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PROGNOSTİC VALUE OF Kİ67 İN BORDERLİNE MUCİNOUS OVARİAN TUMORS

BORDERLİNE MÜSİNÖZ OVER TÜMÖRLERİNDE Kİ67'NİN PROGNOSTİK DEĞERİ

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Öz

Amaç

Overin müsinöz borderline tümörleri (MBT), borderline over tümörlerinin en sık görülen ikinci alt tipidir. Belirsiz patogenezleri ve biyolojik davranışları nedeniyle, benign veya malign kategorilere açıkça sınıflandırılamadıkları için klinik seyir hakkında daha prognostik bilgi sağlayan ve rutin pratikte kolaylıkla değerlendirilebilecek bir parametrenin belirlenmesine ihtiyaç vardır. Ki67, tümör hücreleri de dahil olmak üzere hücresel proliferasyonla güçlü bir şekilde ilişkili olan ve rutin olarak kullanılan bir immünohistokimyasal belirteçtir. Bu çalışmada MBT'lerde Ki67 sayımının prognostik önemini değerlendirmeyi ve prognostik eşik değerini belirlemeyi ve klinikopatolojik özellikleri, nüks ve uzun süreli sağkalım durumu ile ilişkisini araştırmayı ve ayrıca literatüre daha fazla bilgi sağlamayı amaçladık.

Gereç ve Yöntem

Müsinöz borderline over tümörü tanısı koyulan toplam 20 vaka çalışmaya alındı. Tümörü en iyi temsil eden örnek üzerinde immünohistokimyasal çalışmalar yapıldı. Nükleer boyanma pozitif kabul edildi ve iki patolog tarafından değerlendirildi

Bulgular

Ki67 proliferasyon indeksi (P.I) medyan %15 (1-47% ve ortalama %16'dır. Ki67 P.I. progresyonla %20 eşik değerinde ve 5 yıllık OS ile %30 eşik değerinde istatistiksel olarak anlamlılığa ulaştı. (sırasıyla p=0.021 ve p=0.032). Ki67 P.I. yaşla birlikte artma eğilimindeydi. Kİ67 P.I. ile tümör boyutu, lateralite, kapsül bütünlüğü, intraepitelyal karsinom ve fokal atipi dahil olmak üzere diğer klinikopatolojik parametreler arasında istatistiksel bir ilişki yoktu.

Sonuç

Çalışmamızda Ki67 %20'den yüksek olduğunda nüksün daha sık oluşu, Ki67 %30'dan yüksek olduğunda 5 yıllık sağkalımın daha düşük oluşu Ki67 indeksinin daha agresif seyir ve ölüm ile ilişkili olduğunu düşündürdü. Bu nedenle Ki 67'nin hastaların takip sıklığını belirlemede ve prognozlarını tahmin etmede faydalı olacağını öngördük. Ancak bu sonucun daha geniş seriler ile desteklenmesi gerektiğini düşünüyoruz.

Anahtar Kelimeler: Borderline, Ki67, Müsinöz, Over, Tümör

Abstract

Objective

Ovarian borderline tumors (OBTs) are an intermediate type of ovarian neoplasm. Ovarian mucinous borderline tumors (MBT) are the second most common subtype of OBT. Because of their uncertain pathogenesis and biological behaviour they cannot be classified clearly into benign and malign categories. There is a need to identify a parameter that provides more prog-

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nostic information about the clinical course and can be evaluated easily in routine practice. Ki67 is a routinely used immunohistochemical marker that is strongly associated with cellular proliferation, including tumor cells. We aimed in this study to evaluate the prognostic significance and to determine prognostic cut-off value of Ki67 counting in the MBTs and to investigate its relationship with clinicopathologic features, recurrence, and long term survival status and also to provide more information to the literature.

Material and Method
A total of 20 cases diagnosed with ovarian mucinous borderline tumors were identified. Immunohistochemical studies were performed on the most representative sample of the tumor. Positive signal was nuclear and it was evaluated by two pathologists.

