# Cerebral Relapsing Meningioma: A Surgical Series with Lack of Reliability of Standard Parameters Establishing Prognosis

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**Abstract.** *Background/Aim: Meningioma is the most frequent meningeal neoplasm, usually without relapse or metastasis. Patient follow-up is challenging, not standardized and is decided in multidisciplinary case discussion. Our aim was to determine the clinical and histological factors influencing the time to relapse. Patients and Methods: We conducted a single-Center retrospective study on 38 patients with surgically-excised relapsing meningiomas and collected clinical and pathological data. Results: Our results show that none of the histological factors included in the WHO classification, nor those not included are related to a shorter time to relapse. Conclusion: In our study, none of the histological, immunohistochemical and clinical parameters evaluated seem to be able to predict the time to relapse in meningioma.*

Meningioma is a frequently encountered tumor in daily neurosurgical and neuropathological practice. Their diagnosis is usually highly suggestive on examining clinical and radiological data, and their pathological diagnosis is usually easy. Their prognosis depends mainly on the extent of the surgical resection and the allowed histological grade according to the World Health Organization (WHO) classification (1). These two main prognostic factors assess the risk of recurrence, but their influence on the time to relapse in not known (2). The frequency and the duration of the follow-up is decided in multi-disciplinary case discussion but is not standardized. Our aim was to determine if the clinical and histological parameters included in the WHO classification and those not included could predict the time to relapse time and therefore influence the follow-up.

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*Key Words*: Meningioma, recurrent brain tumor, meningeal neoplasm, human, WHO classification.

## Patients and Methods

*Patients and clinical data*. From the database of our University Hospital Center Pathology Laboratory, we identified 731 consecutive patients with a diagnosis of meningioma from 1992 to 2012. We extracted the data of patients with two occurrences of meningioma. Occurrence of a meningioma at another site, tumors not classified as meningiomas according to the actual WHO classification (such as haemangiopericytoma/solitary fibrous tumor) and patients whose histological material was not available (clinical or radiological recurrence without histologically-proven relapse) were not included. All patients underwent surgery at our institution between 1992 and 2012. None of them was treated by radiation therapy at the time of the initial occurrence. For all patients, the following clinical data were collected: date of birth, age at diagnosis, gender, date of surgical resection, extent of resection (Simpson grade) and tumor location. The time to relapse was assessed by the time between the first surgical resection and the second one.

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their inclusion in the study.

*Pathological material*. Surgical specimens were obtained after approval of an Institutional Review Board (N° DC-2010-1108) and conducted according to national regulations. Tumor specimens were formalin-fixed, or Bouin's fixed for the older ones, and paraffin-embedded. We also collected the following histopathological data for each resection specimen: WHO grade and its components [histological subtype, number of mitoses per 10 high-power fields with a conversion to mitoses/mm$^2$ (threshold of 2.51 mitoses/mm$^2$) as previously described (1, 2), invasion of brain tissue, increased cellularity, small cells, prominent nucleoli, foci of spontaneous necrosis and patternless or sheet-like growth], and histological characteristics not included in the WHO grading such as invasion of bone or the *dura mater*.

*Immunohistochemistry*. Ki67 expression (clone MIB1, dilution 1:200; DAKO, Les Ulis, France) was performed on 5 μm-thick sections using an automated immunohistochemical procedure on Ventana Benchmark devices (Ventana, Tucson, AZ, USA). The proliferative index was evaluated by consensus with a semi-quantitative method in the most proliferative area by two neuropathologists (FF, MP).

*Statistical analysis*. Descriptive statistical analysis was carried out for all patients. Analysis of variance was applied (univariate and multivariate analyses) and SAS Inc. software Version 8 (SAS inc, Brie Comte Robert, France) was used for analysis.

## Results

*Patients and time to relapse*. The patients had an average age at initial diagnosis of 53 years and 6 months. The average age at initial diagnosis for men was 56 years and 8 months (n=16), and 51 years and 2 months for women (n=22). A total of 18% (n=7) of patients were aged below 40 years at initial. Each tumor was supratentorial and *dura mater*-based without prominent localization.

