Araştırma Makalesi / Research Article

Abant Tıp Dergisi

Abant Medical Journal

Abant Med J 2023;12(1):43-50, doi:10.47493/abantmedj.1177937

Ki-67 Proliferation Index Positivity Limit (Cut-off) Value in Meningiomas

Meningiomlarda Ki-67 Proliferasyon İndeks Pozitiflik Sınır Değeri

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Geliş Tarihi (*Received*): 20.09.2022 **Kabul Tarihi (*Accepted*):** 03.01.2023 **Yayın Tarihi (*Published*):** 28.04.2023

Abstract

Objective: Meningiomas are usually slow-growing grade 1 tumors according to World Health Organization (WHO) classification. Histological and molecular criterias were defined for the determination of meningiomas of high grade and more aggressive. The proliferation activity is also considered among histopathological criterias. A commonly used parameter for determining proliferation activity is the Ki-67 index. This study was formed retrospectively to identife the positivity limit (cut-off) value of the Ki-67 proliferation index in cases diagnosed with meningioma.

Materials and Methods: The Ki-67 indices of a total 190 patients diagnosed with meningioma was compared with the histological degrees of the tumors. The ROC analysis method was used in the statistical analysis for Ki-67 values.

Results: The mean Ki-67 proliferation index was found to be 6.3% for grade 1, 11.2% for grade 2 and 26% for grade 3 in the cases diagnosed with meningioma in our center. The Ki-67 proliferation index, which can be used in addition to histopathological findings in the distinction of grade 1 and grade 2 meningiomas in our laboratory, was determined as a positivity limit value of 6.5 ($p>0.05$).

Conclusion: The Ki-67 proliferation index in meningioma is an important parameter that can be used to determine the histological grade of atypical meningioma in particular. Although the index seems to be easy to use, it is a value that can create difficulties in borderline cases and also in interobserver and intraobserver evaluations. Therefore, each pathology laboratory should determine the Ki-67 value that they can accept as a limit for meningioma grading.

Keywords: Meningioma, ROC Analysis, Positivity Limit Value (cut-off value)

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Öz

Amaç: Meningiomlar genellikle yavaş büyüyen Dünya Sağlık Örgütü (DSÖ) sınıflandırma sistemine göre derece 1 tümörlerdir. Meningiomların yüksek derece ve daha agresif olduğunu belirleyebilmek için bazı histolojik ve moleküler özellikler tanımlanmıştır. Proliferasyon aktivitesi bu histopatolojik özellikler arasında yer almaktadır. Proliferasyon aktivitesini belirlemek için kullanılan en yaygın parametrelerden biri Ki-67 indeksidir.

Gereç ve Yöntemler: Bu çalışma retrospektif olarak meningiom tanılı olgularda Ki-67 proliferasyon indeksinin pozitiflik sınır değerinin belirlenmesi için yapıldı. Meningiom tanısı alan toplam 190 hastada Ki-67 değerleri tümörlerin histolojik dereceleri ile karşılaştırıldı. Ki-67 değerlerinin istatistiksel analizi için ROC analiz yöntemi uygulandı.

Bulgular: Merkezimizde meningiom tanılı olgular için ortalama Ki-67 proliferasyon indeks değerleri derece 1 için %6,3, derece 2 için %11,2 ve derece 3 için %26 bulundu. Derece 1 ve derece 2 meningiomların ayrımında histopatolojik bulgulara ek olarak laboratuvarımızda uygulanan Ki-67 proliferasyon indeks pozitiflik sınır değeri 6,5 olarak bulundu ($p>0,05$).

Sonuç: Menenjiyomda Ki-67 proliferasyon indeksi, özellikle atipik menenjiyomun histolojik derecesini belirlemede kullanılabilecek önemli bir parametredir. İndeks kullanımı kolay gibi görünse de borderline durumlarda ve ayrıca gözlemciler-arası ve gözlemci-içi değerlendirmelerde güçlük yaratabilecek bir değerdir. Bu nedenle her patoloji laboratuvarı menenjiyom derecelendirmesi için sınır olarak kabul edebileceği Ki-67 değerini belirlemelidir.

