Classification of Meningiomas Based on Their Surgical Removal, World Health Organization Grade, and Cytogenetic Profile: A Treatment Algorithm

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■ BACKGROUND: **Meningiomas are the most common primary intracranial tumor, but the lack of prospective randomized trials has led to different guidelines for their treatment. We proposed a classification of meningiomas that considers surgical removal, histology, and cytogenetic profile, based on a literature review of these 3 criteria. The classification can be used to guide adjuvant treatment and follow-up.**

■ METHODS: **A retrospective literature review was performed of PubMed from 2007 to 2016. Search terms were "meningioma," "surgery," "WHO classification," "cytogenetic," and "algorithm."**

■ RESULTS: **Meningiomas were classified into 5 groups (A–E) according to the Simpson resection grade, World Health Organization grade, and cytogenetic profile. Adjuvant therapy, follow-up magnetic resonance imaging, and management of recurrence and/or regrowth were proposed according to the classification.**

■ CONCLUSIONS: **The proposed meningioma classification was based on our experience and retrospective evidence collated from the literature and supported by recommendations. The application of the classification criteria yielded an algorithm for treatment and follow-up of patients with meningioma.**

INTRODUCTION

Meningiomas are the most common primary intracranial tumor,[1] but the lack of prospective randomized trials has led to different guidelines for their treatment. Innumerable combinations of surgery, radiosurgery, and stereotactic fractionated radiotherapy (SFRT) protocols are described in the literature and reflect the preferred approach of each reference center. We carried out a retrospective review of the surgical Simpson grade, World Health Organization (WHO) classification criteria, and a cytogenetic profile of a series of meningiomas to propose a classification for these tumors. This classification reflects our experience and recommendations for the management of meningiomas and was used in the design of an algorithm for adjuvant therapy, follow-up, and management of recurrence and/or regrowth.

Materials and Methods

A retrospective PubMed search for English language literature reviews from 2007 to 2016 was carried out using the search term "meningioma" as well as the terms "surgery," "radiosurgery," "WHO classification," "cytogenetic," and "algorithm." This period was established so as to obtain studies published after the 2007 WHO classification of meningiomas. A review limited to PubMed using filters of 10 years and review articles was applied to select the most relevant studies. We excluded articles that considered limited information about progression-free survival (PFS) and recurrence rates. Studies of revision treatments for meningioma presented some series included in a wider revision article were also excluded; however, the largest study was included. No minimum follow-up period was observed for inclusion of a revision article. Articles providing PFS and recurrence rates in any meningioma topography were included. Bibliographies of selected articles were also reviewed to identify further relevant publications. Studies citing the Simpson surgical resection grade and the dose used in radiosurgery were included. Seminal articles, which presented the basic concepts included in the terms of the review and those cited in the review articles, were also included, even if their publication dates were previous to 2007. Outcome endpoints were recorded together with PFS and recurrence rates. The study was approved by the local research ethics committee at Hospital

Key words
- Cytogenetic
- Meningiomas
- Simpson grade
- WHO grade

Abbreviations and Acronyms
MRI: Magnetic resonance imaging
PFS: Progression-free survival
SFRT: Stereotactic fractionated radiotherapy
WHO: World Health Organization

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Table 1. Meningioma Classification and Management Algorithm

Group	Simpson Grade	WHO Grade	Cytogenetic	Adjuvant Treatment	Follow-Up MRI	Recurrence/Regrowth
A	I and II	I	N/DEL22	None	Every 6 months for 2 years, then every 12 months	SURG
B	≥III*	I	Abnormal*	None	Every 6 months for 5 years, then every 12 months	SURG + RADIO/SFRT
C	I and II	II	N/DEL22	None	Every 3 months for 2 years, then every 6 months for 2–5 years, then every 12 months	SURG + RADIO/SFRT
D	≥III*	II	Abnormal*	RADIO/SFRT	Every 3 months for 2 years, then every 6 months for 2–5 years, then every 12 months	SURG + RADIO/SFRT
E	Any	III	Any	RADIO/SFRT	Every 3 months for 5 years, then every 12 months	SURG + RADIO + CHEMO

WHO, World Health Organization; MRI, magnetic resonance imaging; N, normal; DEL22, deletion chromosome 22; SURG, surgery; RADIO, radiosurgery; SFRT, stereotactic fractionated radiotherapy; CHEMO, chemotherapy.
*Inclusion criteria for the group.

