameters, E-Ca, Ki-67, and β-catenin have been identified as factors that are strongly related to post-operative recurrence [26,27]. Review that was conducted in a Norwegian cohort of 1469 consecutive patients with meningiomas, and they confirmed that the only significant patient-related factor for recurrence after the first surgery is age, while skull-base location and WHO grade are the only two tumor-related factors with any significant impact on tumor recurrence [24]. In our series, all patients underwent surgery at diagnosis with 71.5% of the gross total/subtotal resection that was performed, which confirmed the attitude. The high percentage of gross total/subtotal resection could be explained by the high number of convexity sites. This generally allows an easier and quicker approach than skull-base meningiomas that predominantly received a partial resection because of the high risk of adverse events and sequelae.

Whenever tumor location is favorable, it is crucial that the first approach should comprise the most radical resection possible, including the excision of 2 cm of dural margin and all hyperostotic bone (to reach the lowest Simpson grade possible) [23]. HGMs also require close clinico-radiological follow-up to assess the likelihood of and time to recurrence, especially in patients who were identified as being at a higher risk. In such cases, a repeat surgery may likely remain the best approach available, provided the time of intervention is carefully considered in the context of the different benefit-to-risk ratios that each recurrence presents even for the same patient. Considerations of the physical performance status and neurological meningioma-related symptoms of each patient must, therefore, be weighted heavily when balancing the risks and benefits of any surgical approach for each recurrence in recurrent HGMs.

The extent of resection represents an important significance over survival of patients with 5-year survival rate of 95% in GTR compared with 67% of partial resection (\(p = 0.002\)), but also over PFS (5.3 years in GTR vs. 2.5 years in partial resection, \(p = 0.003\)). The impact of Simpson grade I–II resection on disease control is supported by numerous systematic reviews. However, conflicting opinions have been reported on the efficacy of its classification as well as on its effect on PFS. Sughrue et al. reported that, in their experience with malignant meningiomas, patients with STR had a better clinical course than did those with GTR [28]. Authors related this issue to the fact that STR is associated with fewer neurological sequelae. Thus, Adeberg et al. concluded that histological grading is the only factor that is correlated with survival [7,29].

Additionally, our analysis showed that the histologic grade seemed to be strictly correlated with the prognosis. Although no differences were found in PFS, a statistically significant difference in survival between atypical and anaplastic/rhabdoid subtype with median OS of 10.3 years vs 5 years (\(p = 0.03\)) emerged. Our data on PFS and OS in the group of atypical and anaplastic meningioma is only in part in line with the literature. This could be explained by the fact that in literature there are differences in OS and PFS in this type of patients. This inconsistency in the reported survival rates could be explained mainly by the low incidence of these tumors, and by possible variations in diagnostic classification (atypical vs rhabdoid vs anaplastic) and patient management. Moreover, another factor could influence the prognosis, as follows: higher expression of Ki-67/MIB-1 seems to be associated with a higher risk of death (HR: 1.06 with 95% CI, 1.00–1.12, \(p = 0.03\)). Consistent with our findings, Bruna et al. [30], confirmed that in patients with aggressive meningioma, this index is an independent predictor of both tumor recurrence and OS. We believe that the possible correlation between the Ki-67/MIB-1 values and the histological grades can predict potentially aggressive tumor behavior and support physicians in the management of patients.

Although this index is certainly one of the most common approach to determine proliferative activity, there are no established thresholds for MIB-1 proliferative indices, due to considerable overlap in the indices of different malignancy grades. For instance, a meta-analysis found that MIB-1 ranged from 1% to 16%, 2–20%, and 7–32% for WHO grades I, II, and III, respectively. Thus, many laboratories have established their own cutoff values [31]. In our group of patients, we assumed as high cutoff of
MIB1 index a value >15%.

Except for 21.3% of patients who were managed with a wait-and-see strategy because they had a small residual tumor (<2.5 cm) without any neurological symptoms, the most common post-surgery approach was radiation therapy. The majority of patients underwent adjuvant standard fractionated RT, and a small percentage of patients with multifocal disease was treated either with standard fractionated RT and radiosurgery or exclusive radiosurgery, for either single or multisession approaches. In our series, data showed no statistically significant differences in OS among the group; the 5-year survival rate was 86% in the cohort that was managed with a wait-and-see strategy and 78% in the cohort that was treated with RT and/or SRS (p = 0.42). However, RT and/or SRS seems to play a role in PFS by increasing disease-free results in the irradiated group (p = 0.03). However, because of the low number of cases, no clear conclusions could be drawn.