Results
Ki67 proliferating index (P.I) value with a median of 15%(1-47%) and a mean of 16% Ki67 P.I. reached statistically significance at 20% cut-off value with progression and at 30% cut-off value with 5-year OS. (p=0.021 and p=0.032, respectively). Although the Ki67 P.I. tended to increase with age, there was no statistical association between Kİ67 P.I. and other clinicopathological parameters including tumor size, laterality, capsule integrity, intraepithelial carcinoma and focal atypia.

Conclusion
In our study, recurrence was more frequent when Ki67 was greater than 20%, and 5-year survival was lower when Ki67 was greater than 30%, suggesting that the Ki67 index was associated with a more aggressive course and death. Therefore, we predicted that Ki 67 would be useful in determining the frequency of follow-up of patients and predicting their prognosis. However, we think that this result should be supported by larger series.

Keywords: Borderline, Mucinous, Ovary, Tumor, Ki67

Introductıon

Ovarian borderline tumors (OBTs) are an intermediate group of neoplasm that do not classify clearly into benign and malign categories, due to their lack of understanding biological behavior, uncertain pathogenesis, and unclear management (1). Ovarian mucinous borderline tumors (MBT) are the second most common subtype of OBT with a rate of about 30% to 50% in North America and Europe, but they are the most common subtype of OBT in Asia.(2)MBT is defined as an architecturally complex non-invasive mucinous neoplasm showing gastrointestinal-type differentiation (2). MBTs usually present as large, unilateral, variable-sized cystic masses and may contain multiple cystic areas (3). The mean tumor size is about 20 cm, some cases may be as large as 50 cm (2). Epithelial stratification with small papillary infoldings or tufts must cover at least 10% of all the tumors (4). Otherwise, the diagnosis should be mucinous cystadenoma with focal epithelial proliferation. The nuclear atypia is generally low grade (2). A part of the tumors may contain acellular mucin pools within the stroma and may develop granulomatous response against the ruptured glands and extracellular mucin (5).

The distinction of MBTs from their benign forms is very important but establishing the correct diagnoses can be difficult in these tumors. Overdiagnoses should be avoided because of their clinical outcomes regarding staging and follow-up (3). For this reason, detailed macroscopic examination and enough sampling are mandatory for these tumors, and at least one section per centimeter's largest tumor size should be sampled. In addition, it is recommended to increase to two blocks sampling in mucinous tumors that are larger than 10 cm (4). Standart treatment protocol consists of total surgical resection and surgical staging includes omentectomy, peritoneal sampling, appendectomy, and peritoneal washing for cytology (6, 7).

Clarifying the biology of borderline tumors and their risk of progression to invasive form has been wondered by researchers since the category was identified (8). However, over the years, it was observed that these tumors were related to quite heterogeneous behavior and many potential prognostic parameters were investigated (9). There is a need to identify a parameter that provides more prognostic information about the clinical course and can be evaluated easily in routine practice. Ki67 is a routinely used immunohistochemical marker that is strongly associated with cellular proliferation, including tumor cells. It labels nuclear protein (encoded by MKI67 gene) of the proliferating cells (10). Ki67 proliferation index is often related with the clinical course of cancers (8). There are neoplasms such as neuroendocrine tumors that Ki67 assessment has been accepted an independent prognostic parameter so that their grading system based on the Ki67 counting (11). In several tumors such as breast

cancers, in addition to assessment of hormonal status, Ki67 counting is used to make risk stratification. To date, the prognostic importance of Ki67 counting has not been adequately evaluated in OBTs. There is limited reports in the literature on this subject.

Our purpose in this study was to evaluate the prognostic significance of Ki67 counting in the MBTs and to investigate its relationship with clinicopathologic features, recurrence, and long term survival status and also to provide more information to the literature.