Ernesto Dornelles (Comitê de Ética em Pesquisa—HED). Patient information was deidentified before analysis.

RESULTS

The PubMed review criteria selected 55 articles. Of these articles, 19 were reviewed and included, and 21 articles from references were included. Also included were articles that supported the major results of the selected articles. Such references went back >10 years. The classification proposed reflects the experience of our department dealing with meningiomas.

The above-described information reported in the literature was used to support a classification of meningiomas based on the extent of their surgical removal, WHO grade, and cytogenetic profiles of the tumors (Table 1). Accordingly, 5 groups of meningiomas (A—E) with the following characteristics were defined:

- Group A meningiomas are meningiomas that were treated by total resection, corresponding to Simpson grades I and II and WHO grade I, and with a normal cytogenetic profile or with an isolated deletion of chromosome 22. In such cases, no adjuvant therapy is required, but follow-up magnetic resonance imaging (MRI) should be performed every 6 months during the first 2 years after treatment. If the patient is recurrence-free for 2 years as determined by MRI, the examination is repeated annually. In case of any recurrence, the most radical removal possible is recommended, followed by a review of the WHO grade and the cytogenetic abnormalities of the tumor.
- Group B meningiomas are meningiomas that are WHO grade I and Simpson grade III or greater and/or with any cytogenetic abnormality other than described for group A. These patients should be followed more closely than patients in group A, with MRI performed every 6 months for 5 years. Any recurrence and/or regrowth during that time is treated with the most radical surgery possible and radiosurgery or SFRT.
- Group C meningiomas are WHO grade II meningiomas that were treated with radical removal. They have the same favorable cytogenetic profile as defined for group A. Patients in group C should be closely followed with MRI performed every 3 months during the first 2 years and every 6 months for 2–5 years postoperatively. Recurrence is treated by the most radical surgery possible and radiosurgery or SFRT.
- Group D meningiomas are WHO grade II meningiomas that are Simpson grade III or greater or that have an abnormal cytogenetic profile. Patients in group D should undergo radiosurgery or SFRT as adjuvant treatment and the same protocol for MRI follow-up described for patients in group C.
- Group E meningiomas are WHO grade III meningiomas and are treated with adjuvant radiotherapy or SFRT. Close MRI-based follow up is recommended, with alternative treatment protocols in case of recurrence.

After establishing the criteria for our classification system, the meningiomas of 45 patients were classified, and the patients were followed accordingly. Table 2 presents the distribution of the patients.

Simpson Grade

Since the seminal paper of Simpson,[2] there has been broad agreement that the extent of surgical resection impacts the local control of meningioma. With only a few exceptions, in most

Table 2. Distribution of Meningiomas According to Proposed Classification

Group	Number (%)*
A	24 (54.7)
B	10 (23.8)
C	4 (4.7)
D	6 (14.2)
E	1 (2.3)

*$N = 45$.

literature reports, Simpson grades I, II, and III correlate with a longer PFS. Meningiomas of Simpson grades IV and V are clearly associated with higher local recurrence.[2-11] In a review of the literature, Rogers et al.[12] selected studies comprising 923 patients who underwent gross total removal. Local recurrence rates at 5, 10, and 15 years were 7%–23%, 20%–39%, and 24%–60%.[12-17] In 450 patients with subtotal removal, the recurrence rates at 5, 10, and 15 months were 37%–62%, 52%–100%, and 70%–91%.[12,13,15-20] Gousias et al.[5] retrospectively analyzed 901 patients at a single institution and observed that the risk of recurrence more than doubled between Simpson grades I and II in patients with 10 years of follow-up (8.5% vs. 18.8%). In meningiomas with higher WHO grades, aggressive surgical removal seemed to be even more important for local control. Most series report total removal rates of 90% for meningiomas located in a convexity compared with 50%–65% for meningiomas at different sites.[13,21,22]