Anahtar Kelimeler: Meningiom, ROC Analizi, Pozitiflik Sınır Değeri

Atıf/Cite as: Yeldir, N. , Doğan, E. , Özer, H. , Söylemez, B. , Çelikgün, S. & Eğilmez, R. (2023). Ki-67 Proliferation Index Positivity Limit (Cut-off) Value in Meningiomas. Abant Tıp Dergisi, 12 (1) , 43-50 . DOI: 10.47493/abantmedj.1177937

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Introduction

Meningiomas are tumors that originate from meningothelial cells in the arachnoid layer, most commonly seen in middle and advanced-age adults and women. These tumors often show slow growth. Most are among the grade 1 tumors in the classification of the central nervous system of the World Health Organization (WHO) (1). Although the exact etiology of meningioma is unknown, it has been suggested that trauma, radiation, oncogenic viruses, chromosome anomalies, and hormonal factors are likely to play a role. Histological grading is one of the major prognostic parameters in meningioma. Some histological criteria for high grade and more aggressive meningioma have been identified (2, 3).

Classification of Tumors of the Central Nervous System (CNS) was last updated by WHO in 2021. This fifth update contains major changes related to molecular diagnoses of tumors. Fifteen subtypes of meningioma have been identified according to their histopathological features. Among them, meningothelial, fibrous, and transitional meningiomas are the most common.

Most meningioma subtypes are benign and grade 1 tumors. The tumors such as chordoid and clear cell meningiomas are considered grade 2 due to the higher recurrence rates compared to grade 1 tumors. Until recently, papillary and rhabdoid meningiomas were considered grade 3. According to the recently updated WHO classification system, it is suggested that the tumor should be evaluated together with immunohistochemical and molecular features instead of being graded only based on morphological features (1).

The histopathological criteria defined for atypical (WHO grade 2) meningioma are characterized by having at least three features including the 4-19 mitotic figures in 10 consecutive HPF (each 0.16 mm^2) or brain invasion or specific morphological subtype (chordoid or clear cell) or visible nucleoli, increased cellularity, growth without a pattern, increased nucleocytoplasmic ratio, and foci of necrosis (4). Anaplastic meningioma (WHO grade 3) is a highly aggressive tumor that morphologically resembles a high-grade sarcoma or carcinoma. Typically, much higher rates of mitosis are observed compared to atypical meningioma.

Criteria defined for anaplastic (WHO grade 3) meningioma are characterized by 20 or more mitotic figures in 10 consecutive HPF (each 0.16 mm^2) or TERT promoter mutation or homozygous deletion of CDKN2A and/or CDKN2B (2, 5).

Materials and Methods

This study was conducted retrospectively with a total of 190 patients diagnosed with meningioma between 1998 and 2021. Data on the age, gender, tumor localization, histopathological diagnosis, tumor histological grading, and immunohistochemical staining results of the patients were obtained from the hospital archive. Descriptive statistical methods were applied to the data and Ki-67 indexes were compared with tumor histological grades. The ROC analysis method was used in the statistical analysis for Ki-67 values.

This study was approved by the Ethics Committee of Non-Interventional Clinical Research of Sivas Cumhuriyet University (date: 10.03.2021 and approval number: 2021/03-21).

Results

The study included a total of 190 patients diagnosed with meningioma. The sex distribution of these patients was 135 female (71%), 55 male (29%) and the mean age of them was 55 (age distribution 20-88). The localizations of tumors of patients are most often intracranial (173 cases) and a smaller number of cases are intraspinally located (17 cases).

The distribution of histopathological subtypes of meningioma cases; meningothelial meningioma 34% (Figure 1), transitional meningioma 27%, fibrous meningioma 17%, atypical meningioma 8%,

psammomatous meningioma 4% (Figure 2), clear cell meningioma 2%, secretory meningioma 2%, malignant meningioma 1%, angiomatous meningioma 1%, chordoid meningioma 1%, anaplastic meningioma 1%, microcystic meningioma 0.5% and papillary meningioma 0.5%. Histological subtypes and localizations of tumors according to the grades of cases are indicated in the table.

