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CLINICAL STUDY

The relationship between histomorphological characteristics and Ki-67 proliferation index in meningiomas

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Abstract: *Objectives:* This study had two aims. The first was to use the Ki 67 proliferation index (Ki-67 PI) to study the relationship between the proliferation potential and histopathological features such as mitosis, necrosis, loss of architecture, small cell change, hypercellularity, pleomorphism, brain invasion, dura invasion, bone invasion, and histological grade. The second aim was to compare primary and recurrent meningioma with respect to morphological characteristics and Ki-67 PI values.
Background: Meningiomas are tumors whose histological features do not predict their biological behavior. Despite their slow growth and even after total resection, recurrence may occur
Methods: A total of 245 meningioma cases in whom Ki-67 PI was studied were included in the study. The cases were assessed with respect to 10 morphological characteristics, and a possible significant relationship between these and Ki 67 PI was statistically tested.
Results: We found a statistically significant relationship between Ki-67 PI and mitotic activity, necrosis, loss of architecture, small cell change,brain invasion. In contrast to brain invasion, no significant relationship was present between dura or bone invasion and Ki-67 PI. We identified asignificant increase in the histological grade, mitotic activity and Ki-67 PI value of recurrent tumors, as compared to primary ones
Conclusion: Ki-67 PI values overlap in different grades. This overlapping might be due to the heterogeneity of biological activity within the tumor tissue *(Tab. 2, Fig. 7, Ref. 21).* Full Text in free PDF *www.bmj.sk.*
Key words: meningioma, MIB-1, proliferative potential, recurrence, invasion.

Meningiomas are tumors whose histological features do not predict their biological behavior. Despite their slow growth and even after total resection, recurrence may occur (1). The clinical factors associated with tumor recurrence include age, sex, the location of the tumor, and incomplete surgical resection (2). Many histopathological findings such as sheetlike pattern (loss of architecture), necrosis, nuclear pleomorphism, increased cellularity, distinct nucleoli, high mitotic activity, and increased nucleus/cytoplasm proportion (small cell change) have also been associated with recurrence (2–6).

Cell cycle kinetics plays a vital role in tumor behaviors. Proliferative activity is accepted as a prognostic indicator in solid tumors (7). In meningioma, proliferative potential is claimed to explain the biological behavior differences in the tumor. One of the methods used to assess cell proliferation is the immunohistochemical indication of the Ki-67 antigen, which is a nuclear protein synthesized in the active phase of the cell cycle (6–8).

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In this study, we described our own experience concerning the pathology of a large number of meningiomas. This study had two aims. The first was to use the Ki 67 proliferation index (Ki-67 PI) to study the relationship between the proliferation potential and histopathological features such as mitosis, necrosis, loss of architecture, small cell change, hypercellularity, pleomorphism, brain invasion, dura invasion, bone invasion, and histological grade. The second aim was to compare primary and recurrent meningioma with respect to morphological characteristics and Ki-67 PI values.

Materials and methods

We reviewed our experience with 356 patients who were diagnosed with meningioma at Department of Pathology during the years 2001 through 2008. A total of 245 subjects in whom Ki-67 PI was studied were included in the study. Histopathological diagnosis of all meningiomas was done according to the actual published WHO classification of tumors of the nervous system (9). These 245 meningioma cases were assessed with respect to 10 morphological characteristics (mitosis, necrosis, loss of architecture, small cell change, hypercellularity, nuclear pleomorphism, brain invasion, dura invasion, bone invasion, histological grade), and a possible meaningful relationship between these and Ki 67 PI was statistically tested. The mitotic count was established by counting mitotic figures in 10 random high

Tab. 1. Mean Ki-67 PI values with respect to histological grades.

Grade	Ki-67 PI (%)
Grade I	
Mean	2.78
Minimum	0
Maximum	13
Grade II	
Mean	7.23
Minimum	2
Maximum	18
Grade III	
Mean	23.78
Minimum	2
Maximum	45

power fields. MIB-1 immunostaining was performed on 1 block from each case. The Ki-67 PI value was recorded as the percent of all positively stained tumor cell nuclei evaluated.

The subjects were also divided into two groups: primary or recurrent meningioma. Group 1 included 219 patients who were operated for the first time for meningioma, while Group 2 included 25 subjects who had previously undergone one or more meningioma resection surgeries and were operated again for recurrence. One subject was excluded from both groups as there was no information available. The histopathological characteristics and Ki-67 PI values of 219 primary meningioma and 25 recurrent meningioma cases were compared. In primary meningioma cases, later recurrence was not considered; first-time surgery was required as a condition.

