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Prognostic Factors in Meningioma

Ulrich Roelcke

Abstract: Age, WHO grade, and extent of resection represent strong prognostic factors in meningiomas. The majority of further clinical factors and laboratory findings reflects disease according to the WHO grade. Therefore, research

should focus on heterogeneity of prognostic factors within a given WHO grade. This may allow to identify also factors predictive for response to systemic therapy, and to promote the design of studies which stratify according to these factors.

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Key words: meningioma, prognosis, WHO grade, hormone receptors, angiogenesis, VEGF receptor, osteopontin

■ Introduction

The term “prognostic” relates to the behaviour of a tumour with regard to the spontaneous course as well as to the course after medical intervention. In contrast, the term “predictive” indicates the chance to respond to a given therapy. In meningiomas, the term “prognostic” is differently used across the literature and includes risk for incidence, risk for tumour development as well as risk for meningioma progression and recurrence. In the following, the term “risk factor” is used with regard to meningioma aetiology. „Prognostic“ denotes factors which may determine the clinical course once a meningioma is diagnosed. “Predictive factors” particularly with regard to systemic therapy have not been evaluated in meningiomas.

■ Risk Factors

Genetic alterations, status of sex hormones, and ionizing radiation represent well-established risk factors in meningiomas. These tumours can be part of hereditary syndromes such as neurofibromatosis type 2 (NF2), Li-Fraumeni, Turcot, Gardner, von Hippel-Lindau, Cowden, Gorlin, and multiple endocrine neoplasia type 1 [1]. In neurofibromatosis type 2, there are probably several genes involved in the development of meningioma, ie, a significant risk was observed also in the absence of alterations on the NF2 gene [2]. The association between hormones and meningiomas is evident by the increased incidence of these tumours in women (female:male ratio up to 3:1), the presence of female hormone receptors on meningiomas, meningioma growth during pregnancy, and regression of meningioma after cessation of oestrogen agonist therapy [3–5]. In addition, also long-term use of oral contraceptives and post-menopausal hormonal replacement therapy increases the risk of developing meningioma [3]. Ionizing radiation induced meningiomas as a long-term complication of prophylactic cranial irradiation for leukaemia in childhood [6]. Whether radiographs of the mouth [7] or the use of mobile phones [8] represent risk factors is still a matter of debate.

■ Prognostic Factors

Prognostic factors can be grouped into clinical factors at first presentation, extent of resection, and laboratory markers obtained from tissue. Most studies present data on prognostic factors which show significant correlation with the WHO tumour grade.

Clinical Factors and Extent of Resection

Tumour recurrence and progression depend on characteristics of the individual tumour presentation as well as on treatment modalities. Histology predicts mortality and recurrence: relapse rates in WHO grade I (benign) / II (atypical) / III (malignant) of 7 / 40 / 80 % have been reported, and median survival in these studies was > 10 / 11.5 / 2.7 years, respectively [9, 10]. Of note, even in the absence of the cellular criteria of WHO grade II also brain invasion qualifies for WHO grade II because recurrence and mortality rates are similar to atypical meningiomas [11]. Also meningiomas which present with bone invasion show poorer outcome compared to non-invasive tumours [12]. Apart from WHO grade, age and extent of resection [13] represent strong prognostic factors as well. The extent of resection is graded according to the original description of Simpson (grades 1–5). Grade 1 denotes macroscopic gross total resection with excision of dura, sinus, and bone, whereas grade 5 denotes biopsy only [14]. On multivariate analysis, age < 40 years, male gender, less than gross-total resection, and a high mitotic index are independently associated with shorter progression-free survival [15]. However, although many patients with completely resected grade-I meningiomas can be considered as cured, late recurrences are observed even after 20 years [16]. As surgical options are determined by tumour location this factor has to be considered as well. While gross-total resection can be achieved in many tumours of the convexity, patients with skull-base tumours involving the petroclival region, cavernous sinus, or orbit are post-operatively left with a residual tumour of varying size. On the other hand, a follow-up study on incidental non-operated meningiomas showed that 26 % of skull-base tumours grow with a relative growth rate of 6.8 % per year, whereas 95 % of non-skull base tumours grow faster with a relative growth rate of 13.8 % per year during a median observation time of 49 months [17]. In line with this observation, Kane et al reported on a series of 378 operated meningiomas (82 % WHO grade I; 56 % skull base, 44 % non-skull base tumours) where patients with non-skull base lesions were significantly more likely to have atypical or malignant meningiomas on uni- and multivariate analysis [18]. The authors discussed that

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this difference may reflect the distinct embryologic origin of skull base and non-skull base dura, which may imply different genetic alterations and, therefore, a different biological behaviour [19–21].

Laboratory Markers

The proliferation markers Ki-67 and MIB labelling index correlate with the WHO tumour grade, and therefore – not surprisingly – with prognosis [22]. Within a specified WHO grade the correlation between Ki-67, the status of the tumour suppressor gene, p53, and prognosis is maintained (WHO grade I [23]). Also the expression of sex hormone receptors correlates with the tumour grade and impacts prognosis. Progesterone receptors are more frequent in benign meningiomas and correspond to a median recurrence rate of 5 %. Meningiomas which express oestrogen receptors, or tumours lacking sex hormone receptors, belong more frequently to WHO grades II and III and are associated with recurrence rates of up to 30 % [24]. Furthermore, telomerase activity, which indicates immortal cells characterized by clonal expansion and growth potential, was found in 95 % of atypical and malignant meningiomas [25]. The frequency of telomerase positivity is much lower in benign meningiomas [25, 26]. Of note, telomerase-positive benign meningiomas may show early recurrence even following gross-total resection [25].

The identification of prognostic factors which show a substantial range of expression within a distinct subgroup of meningioma (eg, WHO grade) and which relate to targets where treatment is available may allow to allocate patients to distinct molecular subgroups with regard to therapy. It has been established that meningiomas of all grades exhibit vascular endothelial growth factor (VEGF) to a variable degree [27, 28]. VEGF receptor mRNA expression varies within benign meningiomas. One study demonstrated that 6/8 benign meningiomas which recurred within a median of 3.9 years express VEGF receptor mRNA, whereas non-recurrent tumours did not [29]. Also, the balance between pro-angiogenic (VEGF) and anti-angiogenic (semaphorin 3A [SEMA3A]) factors corresponds to the prognosis of meningiomas. Barresi et al reported that low scores (ie, a VEGF:SEMA3A expression ratio < 3.0) are associated with longer progression-free survival [30]. Furthermore, the expression of the integrin-binding osteopontin protein, which is involved in angiogenesis, cell proliferation, and migration, impacts prognosis. In a series of 32 operated patients with WHO grade-I meningiomas, 28 % recurrences were observed during a mean follow-up of 34 months. In patients with “early” recurrences, the osteopontin staining score was approximately 6 times higher compared to non-recurrent tumours [31]. Similar findings were reported for atypical meningiomas [32]. These studies accentuate the importance to assess the biological variability within distinct prognostic groups (WHO grade). Results may prompt prospective trials which evaluate eg antiangiogenic strategies in osteopontin-positive meningioma.

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Conflict of Interest

The author states that no conflict of interest exists.

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