As a surgery-oriented group, our goal in the surgery of any meningioma is the most radical resection possible. Even patients with large and giant meningiomas of the skull base are candidates for extensive tumor removal.[23,24] The most relevant aspect in the evaluation of the surgical results is a correct Simpson grade assignment. For skull base lesions, radical removal that takes into account the dura mater and bone is more difficult. Gross total removal has been described in some series as the aggressive surgical removal of skull base meningiomas. This can be confirmed by follow-up MRI and leads to symptom relief, but the implications for local control of the disease are different. Meningioma recurrence and/or regrowth is significantly higher in patients with Simpson grade III versus Simpson grade I and II resections.[2] Therefore, we divided our patients into groups including patients receiving the most radical surgery (Simpson grades I and II) and patients who despite surgery had a high potential of recurrence and/or regrowth (Simpson grade III or greater).

WHO Classification of Meningiomas

The WHO grade is the most useful morphologic predictor of recurrence. WHO grades I, II, and III are associated with recurrence rates of 7%–25%, 29%–52%, and 50%–94%.[25] The evolution of the WHO criteria for classification of meningiomas from 2000 to 2007 to 2016 has resulted in a change in the distribution of the lesions.[25,26] Before 2000, WHO grade II meningiomas were identified in approximately 5% of the reported cases, but with the most recent criteria, they represent 20%–35% of newly diagnosed meningiomas. WHO grade III represents <3% of cases.[12,27-29] The 10-year period of the literature review reflects articles published after the WHO classification of 2007 and the trend of the distribution of WHO grades I, II, and III in the literature.

Correct application of the WHO criteria is crucial because the prognosis of patients with WHO grade II and III meningiomas is clearly different from the prognosis of patients with WHO grade I meningiomas in terms of recurrence and PFS.[12,30] WHO grade II meningiomas, which include atypical, clear cell, and chordoid meningiomas, usually have a higher Ki-67 proliferation index and higher recurrence rates. Some studies have examined the proliferation index as an independent factor and determined a correlation between Ki-67 >4% and rates of recurrence similar to those of atypical meningiomas.[25] Another important immunophenotypic marker is progesterone receptor expression, which is inversely associated with meningioma grade. Most WHO grade III meningiomas are progesterone receptor negative.[25] Anaplastic, papillary, and rhabdoid meningiomas correspond to WHO grade III meningiomas. The average survival time of patients with anaplastic meningioma is 2–5 years depending on the Simpson resection grade.[12,25]

WHO grade II meningiomas are the most controversial in terms of optimal management. There are no prospective randomized studies and no consensus based on retrospective analyses of the literature.[30-33] The authors of a recent series found evidence supporting radiosurgery after surgical removal of the tumor in all patients with WHO grade II meningiomas, whereas in other studies the recurrence rates were >7-fold to >8-fold higher after 5 years for WHO grade II versus WHO grade I meningiomas.[30-33] For WHO grade II meningiomas, 84% of centers in Germany and 80% of centers in the United Kingdom recommend surgery alone following gross total removal.[34,35] In older patients and in patients with meningiomas accompanied by multiple chromosomal abnormalities, the use of radiosurgery and SFRT is less controversial. However, in younger patients (<65 years old) scheduled for radical resection of a meningioma (Simpson grades I and II) with a favorable cytogenetic profile (group C), there is cause for concern because the benefits of radiation are less well established, and recurrences could be radiation-related tumor progression.[36,37] The cytogenetic changes in previously irradiated meningiomas lead to aggressive biologic behavior during the recurrence and/or regrowth period.[36,37] In our institution, the recurrence of a WHO grade II meningioma previously removed in a Simpson grade I or II resection but with a normal cytogenetic profile is treated by removal that is as aggressive as possible, followed by adjuvant radiation as a further treatment step. If cytogenetic analysis of a WHO grade II meningioma indicates at least 2 abnormalities or Simpson grade III or greater, radiosurgery is indicated as adjuvant treatment after the initial surgery because the risks of grade III progression and tumor regrowth are higher.[38] WHO grade III meningiomas present multiple cytogenetic abnormalities and have a 5-year recurrence rate of almost 100%.