Material and Method

A total of 20 cases diagnosed with pure mucinous borderline ovarian tumors from hysterectomy ± unilateral or bilateral salpingooferectomy surgery and no other malignancy between the years 2010 to 2019 in the Izmir Katip Celebi University Ataturk Training and Research Hospital were included in the study. The clinicopathological informations including tumor size, laterality, age at diagnoses, and death if occurred, were obtained from the hospital database. An extensive sampling was performed to all the tumors. Then, the most demonstrative Hemotoxylin-Eosin (H&E) section was selected for Ki67 immunohistochemical staining. Full-thickness 5 µm sections were obtained from formalin-fixed, paraffin-embedded blocks from all cases. Immunhistochemical staining was evaluated on microwave oven processed formalin-fixed paraffin-embedded tissue, and citrate pH 6 as antigen retrieval. The immunohistochemical staining was provided by Ventana Detection System. The Ki67 antibody clone was 30-9 rabbit monoclonal primary antibody (Ventana). Brown nuclear staining was considered positive and was evaluated by two pathologists independently. Discordant results were reevaluated in double-headed microscopes and a consensus was reached. All H&E sections were scanned at low magnification to chose the “hot spot” area for Ki67 proliferating index (P.I.) assessment. Then, cells showing nuclear staining were counted in at least 500 neoplastic cells and the average of the obtained values were calculated (figure 1).

Statistical Analyses

Disease-free survival (DFS) was evaluated from the surgery time to any status related to disease (disease relapse, metastasis) or death. Overall survival (OS) was defined as the period from the surgery time until the date of death from any event or the date who was alive on the last follow-up. For survival status, the last follow-up date was February 2021.

Pearson’s Chi-square and Fisher’s exact tests were performed to evaluate the association between the Ki67 P.I. and clinicopathological variables. We investigated statistical association of Ki67 P.I. with progression, 5-year DFS, and 5-year OS with increasing values of ten percent (eg. 10%, 20%, and 30%). SPSS for Microsoft Windows Sofware (version 18.0, SPSS Chicago, IL, USA) was used for statistical analyses. A P-value ≤ 0.05 was considered statistically significant. Kaplan-Meier curves were used to determine 5-year DFS, 5-year OS with the long-rank test.

Results

The study population consisted of totally 20 patients. The medical data of all patients were reviewed retrospectively (Table 1). The age at diagnosis of patients ranged from 29 to 94 with a median of 50.5 years. The tumors tended to be predominantly located in left over (left over, n=15/20 (75%) and right over, n=4/20 (%25)). The tumor diameter ranged from 4 cm to 30 cm with a median size of 17 cm and an average size of 18.9 cm. There were accompanying intraepithelial carcinoma (figure 2) and focal atypia in two cases (case 1 and case 4, respectively). Except two cases (case 11 and case 17), the capsule was intact in the remaining cases. The surgical procedures were hysterectomy and adnexectomy. Hysterectomy was performed to 11 patients (55%) and adnexectomy was performed to 9 patients (45%).

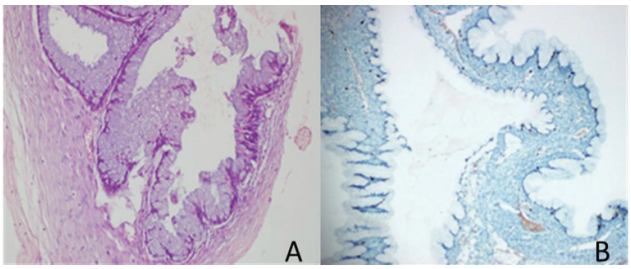

Figure 1:
A-B) Borderline mucinous ovarian tumor (case 16) (Hematoxylin and eosin stain, X20) and Ki67 P.I. (X10) in the same case.

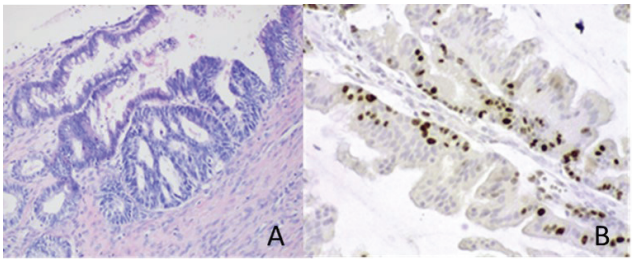

Figure 2:
A-B) Borderline mucinous ovarian tumor with intraepithelial carcinoma (case 1) (Hematoxylin and eosin stain, 20x magnification) and Ki67 P.I. (40X magnification) in the same case.

