

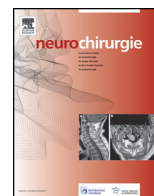


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General review

Recent advances in the management of atypical meningiomas

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ABSTRACT

Based on the 2007 WHO classification, the proportion of atypical meningiomas has steeply increased. Complete resection is usually considered curative, however, the recurrence rate remains high. The treatment of more aggressive meningiomas remains problematic. We performed a literature review via the PubMed database with specific attention to radiological, pathological, genetic and molecular aspects particular to WHO grade II meningiomas and current therapeutic strategies. We also reviewed the role of surgery and summarized the results of the principal studies dealing with adjuvant strategies based on the most recent evidence. Adjuvant radiotherapy, administered as stereotactic radiosurgery or conventional external beam irradiation, should be strongly considered in selected cases. Limited data exist regarding the role of hormonal treatment or chemotherapy as adjunct therapy. A target therapy modulating the altered molecular balance may be the key to revolutionize the prognosis of these patients.

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1. Introduction

Meningiomas represent the most common primary brain tumor [1]. They account for 20% and 38% of all primary intracranial neoplasms in males and in females, respectively, with an incidence of 4–6 per 100'000 persons [2]. Based on the 2007 World Health Organization (WHO) classification system [3], meningiomas are classified into three categories according to specific histological criteria: benign (WHO grade I), atypical (WHO grade II) and malignant or anaplastic (WHO grade III) meningiomas. Classically, most meningiomas were considered benign; currently, the incorporation of the criteria of brain invasion into the 2007 WHO grading system has noticeably increased the incidence of atypical meningiomas and they now constitute between 20 and 35% of newly diagnosed meningiomas [1,4]. This classification is the most accurate predictor of tumor recurrence and survival rate

[5]. At 5 years following surgical excision, the recurrence rate is approximately 3% for WHO grade I meningiomas [6], 41% for WHO grade II [7], and between 70 and 91% for WHO grade III meningiomas [8]. When compared to benign meningiomas, atypical meningiomas also show a statistically significant increased risk of mortality [9]. In addition to the histological grade, the recurrence rate is also related to the completeness of resection [10,11].

Epidemiological studies have shown how the female gender is a risk factor for developing meningioma, with a female to male ratio of 3:1 [12]. However, women are more prone to benign meningiomas, whereas atypical and malignant meningiomas show a slight male predominance [13]. Hormonal therapy and hormone dependent conditions like breast cancer [14], pregnancy [15] and obesity [16] were associated with an incidence of meningiomas, higher than expected in the general population. Cranial irradiation is also a recognized risk factor to develop meningiomas and radiation-induced meningiomas usually show higher histological grades, especially when presenting in younger age groups [3]. Convexity localization and age > 65 are other risk factors for higher-grade meningioma [17].

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In atypical meningiomas, early diagnosis and treatment are therefore of paramount importance to achieve the best outcome. Adjuvant treatments, like radiotherapy or chemotherapy should be considered in selected cases. Although the benefit of these treatments is clearly established for malignant meningiomas, atypical meningiomas still remain a subject of debate. A heterogeneous behavior is in fact often observed within the class of atypical meningiomas: a better stratification is necessary in order to delineate the appropriate management strategies. The aim of this article is to review the existing literature regarding the recent advances in the field of atypical meningiomas and to summarize the best evidence for decision-making in the management of these tumors.

2. Pathology

Meningiomas are thought to arise from the meningeothelial cells of the arachnoid layer. They present with evidence of epithelial as well as mesenchymal lining. WHO grade II meningiomas are defined as tumors with increased mitotic activity (4 or more mitoses within any 10 consecutive high-power fields) [9] and/or brain invasion and/or three of the following characteristics [3]:

- sheet- or pattern-less growth;
- foci of spontaneous necrosis;
- increased cellularity;
- prominent nucleoli;
- small cells with high nuclear to cytoplasmic ratio.