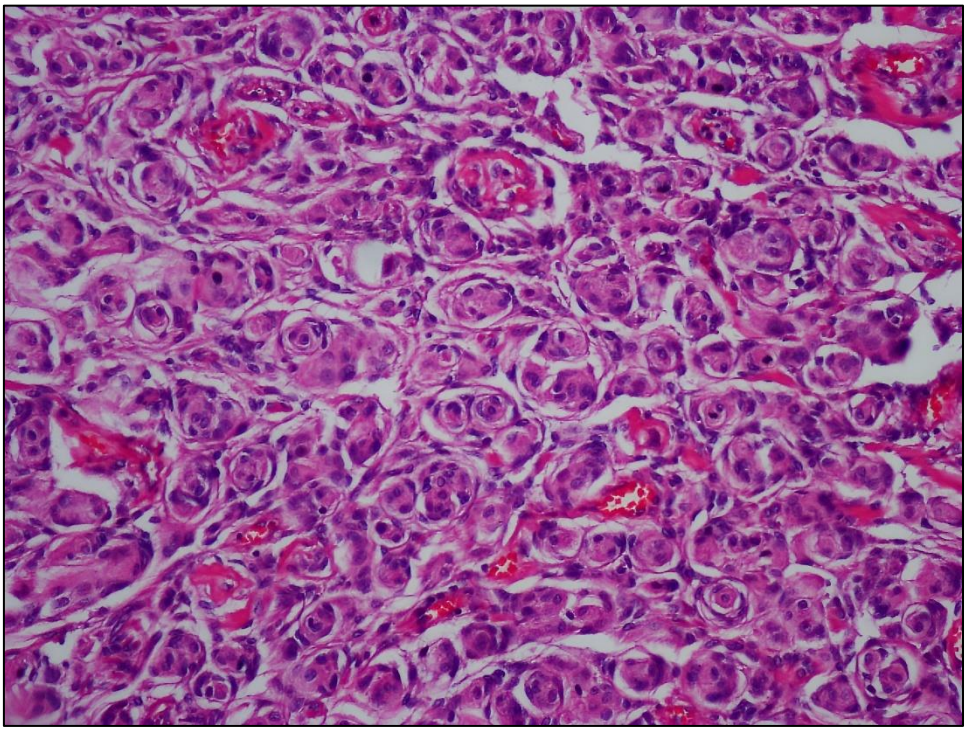

Figure 1. A case of meningothelial meningioma (Hematoksilen eosin stain, x200)