SPSS for Windows 13.0 (Chicago, IL) package program was used in the analyses. The continuous variables of the study were reported together with mean, standard deviation, and max-min values. The Shapiro-Wilk test was used for the normality test of continuous variables. The Mann–Whitney U test was used for the comparisons of the continuous variables that did not show normal distribution between two groups; the Kruskal-Wallis test was used for comparisons among more than 2 groups. Pearson chi-square and Fisher's exact chi-square tests were used in the comparisons between categorical variables and groups.

Results

Overall results of meningioma cases

Of the 245 meningioma cases, 74 were male and 171 were female. Mean age was 53.82; for males it was 55.49; for females it was 53.4. No difference with respect to age was found between males and females (p>0.05). Mean tumor diameter was 5.53 cm. Of the tumors, 27 % was located in the skull base, 5 % in orbita, 4% in the spinal canal, whereas the remaining 64 % was located in intracranial areas other than the skull base and orbita.

Of all the subjects, 201 (82 %) were grade I, 30 (12 %) were grade II, 14 (6 %) were grade III. Mean Ki-67 PI values for grade I, II and grade III were 2.78 % (range, 0 to 13 %), 7.23 % (range, 2 to 18 %), and 23.78 % (range, 2 to 45 %), respectively (Tab. 1).

A significant statistical relationship was observed between

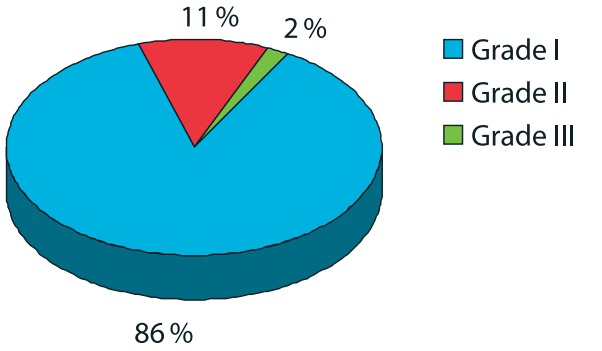

Fig. 1. Distribution of primary meningiomas with respect to histological grade.

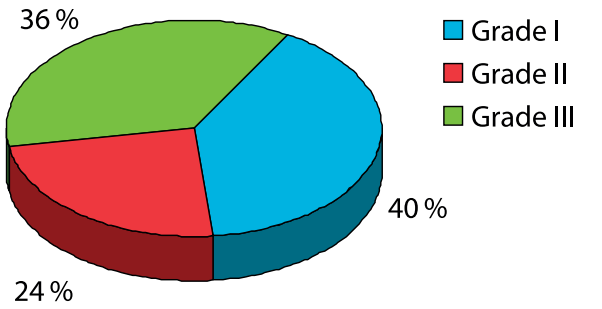

Fig. 2. Distribution of recurrent meningiomas with respect to histological grade.

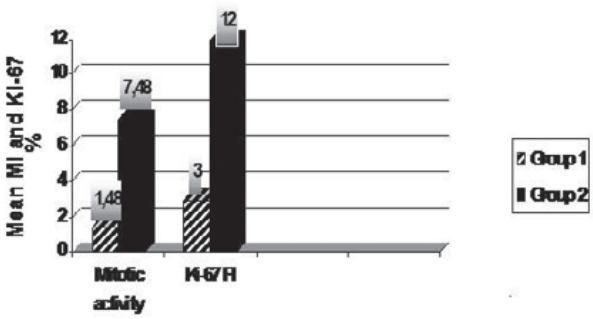

Fig. 3. Mitotic activity and Ki-67 PI values (%) in Groups 1 and 2.

Ki-67 PI and mitotic activity, necrosis, pattern loss, small cell change, and brain invasion (overall p=0.001). No relationship was found between Ki-67 PI and dura and bone invasion (p=0.138 and p=0.968, respectively).

As the number of mitosis increased, so did necrosis (p<0.001), pattern loss (p<0.001), small cell change (p<0.001) and brain invasion proportions (p=0.001). Dura and bone invasion were not related to mitotic activity (p>0.001).