The mean time to relapse was 4 years and 4 months (range=4 months and 15 days to 18 years and 6 months, median=3 years and 10 months). All patients except one had a relapse before completing a follow-up of 8 years; this one patient had a late relapse at 18 years and 6 months at the same site.

*Correlation between the time to relapse, and clinical and histological parameters*. The clinical, surgical and histological data at initial resection and their correlation with the time to relapse are summarized in Table I.

Age was not significantly correlated with the time to relapse ($p>0.05$ in univariate and multivariate analyses). Bone or *dura mater* invasion by the tumor and the age of patients was not significantly correlated with the time to relapse in multivariate or univariate analyses. The proliferative index as evaluated by Ki67 immunohistochemistry ranged from 0.2 to 15% (mean=1.85%) and was also not correlated with the time to relapse ($p>0.05$) in univariate and multivariate analyses. Six meningiomas had a higher grade than the first resection on the second occurrence. No correlation between Simpson grade and the time to relapse was found.

The mean time to relapse for grade I meningioma for men is 3 years and 5 months (n=7) whereas it is 2 years and 8 months (n=9) for grade II. The mean time to relapse for grade I meningioma for women is 5 years and 4 months (n=15) whereas it is 4 years and 9 months (n=7) for grade II. The statistical analysis of the time to relapse as a function of gender adjusted histological grade (linear multiple regression model) gave an adjusted mean of 45.6 months for those with grade I tumour, 43.8 months for those with grade II, 53.4 months for women and 35.9 months for men. The *p*-value for gender was 0.0918 and for grade was 0.5639.

## Discussion

WHO grading and the extent of surgical resection are the two most important parameters for assessing the risk of relapse (1, 2). The surgical evaluation of the extent of the surgical resection does not correctly assess the entire

Table I. *Clinical, surgical and histological data of the initial resection and their correlation with the time to relapse*.

| | Average time to relapse | *p*-Value (multivariate analysis) | *p*-Value (univariate analysis) |
|---|---|---|---|
| Gender | Men: 3 years<br>Women: 5 years and 1 month | 0.0587 | 0.0202 |
| Simpson grade | 1: 4 years and 11 months<br>2: 4 years and 4 months<br>3: 5 years ans 9 months<br>4: 3 years and 7 months<br>Not specified: 2 years and 9 months | | |
| WHO histological grade | Grade I: 3 years (n=22)<br>Grade II: 3 years and 6 months (n=16) | 0.3193 | 0.5709 |
| Mitoses/mm$^2$ | <2,51/mm$^2$: 4 years and 3 months (n=31)<br>>2,51/mm$^2$: 4 years (n=7) | 0.7364 | 0.6944 |
| Brain invasion | Brain tissue present not invaded: 5 years and 7 months (n=11)<br>Brain tissue present invaded: 4 years (n=11)<br>Brain tissue absent: 3 years and 6 months (n=16) | 0.5303 | 0.8023 |
| Spontaneous necrosis | Absent: 4 years and 7 months (n=22)<br>Present: 3 years and 8 months (n=16) | 0.4266 | |
| Small cells | Absent: 6 years and 10 months (n=1)<br>Present: 4 years and 2 months | 0.4488 | 0.0792 |
| Prominent nucleoli | Absent: 4 years and 10 months (n=29)<br>Present: 2 years and 5 months (n=9) | 0.0670 | 0.2798 |
| Cellularity | Low: 3 years and 5 months (n=8)<br>High: 4 years and 5 months (n=31) | 0.4508 | 0.7990 |
| Patternless or sheet-like growth | Absent: 4 years and 1 month (n=34)<br>Present: 5 years and 3 months (n=4) | 0.3079 | 0.1928 |

removal of a meningioma (2). We chose to use the term 'relapse' rather than the terms of re-growth or recurrence which refer to tumor growth after incomplete surgical removal and after complete surgical resection, respectively. There is no clear definition of a relapse for meningiomas, which could be a radiological or histological definition. This is why we restricted our study to surgically excised meningiomas with histologically proven relapse because some dural lesions can radiologically mimic meningiomas (3). As in our study, the time to relapse reported in the literature is highly variable: a clinical article of 32 recurrent meningiomas found a mean time to first relapse of 4 years and 7 months (range from 5 to 183 months) without prognostic analysis of the histological parameters on the time to relapse (4). But the histological grading used was not that currently used (5); this grading was highly subjective (6). As expected, none of the histological parameters of the WHO grading of meningiomas has any influence on the time to relapse, but they do have a well-known importance in the histological grading of meningiomas, which can predict the risk of relapse (2).