Table 1 Clinicopathological features of the patients in the study

Cases	Age (y)	Size (cm)	Lateralite	Surgery	Surface	Ki67	Prognostic factors	Recurrence	Death
1	59	10	left	H	intact	18%	İntraepithelial carcinoma	no	no
2	37	13	left	U	intact	18%	no	no	no
3	52	10	left	H	intact	20%	no	no	no
4	50	15	left	H	intact	30%	focal atypia	yes	yes (after 5 years)
5	73	35	right	H	intact	25%	no	yes	yes
6	40	18	left	U	intact	4%	no	no	no
7	48	7	left	H	intact	2%	no	no	no
8	53	25	right	H	intact	32%	no	no	no
9	55	23	left	H	intact	32%	no	no	no
10	35	10	left	U	intact	3%	no	no	no
11	59	30	right	H	interrupted	2%	no	no	no
12	33	30	left	U	intact	22%	no	no	no
13	41	30	left	U	intact	2%	no	no	no
14	29	15	left	U	intact	1%	no	no	no
15	77	28	left	H	intact	12%	no	no	no
16	51	20	left	U	intact	5%	no	no	no
17	28	16	right	U	İnterrupted	9%	no	no	no
18	94	15	left	H	intact	47%	no	yes	no
19	31	10.5	left	U	intact	29%	no	no	no
20	57	18	left	H	intact	7%	no	no	no

The median follow-up time was 49 months (ranged 1-120 months). 5-yr OS could be evaluated for 16 patients. During the follow-up time, disease progression was observed in three patients as lung metastases (case 4), periton metastases (case 18) and local recurrence (case 5). The lung metastasis occured at her 2nd month after the operation and the patient was lost in 58th month. The reason of death was unknown. The periton metastasis was observed at her 1st month after the operation and the patient was alive at her last follow-up. All metastases were confirmed to be of ovarian origin radiologically and immunohistochemically.

Ki67 P.I. was a median of 15% (1-47%) and a mean value of 16%. It has reached statistically significance at 20% cut-off value of Ki67 P.I. with progression and at 30% cut-off value of Ki67 P.I. with 5-year OS. (p=0.021 and p=0.032, respectively). According to the death/alive status data of patients, the 5-year OS was 95%. The 5-year DFS was 89.4%. Although the Ki67 P.I. tended to increase with age, no statistical correlation was found. Also, there was no statistical association between the Ki67 P.I. and the other prognostic factors including intraepithelial carcinoma, focal atypia, capsule integrity, and tumor size (Table 2).

Discussion

Borderline mucinous ovarian tumors which were defined as an intermediate category of neoplasia. In the present study were discussed and evaluated the prognostic significance of Ki67 P.I. and whether it correlates with clinicopathological characteristics of borderline mucinous ovarian tumors.

Table 2 Relationship between Ki67 proliferating index and clinicopathologic prognostic factors

	Ki67 P.I. (cut off 10%) p-value	Ki67 P.I. (cut off 20%) p-value	Ki67 P.I. (cut off 30%) p-value
Age (<45, >45)	0.19	0.26	0.06
Tumor size (<10 cm, >10 cm)	0.25	0.4	0.6
Lateralite (right/left ovary)	0.82	0.64	0.78
Capsul integrity (intact, interrupted)	0.09	0.22	0.45
Prognostic factors (+/-)	0.17	0.76	0.26
Recurrence	0.08	**0.021**	**0.028**
5-yr overall survival	0.3	0.12	**0.032**

MBTs occur in a wide age range with mean age of 45 years, including pediatric patients (2). In our study, similar to Guadagno et al.'s results, the patient's ages were mostly over 40 years old (12). When we compared the age groups with Ki67 P.I. in three cut-off values, there was no statistically significant difference above and before the age of 40. Guadagno et al. observed the Ki67 P.I. tended to be lower in patients under 40 years of age and was statistically significant. They determined the cut of value for Ki67 P.I. as 10% (12). This difference may be due to the fact that this study includes not only MBTs but also borderline serous ovarian tumors. Remarkably, in our population, Ki67 P.I. values were below 30% in all cases before the age of 40. Additionally, the maximum Ki67 P.I. value was detected in the oldest case (case 18-94 years old) and this patient later presented with relapse.