Results of primary and recurrent meningioma groups

The subjects were divided into two groups as primary meningioma (Group 1) and recurrent meningioma (Group 2), and

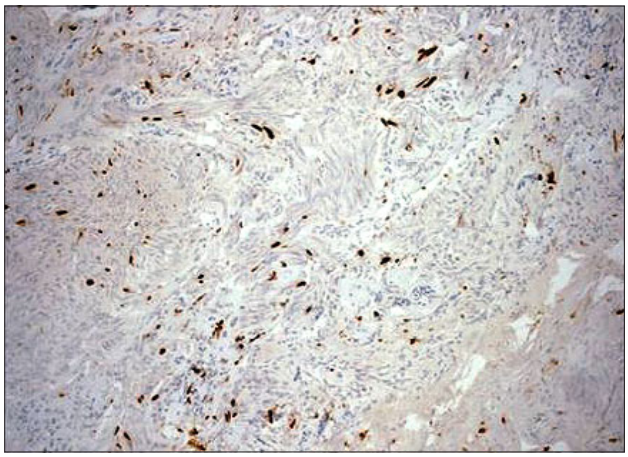

Fig. 4. The light micrograph shows low Ki-67 PI in primary meningioma (x200).

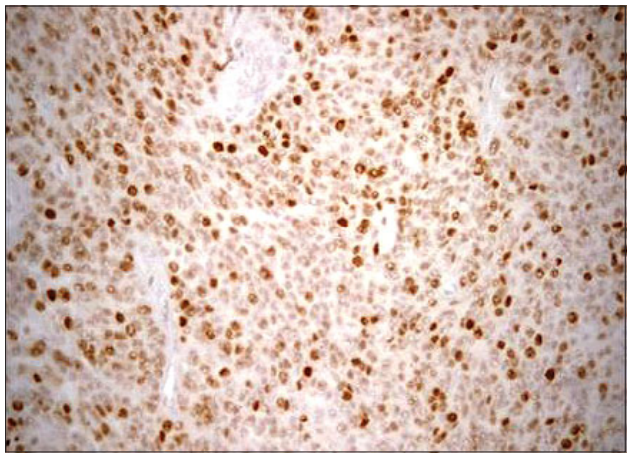

Fig. 5. The light micrograph shows high Ki-67 PI in recurrent meningioma (x200).

examined. Group 1 had 219 patients (67 males and 152 females), whose median age was 54 (with a range of 2–81 years). Group 2 had 25 patients (7 males and 18 females), with the median age 52.50 (with a range of 30–80 years). In Group 1, 27.4 % of the tumors were located in the skull base, 4.6 % in the orbita, 4.6 % in the spinal canal, and the remaining 63.4 % in other intracranial areas than the skull base and orbita. In Group 2, 20 % of the tumors were located in the skull base, 12 % in the orbita, and the remaining in other intracranial areas than the skull base and orbita. No spinal location was observed. While the mean tumor diameter in Group 1 was 3.67 cm, it was 5.4 cm in Group 2.

In Group 1, 191 (87.2 %) of the 219 cases were grade I, 23 (10.5 %) were grade II, 5 (2.3 %) were grade III. In Group 2, 10 (40 %) of the 25 cases were grade I, 6 (24 %) were grade II, and 9 (36 %) were grade III (Figs 1 and 2).

While the mean number of mitosis counted in HPF in Group 1 was 1.48, in Group 2 it was 7.48 ($p<0.05$). A significant difference also existed between the two groups with respect to Ki67 PI. It was 3% on average in Group 1, and 12% in Group 2 ($p=0.001$) (Figs 3–5).

When the groups were compared with respect to the existence of necrosis, it was present in 17.4 % of the cases in Group 1 and 40 % of the cases in Group 2. The difference was statistically meaningful. In Group 2, hypercellularity was observed in 92 % of the cases and pleomorphism in 84 % of them. In Group 1, these values were 67.6 % and 61.5 %, respectively. Pattern loss was seen in 17 (68 %) of the 25 cases in Group 2, and in 81 (37 %) of the 219 cases in the other group. Small cell change was seen in 16 % of the cases in Group 2 and 12.3 % of the cases in Group 1. No significant difference was observed (Fig. 6).

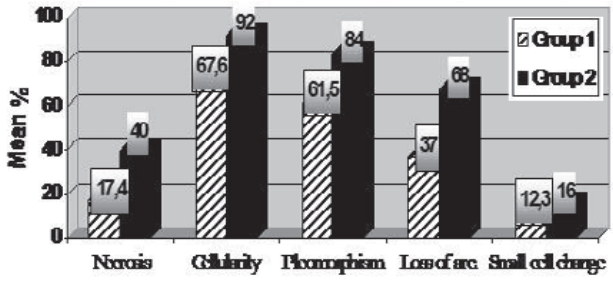

Fig. 6. Comparison of some histomorphological characteristics in Groups 1 and 2
(Loss of arc: Loss of architecture).