It is well known that meningiomas encountered in men are more frequently grade II meningiomas; in our study, for the same histological grade, meningiomas in men seemed to relapse earlier but this was not statistically significant. This could be indicative of a distinct behavior of meningiomas in men. These data are further supported by genetic data suggesting a more frequent occurrence of del(1p36) in men with meningiomas (7). Meningiomas in younger patients or in men are more likely to relapse, but this should be counterbalanced because of the occurrence of tumors with a higher grade in these populations (1).

MIB1 is a monoclonal antibody directed against the Ki-67 protein, which is present only in the active phases of cell cycle (4). Numerous works have studied the expression of Ki67 in meningiomas (4, 8-12). The results are contradictory, showing both a prognostic value, on in other cases no prognostic value of a higher proliferative index (4, 8-12). Regardless, there is an overlap of proliferative index in relapsing and non relapsing meningiomas, and its evaluation is subject to interpretation bias (4, 8-12). Our study confirms these data, showing an overlap of proliferative index between early and late relapses. However, Ki67 is still useful to identify small highly proliferating areas or discordance with the histological grade which could identify patients needing a closer follow-up (4, 13). It is difficult to set a threshold proliferative index that could be included in a histological classification because both the technique and counting method used differ among laboratories (4). The proliferative index cannot substitute for the main prognostic factors: extension of surgical resection and histological grade (1, 2). Our results are consistent with most studies showing a higher proliferative index (3% *vs*. 1.8%) and a higher grade for the specimen of the recurrence (14). Only one study reported a lower proliferative index in the recurrence (15). The higher proliferative index in the recurrence could be a feature of a slow progression of meningioma over time with an increasing proliferative index, accumulation of genetic abnormalities and progression to a higher grade (16).

Certain studies have integrated a multistep approach by histology and genetic analysis to assess the risk of recurrence (17) but there is no clinical validation of this approach, and it is difficult to perform in routine practice.

Few chemotherapy drugs are efficient against meningioma (18). Some have demonstrated modest efficacy of immunotherapy with interferon alpha-2B in some cases (19). There is a need for new therapies in this frequently encountered meningeal tumor, especially for relapsing meningiomas and when complete surgical excision is difficult (20, 21).

Our work supports the lack of predictive value for the time to relapse not only of the WHO classification criteria used in the histological grading of meningiomas but also of other clinical and histological parameters.

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## References

1 Louis DN, Ohgaki H, Wiestler OD and Cavenee WK (eds.): WHO Classification of Tumours of the Central Nervous System. IARC, Lyon: 2007.

2 Perry A, Stafford SL, Scheithauer BW, Suman VJ and Lohse CM: Meningioma grading: an analysis of histologic parameters. Am J Surg Pathol *21*: 1455 1465, 1997.

3 Forest F, N'guyen AT, Fesselet J, Metellus P, Bouvier C, de Paula AM, Roche PH, and Figarella-Branger D: Meningeal Rosai-Dorfman disease mimicking meningioma. Ann Hematol *93*: 937-940, 2014.

4 Abramovich CM and Prayson RA: Histopathologic features and MIB-1 labeling indices in recurrent and nonrecurrent meningiomas. Arch Pathol Lab Med *123*: 793 800, 1999.

5 Kleihues P (ed.): Histological Typing of Tumours of the Central Nervous System. Second Edition. Springer-Verlag, Berlin: 1993.