Intraepithelial carcinoma has been observed in approximately 40% to 55% of MBTs and defined as the fields showing high grade cytologic atypia (hyperchromasia, prominent nucleoli, and a significantly increased mitotic activity) and usually with marked demarcation (12, 13, 14). The diagnoses of intraepithelial carcinoma should be given based on the nuclear cytomorphology. Epithelial stratification or cribriform growth pattern is not compulsory. Although some studies in the literature observed that higher recurrence risk is associated with intraepithelial carcinoma most of studies reported no significant difference in overall survival (5, 15, 16). In our study, the results were concordant with the literature and there was no statistical significance in cases with or without intraepithelial carcinoma (p-value < 0.05). We had not observed recurrence or death in the patient who had an area of intraepithelial carcinoma.

Due to the heterogeneous clinic behavior of borderline over tumors, it is difficult to predict the risk of disease progression. Therefore, supportive markers were needed and were thought that Ki67 could be an indicator for reflecting the disease progression. Although there are very few studies, the results were similar. In some studies in the literature reported that benign over tumors (7.5-12%) showed lower Ki67 expression than borderline neoplasms (22-40%) and higher positivity levels in carcinomas (55-70%). (17,18) Similarly, Giurgea et al. investigated the Ki67 immunopositivity in borderline tumors and it's benign and malign counterparts. They observed that benign and borderline tumors presented low proliferation index (9.09% and 13.3%, respectively). Contrarily, the malign tumor's Ki67 P.I. was more than 50% (8). However, the number of studies which investigate the relationship between Ki67 proliferation index and risk of progression to malign form is quite rare, the available studies demonstrated the same results: low Ki67 expression in benign tumors is increasing in borderline and malignant forms. But it seems to be there is a significant difference between benign and malign forms but this difference does not exist between benign and borderline forms. From these results, we thought that increased expression may be associated development of malignancy. Munstedt et al. followed 92-patients with early stages of ovarian carcinomas and observed tumor recurrences and

overall survival status. Then, the patients who showed lower Ki67 expression (<10%) no recurred during the follow-up times but the recurrences occurred mostly in the patients who showed Ki67 expression more than 15% (19). This supports the relationship between higher Ki67 proliferating index and recurrences. In a large population study (n=202), it was found that 88% of BOTs showed less than 10% Ki67 expression (20).

Guadagno et al. observed Ki67 immunopositivity in their series of serous and mucinous borderline over tumors with an average value of 14% (12). In our study, MBTs had Ki67 P.I. with the average value was 16% and was slightly higher than that reported in the literature (8, 12). We have thought this difference might be due to the fact that our study only included MBTs. The reason we included only mucinous type of borderline over tumors in this study was to find more independent an objective Ki67 cut-off value in a more homogeneous group. We investigated whether there is a cut-off value such as in neuroendocrine tumors associated with progression or survival in our population. When we compared statistically with values increasing by ten percent (eg: 10%, 20%, and 30%), we found that at 20% Ki67 cut-off value was statistically associated with progression. (p=0.021). The cut-off value at 30% Ki67 cut off value was statistically significant with 5-yr OS (p=0.032)

Identification of markers that may predict the risk of disease progression in MBTs has a great significiance. Especially, when it comes to fertility status in young women, it becomes more important to predict the risk of progression in terms of treatment modalities. Consequently, in our study, it was found that Ki67 P.I. more than 20% was associated with recurrence and more than 30% was associated with 5-yr OS. However, due to the limited number of patients in our study, we believe that further studies are needed to evaluate this possible correlation more clearly in large populations.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee (Izmir Katip Celebi University Non-Invasive Clinical Research Ethics Committee, Date: 04.03.2021, 2021-GOKAE-0116, Decision No: 0098).

Consent to Participate and Publish
Informed consent forms could not be obtained due to the retrospective design of the study.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
İ.Ö: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft; Writing-review & editing.

S.D: Resources; Writing-review & editing.

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