Patients in groups C and D have WHO grade II meningiomas, but the results of the forthcoming prospective studies of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer consortia could change our treatment approach to these cases. In patients with WHO grade I and II meningiomas without recurrence during 5 years of follow-up, we recommend MRI every 12 months for the next 15 years. Regardless of the treatment modality, the risk of meningioma recurrence increases with increasing duration of follow-up.[25,26,30,31]

Cytogenetic Profile

The most frequent cytogenetic change in meningiomas is monosomy 22, which is detected in 40%–60% of meningiomas and is probably associated with the first stages of the disease.[38,39] However, other isolated chromosomal abnormalities and more complex karyotypes have been described, and they are associated with an aggressive biologic behavior. In general, karyotypic changes consisting of ≥2 altered chromosomes are associated with a more aggressive meningioma.

Genetic alterations of chromosomes 1, 6, 9, 10, 14, 15, 17, 18, and 20 are well established in WHO grade I–III meningiomas, and they correlate with higher recurrence and/or regrowth rates.[38-40] Chromosome 1 deletions are the second most frequent cytogenetic abnormality and have been identified in WHO grade I (13%–26%), grade II (40%–76%), and grade III (70%–100%) tumors.[38] Gains in chromosome 1 are associated with a shorter PFS.[36-40] Chromosome 6 abnormalities occur in approximately 9% of WHO grade I, 25%–33% of grade II, and 50%–63% of grade III meningiomas. Chromosome 9 abnormalities are clearly associated with malignant meningiomas, and chromosome 10 losses are associated with a poorer prognosis and higher recurrence rate. Chromosome 14 abnormalities are the third most frequent karyotypic alteration in meningioma and are associated with a higher recurrence rate. Chromosome 17 gains have been linked to malignant meningioma, and chromosome 18 losses have been linked to a higher tumor grade and recurrence rate.[37,38]

In terms of molecular mechanisms, several markers have been studied. Genomic analysis of non–neurofibromatosis 2 meningiomas has revealed mutations in the *TRAF7*, *KLF4*, *AKT1*, and *SMO* genes. Anterior and medial skull base meningiomas tend to be non–neurofibromatosis 2 variants, whereas lateral and posterior meningiomas are neurofibromatosis 2 related.[38]

The most important clinical consideration in the cytogenetic profile is that even WHO grade I meningiomas may have abnormalities other than those involving chromosome 22. These abnormalities are related to more aggressive biologic behavior. Thus, in our classification, these patients (groups B and D) are closely followed at short intervals. **Table 2** presents our series distribution, consisting of 45 patients who underwent surgery for meningioma between 2013 and 2017. Longer follow-up periods will allow us to monitor recurrence and/or regrowth in the different groups and validate the MRI follow-up interval.

DISCUSSION

There are innumerable aspects to be considered to predict the biologic behavior of meningiomas. Age, MIB-1 labeling index, vascularity, and edema were some examples of such data as described in the literature. Topography is very important considering the differences in growth rates of skull base meningiomas compared with convexity tumors. In addition, radical resection is limited in cranial base lesions. Molecular studies of meningiomas are very important when predicting disease. Nevertheless, we established these particular grading criteria, as such aspects are accepted by most centers. They are relevant for local control of all meningiomas and are universally available to most of the departments involved, even in developing countries.

Simpson grade, WHO classification, and cytogenetic basic profile (karyotype) are low-cost assessments, and the integration of information can provide an additional tool when planning treatment and follow-up of patients. Knowledge of the molecular basis of meningiomas is the most important aspect, as it is this that will probably change the management of these tumors in the near future. However, molecular studies are restricted to technologic centers and are expensive for most developing countries.

In the present classification, the cytogenetic basic profile is used to identify abnormal karyotypes, which signal a higher risk of molecular abnormalities and aggressive biologic behavior. These patients should be followed closely and for a long period of time (>10 years). The follow-up periods were based on our current practices and the recommendation of the National Comprehensive Cancer Network guidelines for central nervous system cancers. After the fifth year, we recommend MRI every 12 months to observe any delayed recurrence and/or progression.

CONCLUSIONS

The classification described in this article is based on our experience dealing with meningiomas and several retrospective literature reviews support the recommendations given. The application of this classification can serve as the basis of a general algorithm for treatment and follow-up of meningioma. Further prospective randomized studies should help to define guidelines based on a higher evidence level.

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