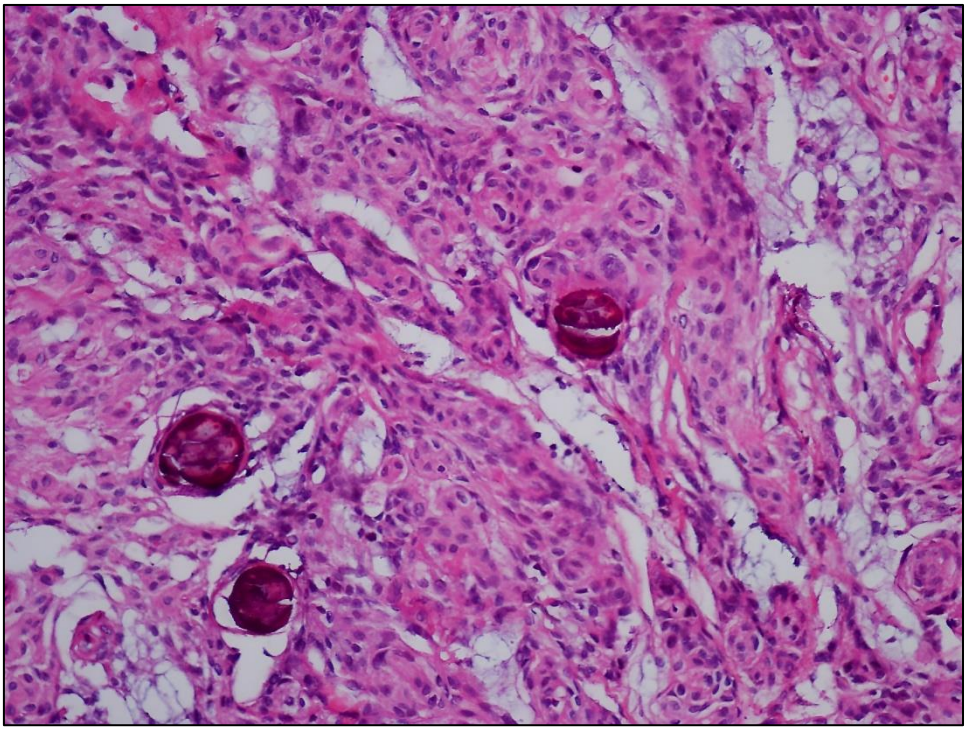

Figure 2. A case of psammomatous meningioma (Hematoksilen eosin stain , x200)

Table 1.
Histological Subtypes and Localizations of Tumors.

WHO GRADE 1 (N=163)				
	LOCALIZATION			
		Intracranial (n=146)		
Histological subtypes	***Intraspinal (n=17)***	***Cerebral***	***Cerebellar***	***Ventricular***
Meningothelial	11	50	1	1
Transitional	1	45	-	1
Fibroblastic	3	20	4	-
Psammomatous	2	6	-	-
Others	-	18	-	-

WHO GRADE 2 (N=20)				
	LOCALIZATION			
		Intracranial (n=20)		
	Intraspinal	***Cerebral***	***Cerebellar***	***Ventricular***
Chordoid	-	2	-	-
Atypical	-	14	-	-
Clear cell	-	4	-	-

WHO GRADE 3 (N=7)				
	LOCALIZATION			
		Intracranial (n=7)		
Histological subtypes	***Intraspinal***	***Cerebral***	***Cerebellar***	***Ventricular***
Rhabdoid	-	4	-	-
Anaplastic	-	2	-	-
Papillary	-	1	-	-

Histologically, the cases were divided into three degrees according to WHO classification criteria. The histological degrees of the cases were 163 cases of grade 1 (86%), 20 cases of grade 2 (10%) and 7 cases of grade 3 (4%) (Figure 3). The Ki-67 proliferation index was found to be 6.3% for grade 1 (Figure 4), 11.2% for grade 2 (Figure 5), and 26% for grade 3 on average in cases diagnosed with a meningioma (Figure 6).

In addition to histopathological findings, the positivity limit value of the Ki-67 proliferation index, which can be used to distinguish between grade 1 and grade 2 meningioma, was determined as 6.5 for our laboratory ($p>0.05$). There was no statistically significant positivity limit value for the Ki-67 index in the distinction between meningioma grade 2 and grade 3 ($p<0.05$).