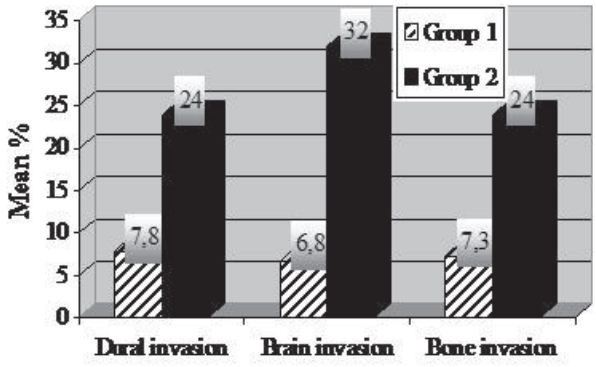

Fig. 7. Dura, brain and bone invasion rates in Groups 1 and 2.

In Group 1, dura invasion was observed in 7.8 % of the cases, brain invasion in 6.8 % and bone invasion in 7.3 %. These values were 24 %, 32 % and 24 %, respectively, in Group 2 (Fig. 7).

As a result, a statistically significant difference was found between the groups of primary and recurrent meningioma with respect to mitotic activity, necrosis existence, loss of architecture, hypercellularity, pleomorphism, dura, brain, bone invasion and Ki-67 LI. No significant difference existed between the two groups with respect to small cell change. Morphological differences between the two groups and p values are given in Table 2.

Discussion

Meningiomas are neoplasms derived from arachnoidal cells. Most meningiomas are benign (grade I), well-circumscribed,

Tab. 2. Comparison of morphological characteristics of primary (Group 1) and recurrent meningioma (Group 2).

Morphological finding	Group 1 n (%)	Group 2 n(%)	P value
Necrosis	38 (17)	10 (40)	p=0.014
Loss of architecture	81 (37)	17 (68)	p=0.003
Small cell change	27 (12)	4 (16)	p=0.536
Brain invasion	15 (6)	8 (32)	p=0.001
Dura invasion	17 (7)	6 (24)	p=0.019
Bone invasion	16 (7)	6 (24)	p=0.015
Hypercellularity	148 (67)	23 (92)	p=0.012
Nuclear pleomorphism	134 (61)	21 (84)	p=0.026

slow-growing and curable by surgery. However, some are clinically aggressive. The two most important factors that determine the likelihood of meningioma recurrence are histological grade and extent of tumor resection (8). In a study comparing totally resected benign and atypical meningiomas, it was shown that there was a higher risk of recurrence in the latter but that recurrence was also possible in benign meningioma (10). Routine histological examination fails to identify the subset of grade I tumors that behave aggressively (8). Therefore, other methods than using morphological characteristics alone were sought to predict the biological behaviors of meningioma. Quantifying the proliferation potential of meningiomas may help to predict the clinical behavior of these tumors. Our study examined the morphological characteristics that correlated with the Ki-67 PI value on the one hand, and compared primary and recurrent meningioma with respect to morphological characteristics and Ki-67 PI values on the other. We found a statistically meaningful relationship between Ki-67 PI and mitotic activity, necrosis, pattern loss, small cell change, and brain invasion. No relationship was found between Ki-67 PI and bone or dura invasion. In addition, the incidence of certain morphological characteristics (necrosis, pattern loss, small cell change, dura, bone and brain invasion) increased along with mitotic activity and Ki 67 PI in the recurrent group. No difference was observed between primary and recurrent tumors with respect to small cell change.

Ki-67 PI

Counts of mitotic charts are central to the World Health Organization system of grading meningiomas. Like the mitotic index, proliferation indices correlate with tumor-doubling time. However, studies about the relationship between Ki-67 PI increase and recurrence have reached conflicting results. The risk of recurrence is claimed to be higher in meningioma where the Ki-67 PI value is over 5–10 % (1). One study reports a mean Ki-67 PI value of 3.8 % in primary tumors and 7.1 % in recurrent tumors (3). Torp et al (11) examined 23 benign, 17 atypical and 9 anaplastic meningioma cases, and found a meaningful difference between benign meningioma and atypical and malignant meningioma with respect to Ki-67 PI, observed no meaningful difference between atypical and anaplastic meningioma, and attributed this unexpected finding to overlapping Ki-67 results in different grades (11). On the other hand, Schiffer et al (12) compared initial and recurrent tumors in 76 recurrent meningioma cases and showed that histopathological characteristics did not vary in most cases, and that the histological grade, mitotic activity and Ki-67 PI did not increase. In our study, we identified a meaningful increase in the histological grade, mitotic activity and Ki-67 PI value of recurrent tumors, as compared to primary ones. Another noteworthy finding from our study has been that Ki-67 PI values overlap in different grades. This overlapping might be due to the heterogeneity of biological activity within the tumor tissue (13).