6 Commins DL, Atkinson RD and Burnett ME: Review of meningioma histopathology. Neurosurg Focus *23*: E3, 2007.

7 Tabernero MD, Espinosa AB, Maillo A, Rebelo O, Vera JF, Sayagues JM, Merino M, Diaz P, Sousa P and Orfao A. Patient gender is associated with distinct patterns of chromosomal abnormalities and sex chromosome linked gene-expression profiles in meningiomas. The oncologist *12*: 1225 1236, 2007.

8 Matsuno A, Nagashima T, Matsuura R, Tanaka H, Hirakawa M, Murakami M, Tamura A and Kirino T. Correlation between MIB1 staining index and the immunoreactivity of p53 protein in recurrent and non-recurrent meningiomas. Am J Clin Pathol *106*: 776 781, 1996.

9 Møller ML and Braendstrup O: No prediction of recurrence of meningiomas by PCNA and Ki67 immunohistochemistry. J Neurooncol *34*: 241 246, 1997.

10 Babu S, Uppin SG, Uppin MS, Panigrahi MK, Saradhi V, Bhattacharjee S, Sahu BP, Purohit AK and Challa S: Meningiomas: correlation of Ki67 with histological grade. Neurol India *59*: 204-207, 2011.

11 Vranic A, Popovic M, Cör A, Prestor B and Pizem J: Mitotic count, brain invasion, and location are independent predictors of recurrence-free survival in primary atypical and malignant meningiomas: a study of 86 patients. Neurosurgery *67*: 1124-1132, 2010.

12 Roser F, Samii M, Ostertag H and Bellinzona M: The Ki-67 proliferation antigen in meningiomas. Experience in 600 cases. Acta Neurochir. *146*: 37 44, 2004.

13 Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM: The prognostic significance of MIB1, p53, and DNA flow cytometry in completely resected primary meningiomas. Cancer. *82*: 2262 2269, 1998.

14 Matsuno A, Fujimaki T, Sasaki T, Nagashima T, Ide T, Asai A, Matsuura R, Utsunomiya H and Kirino T: Clinical and histopathological analysis of proliferative potentials of recurrent and non-recurrent meningiomas. Acta Neuropathol *91*: 504 510, 1996.

15 Madsen C, Schrøder HD: Ki67 immunoreactivity in meningiomas–determination of the proliferative potential of meningiomas using the monoclonal antibody Ki-67. Clin Neuropathol *16*: 137 142, 1997.

16 Boström J, Meyer-Puttlitz B, Wolter M, Blaschke B, Weber RG, Lichter P, Ichimura K, Collins VP, Reifenberger G: Alterations of the tumor-suppressor genes *CDKN2A* (p16(INK4a)), *p14*(ARF), *CDKN2B* (p15(INK4b)), and *CDKN2C* (p18(INK4c)) in atypical and anaplastic meningiomas. Am J Pathol *159*: 661 669, 2001.

17 Barbera S, San Miguel T, Gil-Benso R, Muñoz-Hidalgo L, Roldan P, Gonzalez-Darder J, Cerda-Nicolas M, Lopez-Gines C: Genetic changes with prognostic value in histologically benign meningiomas.Clin Neuropathol *32*: 311-317, 2013.

18 Loven D, Hardoff R, Sever ZB, Steinmetz AP, Gornish M, Rappaport ZH, Fenig E, Ram Z, Sulkes A: Non-resectable slow-growing meningiomas treated by hydroxyurea. J Neurooncol *67*: 221 226, 2004

19 Kaba SE, DeMonte F, Bruner JM, Kyritsis AP, Jaeckle KA, Levin V, and Yung WK: The treatment of recurrent unresectable and malignant meningiomas with interferon alpha-2B. Neurosurgery *40*: 271 275, 1997.

20 Rao G, Klimo P Jr, Jensen RL, MacDonald JD and Couldwell WT: Surgical strategies for recurrent craniofacial meningiomas. Neurosurgery *58*: 874 880, 2006.

21 Raizer JJ, Grimm SA, Rademaker A, Chandler JP, Muro K, Helenowski I, Rice L, McCarthy K, Johnston SK, Mrugala MM and Chamberlain M: A phase II trial of PTK787/ZK 222584 in recurrent or progressive radiation and surgery refractory meningiomas. J Neurooncol *117*: 93-101, 2014.

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