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Prognostic factors in atypical meningioma

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Abstract: Atypical meningioma represent an intermediary group between the benign meningioma (grade I) and anaplastic meningioma (grade III), and are known for high recurrence rate and short life expectancy. After modification of the classification World Health Organization in 2007, subsequent studies have tried to find prognostic factors for recurrence and survival, which are inconstant from author to author. This paper aims to present a short review of the most important prognostic factors in atypical meningioma.
Key words: atypical meningioma, prognostic factors, survival, recurrence

Introduction

Atypical meningioma (AM) represent an intermediate risk group between benign (grade I) and anaplastic meningioma (grade III), being known for their tendency to relapse after the surgery (42, 54, 66) and increased morbidity and mortality (24, 37, 54, 63).

The rarity of AM cases and the inconsistent histological criteria in time regarding their definition led to the difficult understanding of the management of these types of tumours, especially of the prognostic factors (2, 10, 20, 40, 43, 47). Moreover, in recent years it has been noticed an increase in the number of AM diagnostics (13, 48) and that is why, in view of an adequate management, it is necessary to clarify the factors of prognostic in AM.

Incidence

Intracranial meningiomas represent about one third of the primary brain tumours (13, 34), being the most frequent intracranial primary benign tumours (5, 7, 31). Among them, AM represents about 4.7-7.2% of all meningioma diagnoses (33). After introducing the classifications of World Health Organization (WHO) from 2000 and 2007, the percentage of AM increased to 20-30% among all the meningiomas (47, 48, 65). Willis et al., in a study on 314 patients for a period of ten years (1994-2003), concluded that if in agreement with WHO grading system (1993) AM represented 5-7%, according to the new criteria WHO (2000), they represented 20.4% (65).

The anatomo-pathological evolution of AM

The existence of AM and malign meningioma was recognized from 1938, when Cushing and Eisenhardt reported a type of meningioma with mean survival rate of 2.5 years (63). The concept of "atypical grade II meningioma" was introduced for the first time in 1985 by Professor Juha Jääskeläinen from Finland (25).

In 1990, Mayo clinic group suggested a set of criteria for AM, where the absence of anaplasia, an important predicting factor for recurrence was the cerebral invasion (53). Three years later, in 1993, WHO included AM (grade II) as intermediary category between the benign meningioma (grade I) and anaplastic or malign meningioma (grade III). Nevertheless, in 1993 the criteria WHO were not implemented at large scale (48).

Even though Cushing recognized since the 1930s the malign potential of meningiomas (11), no uniform system of classification was accepted until 2000, when the classification WHO became more objective and reproducible (34). It was followed by the revision WHO in 2007, when the criteria of brain invasion became additional criterion in AM, even in the absence of anaplasia or atypia (49).

In 2016, WHO upgraded the classification of meningiomas from 2007 (33). According to this new classification (32), based on three histological grades, AM were divided into: benign meningioma (grade I), atypical meningioma (grade II) and malignant meningioma (grade III).

Currently, the criteria of diagnostic for AM are: clear or chordoid cell histology, brain infiltration, 4 to 19 mitoses per 10 high-power fields, or 3 or more of the following: increased cellularity, necrosis, small cell change, prominent nucleoli and "sheetlike" growth (33). The classification WHO of meningioma from 2016 reinforced "brain infiltration" as a stand-alone histological feature for AM (32, 62).

Factors of prognostic in AM

The factors of prognostic in AM can be divided into: demographic (age, gender), clinical, factors of prognostic related to the morphology of the tumour (location of tumour, tumour dimensions, anatomo-pathological characteristics) and prognostic factors related to the degree of surgery resection (Table I).

I. Demographic factors of prognostic (age, gender)

Age. Current studies have proved that the age of the patient with AM can be considered a factor of prognostic related to the survival (14, 56, 68). Furthermore, some studies have proved that an increased age at diagnosis was a factor of poor prognostic for recurrence (3, 4, 8, 9, 14, 18, 56, 68), some authors mentioning even the age > 65 as being the age limit for poor prognosis (28, 47).

Zaher et al. has proved that age < 50 is a good factor of prognostic for overall survival (OAS) (68), and Durand et al. has found as well as a factor of good prognostic the age < 60 (14). On the other hand, Aboukais et al. has not found any difference between progression-free survival (PFS) in relation to the age at diagnostic (1).

Gender. Unlike benign meningiomas that

seem rather linked to oestrogen levels and thus more frequent in women, AM have different gender demographics, mainly larger in men (19, 35, 64, 70). As for gender as factor of prognostic, the studies are inconsistent. If some authors consider that male gender represents a risk factor for a shorter survival (61), others have reported that on the contrary, female gender would represent a predicting factor for recurrence, having a relapse rate twice as bigger that in male gender (69).

II. Clinic factors of prognostic (motor deficit, Karnofsky Performance Status Scale)

Related to admission simptoms, Zhao et al. concluded that the neurologic deficit (paresis) can be considered a factor of poor prognostic, since these patients had a higher tendency to relapse than the patients with other symptoms (69).