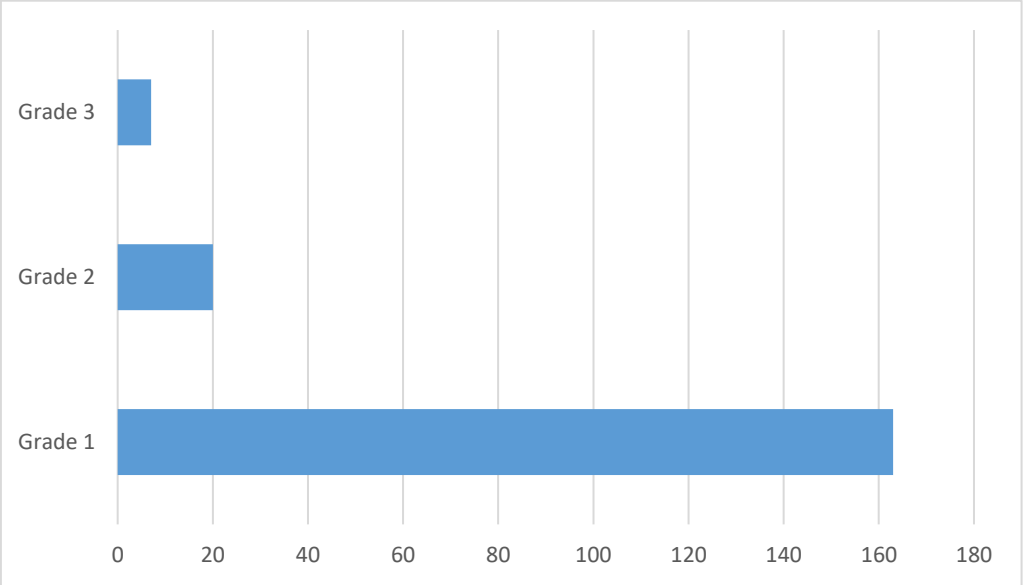

Figure 3. Distribution of grade 1-2-3 in meningioma cases (number of patients).

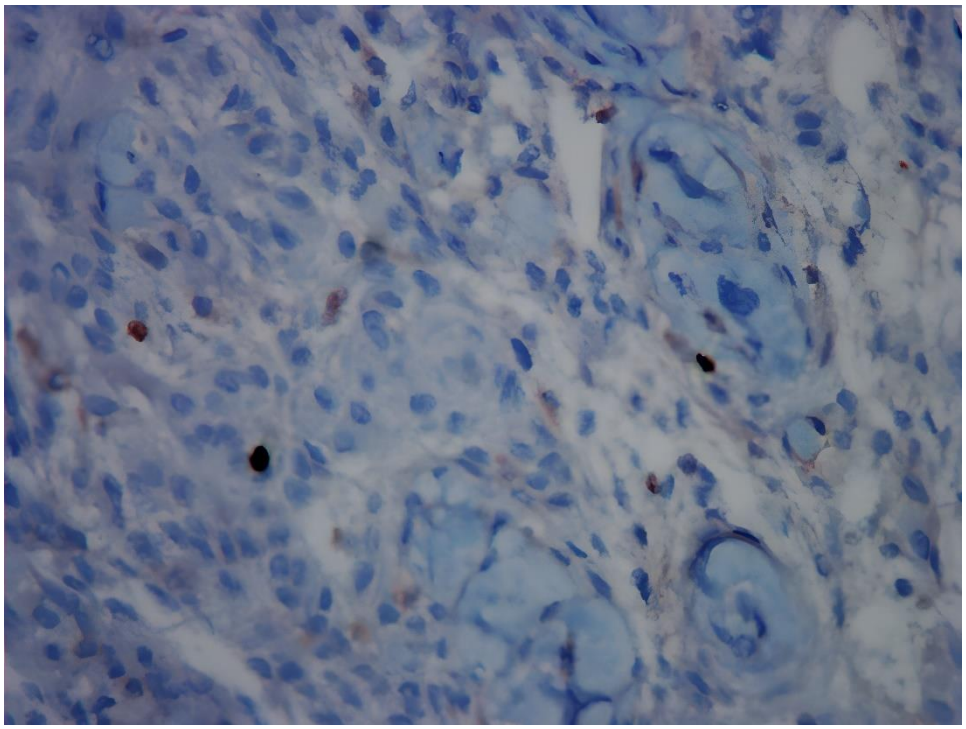

Figure 4. Ki-67 index of a case of grade 1 meningioma (x400)