High mitotic count is the most important criteria for predicting WHO grade II meningiomas. Apoptosis and nuclear pleomorphism are not considered as WHO criteria. However, as stated by Backer-Grondahl et al. [18], a correlation was found between apoptosis, nuclear pleomorphism, higher tumor grade and poorer survival. For this reason, when apoptosis is observed, higher-grade meningioma should be sought. Increased vascularization and hemosiderin deposits were not correlated with tumor grade. At the contrary, classical psammomatous bodies have been found to be a protective factor [18,19].

Four subtypes of WHO grade II meningiomas have been described [3]:

- chordoid meningioma: it presents with trabeculae of eosinophilic epithelioid cells, a mucin-rich stroma and clear vacuoles resembling physaliferous cells. This pattern is usually mixed with meningothelial or transitional tumor areas. It is more often found supratentorially and it is histologically similar to chordoma;
- clear cell meningioma: sheets of polygonal cells with glycogen-rich clear cytoplasm and extensive perivascular and interstitial collagen deposition characterize this subtype. Typical meningioma features, as psammomatous bodies and whorl formation, are rare. This type typically occurs in the cauda equina region and in the posterior fossa in younger patients. A high recurrence rate is associated to this subtype;
- atypical meningioma: it may not be classified as chordoid or clear cell meningioma because of its atypical features, however, it includes features of the WHO criteria to be defined as grade II meningiomas;
- brain invasive meningioma: defined by a protrusion of tumor cells with infiltration of brain parenchyma. Since 2007, any meningioma harboring brain invasion should be considered at least as WHO grade II. Brain invasion is highly linked to a higher recurrence rate even after gross total resection.

Immunohistochemical markers may help in assessing the proliferative potential of meningiomas. Although MIB-1 staining is not included in the WHO grading system, it may have a prognostic value: increased MIB-1 index correlates with increased regrowth after gross total resection [20]. Some authors have suggested considering MIB-1 index above 5% as a diagnostic marker for WHO II meningiomas [20].

3. Genetics

3.1. Cytogenetic profile

The theory of clonal evolution is commonly used to explain the progressive gain in aggressiveness and malignancy in most neoplasms [21]. Less than 2% of benign meningiomas progress to more aggressive variants [22] but the prevalence is significantly higher with recurrent tumors (between 14 and 28,5%) [23]. According to the study of Weber et al. [24] and Lee et al. [25], the number of accumulated genetic alterations and allelic imbalances is correlated with the histopathologic classification (Fig. 1).

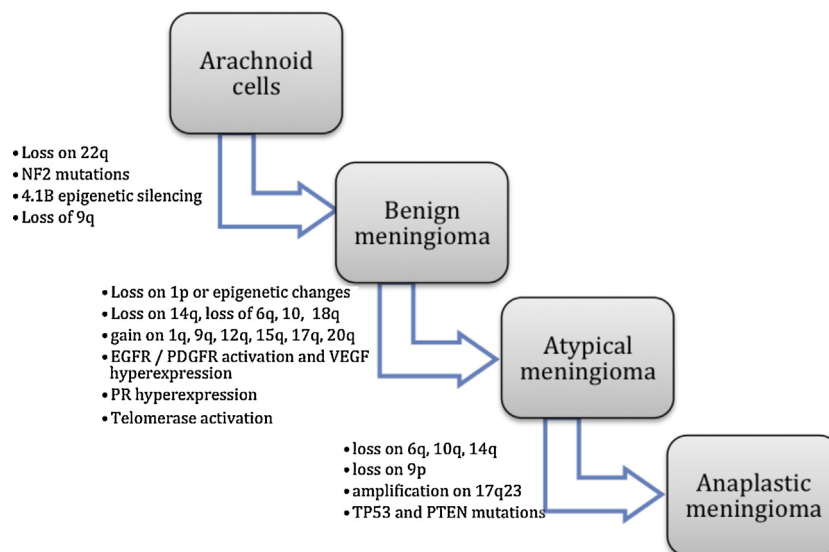


Fig. 1. Cascade of genetic alterations and allelic imbalances correlating with the WHO histologic grade.

Modified and adapted from Weber et al. [24] and Lee et al. [25].

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