Tumor necrosis

Necrosis is known to be related to the aggression of meningioma. As the tumor grade increases, so does the frequency of necrosis. Moradi et al. found the incidence of necrosis to be 3.4 % in grade I tumors, and 36.7 % in grades II and III (14). McLean et al (15) observed necrosis in 8 % of benign meningioma, 42 % of atypical meningioma, and 71 % of malignant meningioma. In our study too, we found a meaningful relationship between necrosis and grade and Ki-67 PI. A meaningful difference also existed between primary and recurrent tumors with respect to the incidence of necrosis, which was 17.4 % and 40 %, respectively, in Groups I and II.

Hypercellularity and pleomorphism

In this study, hypercellularity and pleomorphism were found to be significantly more common in recurrent meningiomas. However, hypercellularity and pleomorphism are subjective criteria. Hypercellularity, for example, is not clearly defined. Even though it was defined in one study as =53 nuclei per HPF, there is in fact no reliable objective measure of hypercellularity at present (10). Willis et al. have claimed that subjective criteria such as hypercellularity or patternless growth lower the reliability of the classification system (16).

Loss of architecture

Neoplnastic cells in atypical meningiomas do not form widespread whorls, fascicles, cords, or nodules as they do in classic meningiomas. Histological features of atypical meningiomas are often described as uninterrupted patternless or sheetlike growths. Sheetlike growth pattern refers to a lack of any specific architectural pattern within the tumor. Toh et al. (17) attributed this to the differences of microscopic water behaviors in atypical meningioma. They speculated that water molecules tend to move with more directionality in atypical meningiomas. In our series, we found a meaningful relationship between Ki 67 PI and pattern loss (p=0.000). Also, more frequent loss of architecture was observed in recurrent cases than primary ones ($p<0.05$).

Small cell change

Even though we found a significant relationship between small cell change and Ki-67 PI (p=0.000), no significant increase was observed in the small cell change frequency in the recurrent group when compared to the primary one. We are of the opinion that this characteristic should be re-evaluated in series with a larger recurrent meningioma group.

Brain parenchyma, dura and bone invasion

Invasion of the brain parenchyma is still an unclear issue. When grade I meningiomas invade surrounding bone and soft tissue, total resection becomes difficult but the grade does not change. However, even though the tumor may be benign, it reveals the same prognosis as atypical meningioma if it has invaded the brain (8). Brain invasion is not a criterion of malignancy but a factor held responsible for recurrence (2). Brain invasion is reported not to correlate with histological grade or Ki-67 LI, but to be an independent prognostic factor (19). On the other hand, another study claimed that recurrence was not seen in any grade I tumors with brain invasion, all recurring tumors were grade II and III tumors with brain invasion, and therefore recurrence was not associated with brain invasion but grade (20). Consistent with these findings, another study reported that while the brain invasion rate in grades II and III was 12 %, it was as low as 1.9 % in grade I (14).

Meningiomas are able to invade dura mater and most frequently recur in the dura mater adjacent to the primary tumor. It has been reported that preventing tumor infiltration in the dura may have positive effects on the prognosis of recurrent patients (20). Bone invasion is a finding that can present even in benign meningioma (14).

Recent cytogenetic studies have shown that malignant progression is possible in meningioma (21). Our results are uninterpretable because the demonstration of the malignant progression of a meningioma warrants a comparative study between the first histological assessment and the pathological findings found at recurrence.

In our study, we found a statistically significant relationship between Ki-67 PI and brain invasion. In addition, the frequency of brain invasion was meaningfully higher in recurrent tumors (p=0.001). In contrast to brain invasion, no meaningful relationship was present between dura or bone invasion and Ki-67 PI. A weak relationship existed between dura and bone invasion and recurrence (p=0.019 and p=0.015, respectively). Differently to bone and dura invasion, brain invasion in our study correlated with Ki-67 PI increase and seen significantly more frequently in the recurrent group.

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