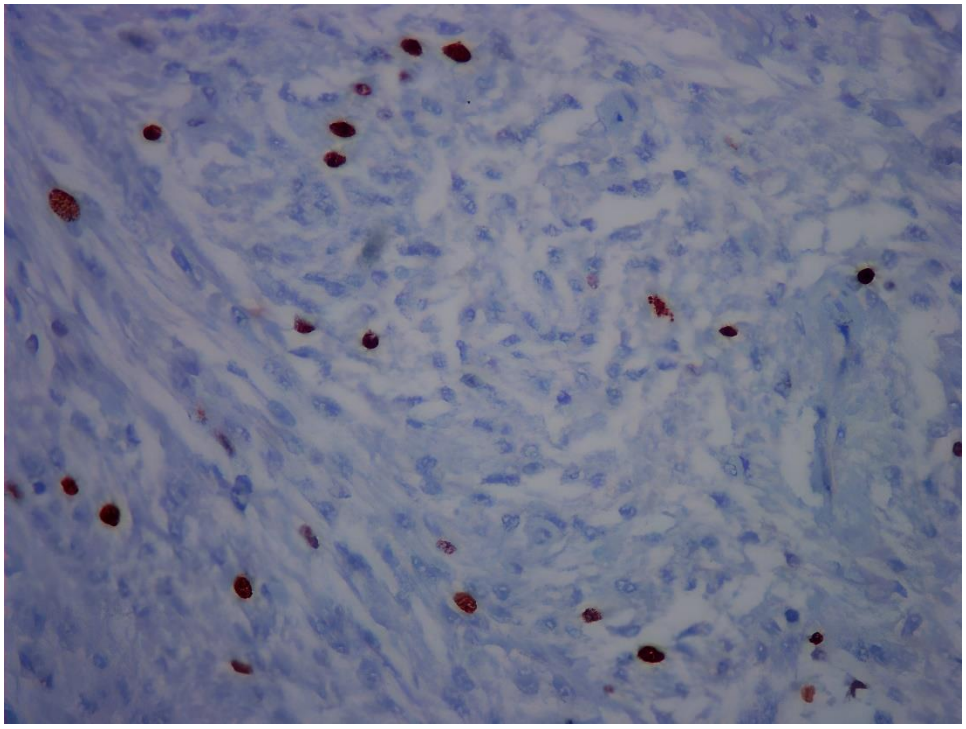

Figure 5. Ki-67 index of a case of grade 2 meningioma; increased proliferation index (x400)

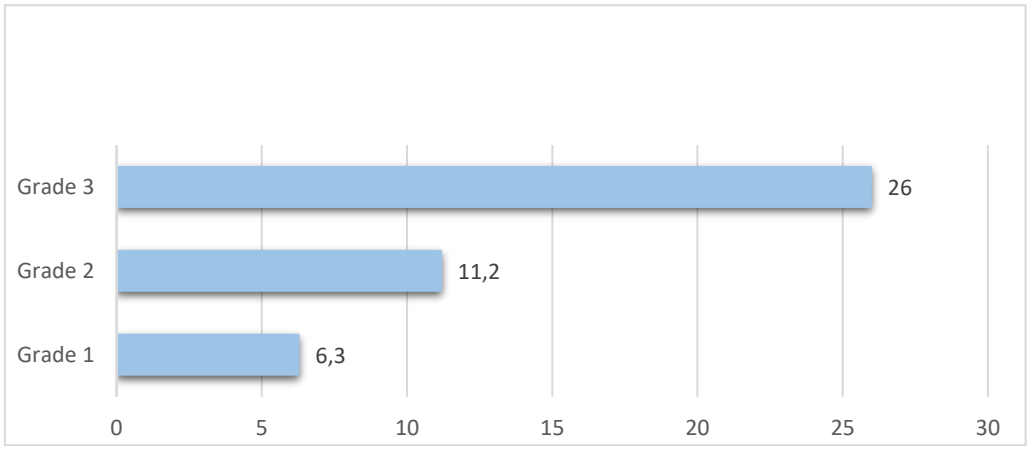

Figure 6. Average values of Ki67 proliferation index in meningioma cases.

Discussion

Meningioma is a well-circumscribed central nervous system tumor most of which have benign features. Meningioma with higher histological grades, more aggressive course, and higher recurrence rates are also present. According to the WHO tumors classification system of the central nervous system, meningioma is graded as 1, 2, and 3 according to its histopathological and molecular features. As the histological grade increases, the risk of recurrence and aggressiveness of the tumor also increases (6).