Also, the Karnofsky Performance Status Scale (KPS) was taken into account as factor of prognostic. Thus, Zhao et al. proved that the patients with KPS >80 presented a higher PFS comparing with the patients with KPS < 80 (69).

III. Factors of prognostic related to the morphology of the tumour (tumour location, the dimensions of the tumour, the anatomo-pathological characteristics)

Tumor location. AM at the level of the cerebral convexity was associated with a longest survival, and it was correlated with the total excision made in case of locating the tumour (45, 55, 68). On the other hand, parasagittal-falcine location of AM led to an increase of recurrence, probably because of the residual tumour along the superior sagittal sinus (61).

Dimensions of the tumour. Another factor of prognostic that influences the survival was found the size of the tumour (12, 18). Garzon-Muvdi et al. noticed that in tumour with dimensions between 50 and 100 mm there is a decrease of survival by the increase of morbidity and mortality (18).

Anatomo-pathological characteristics. With the classification WHO in 2007, the relation between the histological grade of the meningioma and the outcome has become even stronger, studies on long series confirming it (22, 53).

The proliferative activity of meningiomas is measured with Ki-67 labelling index (LI), considered as a potential instrument to establish the recurrence of meningiomas (22, 26, 44). The Ki-67 index proved in a study as being the strongest distinguishing criterion between atypical and classical and anaplastic meningioma (29).

Also, the immunohistochemical overstaining for MIB-1 antigen, CDK4, CDK6, p53, p16, p21, pRB protein, cyclin D1 and mitotic index were proved to be factors of prognostic, showing a statistically higher recurrence rate and also a shorter time of recurrence versus understaining (27, 58, 59, 60). Among them, higher MIB-1 LI proved to be the strongest indicator for poor outcome in AM (16, 46, 47, 61). Also, other anatomo-pathological and immunohistochemical factors with role of factors of prognostic were also discovered, mitosis and osteopontin (6, 30). When mitosis is closer to 20 per 10 high-power fields, it reflects biology of tumour more aggressive comparing with low mitosis (6). Osteopontin, a protein involved in tumour progression was proved to be correlated with

poor clinical outcome and as predictor of AM (30).

IV. Factors of prognostic related to surgery resection

The extent of surgery was reported as being the most important predictor of outcome in patients with meningiomas by reducing both the mortality and the recurrence (3, 14, 15, 19, 20, 21, 23, 34, 38, 47, 53, 57, 67, 68).

The extent of resection (Simpson grading) was proved to be a factor of prognostic also in respect to the OAS. Thus, survival proved to be significantly higher in patients with gross total resection (GTR) (that most authors consider to be Simpson grade 1, 2) than those with subtotal resection (STR) (Simpson grade 3, 4) (1, 14, 17, 20, 27, 36, 46, 68, 69). Also, studies have shown that PFS was better in patients with subtotal resection (Simpson grade 3, 4) comparing with biopsy only (Simpson grade 5) (28, 45, 56, 68).

On the other hand, Pasquier et al. concluded in their study that the extent of surgery resection was not a factor of prognostic for the meningiomas of grade II and III, but its statistic analysis was done on the whole group, without distinction between the grades (47).

Related to the bone invasion of the meningioma, even though initially it was not accepted as factor of prognostic in AM (41), Gabeau-Lacet et al. and Ho et al. proved that it can be an important predictor of poor treatment outcome (17, 22).

Prognostic

Patients with AM have a poor prognosis and increased mortality, with a median survival rate lower than 2 years (33). Also, patients with secondary AM have a risk of recurrence three times higher (69) and a rate of death at 3-5 years twice as higher (50, 51, 52) and about 10-30% of the AM undergoing transformation to WHO grade III (39, 67).

TABLE I

Prognostic factors in AM (recent studies)

Year	Author	No. cases	Prognostic factors for survivals	Prognostic factors for recurrence
2016	Endo (16)	45	Age, degree of resection, MIB1-LI	Age, MIB1-LI
2015	Zhao (69)	89*	Degree of resection, KPS	Paresis, secondary meningioma, female
2014	Hammouche (20)	79	-	Degree of resection
2013	Aboukais (1)	167	-	Degree of resection
2013	Park (46)	83	Age	Degree of resection MIB1-LI
2013	Zaher (68)	44	Degree of resection, age	Degree of resection
2011	Mair (36)	114	-	Degree of resection
2010	Vranic (61)	86*	Male, parasagittal-falcine location	Brain invasion, parasagittal-falcine location, high mitotic index
2009	Durand (14)	166	Degree of resection, age	Degree of resection, age
2009	Gabeau-Lacet (17)	47	Age, bone involvement	Degree of resection, bone involvement
2008	Pasqueir (47)	119*	Age, KPS, high mitotic index	KPS, high mitotic index

**atypical and anaplastic meningioma*

Conclusion

Many of the factors of prognostic for survival or recurrence, as well as the resection extent, histopathological characteristics, age, gender or patient's symptoms on admission remain still unclear and must be verified in larger cohorts.

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