Although radiation treatments play a crucial role in meningioma patient management [32], controversy remains regarding timing, prescription doses, and fractionation of delivery. Because meningiomas often recur even if a complete resection is achievable, radiosurgery, both in a single session and using staged approach, as well as hypo-fractionated stereotactic radiotherapy (HSFRT) and standard fractionated radiotherapy, have been used in primary and adjuvant settings [31]. However, many studies showed that post-surgery RT plays a paramount role to achieve better local control in aggressive meningiomas regardless of the extent of resection. For the literature data, no major radiation-related adverse events were reported and no patient interrupted their treatment because of acute toxicity. Unfortunately, the characteristics of the retrospective database did not allow evaluation of long-term side effects.

To date, National Comprehensive Cancer Network (NCCN) guidelines suggest post-surgery RT in aggressive meningiomas as well as grade I–II partially removed and unresectable meningiomas. If possible, at the time of relapse, the guidelines suggest to perform surgery plus RT, regardless of age, localization, and molecular biomarkers. However, there has been no recommendation for using RT compared to SRS or proton compared to photon therapy [4,33]. Adjuvant RT is currently considered for all grade III meningiomas and frequently for partially resected grade II meningiomas. For gross total resected grade II meningiomas, close radiologic and clinical observation is feasible. The potential benefit of adjuvant radiation in this subset of patients is currently being tested in ongoing clinical trials.

After the second recurrence, the most frequently used treatments were systemic therapies when surgery and radiotherapy were not achievable. In our patients, all CHT treatments had a very limited effect on disease control without an acceptable outcome.

Current schedules, which are generally based on alkylating agents, anthracycline, or ribonucleotide reductase inhibitors, are considered to be ineffective with very poor results on disease control [34]. In 2015, the European Organization for Research and Treatment for Cancer (EORTC) evaluated the antitumor activity of Trabectedin, an alkylating drug that is largely used in sarcomas, against recurrent grade II or III meningioma, but to date, the data are unpublished (NCT02234050). Blended treatments using octreotide and everolimus are currently being investigated in a phase II trial (NCT02335655), to determine if the combination experts anti-tumoral activity in recurrent and/or aggressive meningiomas growth [35]. Additionally, antiangiogenic treatments such as sunitinib and vatalanib seems to prolong progression-free intervals in patients with recurrent grade II and III meningiomas [36,37]. Although the European Association for Neuro-Oncology (EANO) guidelines do not suggest a specific family of anti-cancer drugs for recurrent aggressive meningiomas because of the limited efficacy, NCCN guidelines recommend the use of alpha interferon (α-IFN), somatostatin receptor agonists, and vascular endothelial growth factor (VEGF) inhibitors [4,38].

An innovative non-pharmacological treatment that is already approved for glioblastoma is NovoTTF-100, which is a device that produces alternating electrical fields that cause apoptosis in recurrent atypical and anaplastic meningioma with promising results [39]. An ongoing phase II trial, which is currently recruiting in the United States, aims to determine the effects bevacizumab combined with NovoTTF-100 on atypical/anaplastic meningiomas. In addition to the device, bevacizumab could block vessel growth and might stop tumor growth and possibly shrinking the tumor by keeping it from receiving nutrients and oxygen (NCT02847559).

5. Conclusion

Considering the limitations of a retrospective design, our series is one of the largest studies that collected data on several parameters such as epidemiological, clinical, therapeutic, and survival data on primary HGM patients. The data confirmed the aggressive behavior of WHO grade II–III meningiomas harboring a poor prognosis. In particular, the histology grade seems to be strictly correlated with prognosis with a better outcome for atypical subtype. Regardless, the extent of resection seems to correlate with favorable results in terms of both PFS and OS. Moreover, a higher expression of Ki-67/MIB-1 seems to be associated with a higher risk of death. Thus, we believe that joint evaluation between Ki-67/MIB-1 and the histological grades, can predict the potentially aggressive tumor behavior and support physicians in the management of these patients. Although previous retrospective studies and systematic reviews have confirmed the impact of RT on atypical and malignant meningiomas, some controversies remain regarding doses and timing of the treatment. Our data did not show statistically significant differences in OS among the group that was managed using a wait-and-see strategy and those who were treated with RT and/or SRS, but we confirmed its role in prolonging PFS. However, the management of recurrent HGM remains the real challenge because of the lack of effective CHT agents. To date, none of the pharmacological choices that are available are able to achieve acceptable disease control. A successful strategy for aggressive meningiomas remains unknown. Future research should be based on large prospective trials that focus on biological and molecular predictors to achieve a patient-tailored treatment.

CRediT authorship contribution statement


Acknowledgements

We would like to express gratitude to Dr. Sandro Lodrini, MD for his valuable efforts in the field of malignant meningiomas.

Conflict of interest

The authors declare there are no conflicts of interest.

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