The number of mitosis and proliferation activity in meningioma are also criteria that provide information about the grade of the tumor (7). Although the prognostic significance of proliferation indexes determined by immunohistochemical methods has been emphasized by numerous studies, it has not been included among the grading criteria of meningioma in the latest WHO classification. The most commonly used immunohistochemical markers for this purpose are Ki-67, PCNA, and DNA Topoisomerase II. Universally accepted thresholds do not yet exist for any of these markers. However, it is known that the Ki-67 index, in particular, shows a rather significant increase in meningioma in atypical and malignant forms compared to benign forms (8,9). It is observed that there is a direct proportion between the grade of the tumor and the Ki-67 index. In accordance with this, an increase in the Ki-67 proliferation index and histological grading in our study were also found to be correlated.

In histopathological grading of meningiomas, determining an accurate mitotic index is one of the most important factors. Increased mitotic count is associated with a higher grade and, thus, a worse prognosis. Ho et al. showed that ≥1.5/ mm² mitotic activity rate was one of the best indicators of recurrence (10).

The atypical meningioma limit value of the Ki-67 proliferation index, a parameter that can be used to determine the aggressive course of meningioma, is considered to be >4% (11). However, this limit value may differ in each pathology laboratory. For our laboratory, this value was found to be >6.5%. Differences in the immunohistochemical staining method and the Ki-67 evaluation method are considered to be effective in the detected high value.

Conclusion

In conclusion, the Ki-67 proliferation index in meningioma is an important parameter that can be used to determine the histological grade of atypical meningioma in particular. Although the index seems to be easy to use, it is a value that can create difficulties in borderline cases and also in interobserver and intraobserver evaluations. Therefore, each pathology laboratory should determine the Ki-67 value that they can accept as a limit for meningioma grading.

Ethics Committee Approval: The study was approved by the Ethics Committee of Sivas University (date: 10.03.2021 and approval number: 2021/03-21).

Informed Consent: Written consent was obtained from the participants.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

References

1. Cree IA, Lokuhetty D, Peferoen LAN, White VA (editors). WHO Classification of Tumors of Central Nervous System. 5th ed. IARC;2021.
2. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Branger DF, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, Deimling AV, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-Oncology 2021; 23:1231-51.
3. Solomon DA, Pekmezci M. Pathology of meningiomas. HandbClinNeurol 2020; 169:87-99.
4. Saygın I, Cakır E, Ercin ME. Interobserver variability in mitotic count for meningioma grading: How can we reduce it? TurkNeurosurg 2020; 30:643:50.
5. Terzi A, Saglam EA, Barak A, Soylemezoglu F. The significance of immunohistochemical expression of Ki-67, p53, p21 and p16 in meningiomas tissue arrays. PatholResPract 2008;204:305-14.
6. Buttrick S, Shah AH, Komotar RJ, Ivan ME. Management of atypical and anaplastic meningiomas. NeurosurgClinNAm 2016; 27:239-47.
7. Liu N, Song SY, Jiang JB, Wang TJ, Yan CX. The prognostic role of Ki-67/MIB-1 in meningioma: A systematic review with meta-analysis. Medicine (Baltimore) 2020;99: e18644.

8. Roser F, Samii M, Ostertag H, Bellinzona M. The Ki-67 proliferation antigen in meningiomas. Experience in 600 cases. ActaNeurochir (Wien) 2004; 146:37-44.
9. Mirian C, Skyrman S, Bartek Jr J, Jensen LR, Kihlström, Förander P, Orrego A, Mathiesen T. The Ki-67 proliferation index as a marker of time to recurrence in intracranial meningioma. Neurosurgery 2020; 87:1289-98.
10. Ho DM, Hsu CY, Ting LT, Chiang H. Histopathology and MIB-1 labeling index predicted recurrence of meningiomas: A proposal of diagnostic criteria for patients with atypical meningioma. Cancer 2002; 94:1538-47.
11. Pavelin S, Becic K, Forempoher G, Mrklic I, Pogorelic Z, Titlic M, Andelinovic S. Expression of Ki-67 and p53 in meningiomas. Neoplasma 2013; 60:480-5.