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Factors affecting compliance of intraoperative frozen and final histopathology in borderline ovarian tumors: Retrospective cohort study

Borderline over tümörlerinde intraoperatif frozen ve nihai histopatolojinin uyumunu etkileyen faktörler: Retrospektif kohort çalışması

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Abstract

Aim: Frozen sections (FS) are commonly used in the course of adnexal masses operations, and it assist to select the most appropriate surgical treatment modalities in addition to intraoperative management. In this study, we aimed to investigate the effect of the demographic and obstetric characteristics as well as biochemical findings with the consistency of intraoperative FS findings with the final histopathological diagnosis in patients with borderline ovarian tumors (BOT).
Methods: This retrospective study included a total of 31 BOT patients who underwent intraoperative frozen histopathological study. The study population was divided into two groups; group 1 consisted of patients who had a positive concordance between the findings of intraoperative FS and the final histopathology, while the patients included in the group 2 had a negative concordance between the results of two examinations. We compared two groups in terms of baseline characteristics, tumor markers, tumor size, bilaterality, menopausal status and presence of ascites.
Results: There were no statistically significant differences between the two groups in terms of age, body-mass index, tumor markers (CA125, CA19-9, CEA, AFP, CA15-3, β-HCG) and tumor size ($P=0.74$, $P=0.55$, $P=0.87$, $P=0.55$, $P=0.24$, $P=0.33$, $P=0.70$, $P=0.32$ and $P=0.98$, respectively). Also, the presence of bilateral BOT and ascites as well as menopausal status were not different between both groups ($P=0.12$, $P=0.60$ and $P=0.70$, respectively).
Conclusion: Based on the study findings, we noted that patients whether had concordance or discordance with the findings of intraoperative frozen sections and the final histopathology did not differ in terms of baseline characteristics and tumor markers.
Keywords: Borderline ovarian tumor, Frozen section, Concordance

Öz

Amaç: Frozen section (FS) adneksiyal kitle operasyonları sırasında yaygın olarak kullanılır ve intraoperatif tedaviye ek olarak en uygun cerrahi tedavi yönteminin seçilmesinde yardımcı olur. Bu çalışmada, borderline over tümörlü (BOT) hastalarda demografik ve obstetrik özelliklerin yanısıra biyokimyasal bulguların intraoperatif FS bulgularla final histopatolojik tanıları arasındaki ilişkiyi incelemeyi amaçladık.
Yöntem: Bu retrospektif çalışmaya intraoperatif frozen histopatolojik inceleme yapılan toplam 31 BOT hastası dahil edildi. Çalışma popülasyonu 2 gruba ayrıldı; grup 1 intraoperatif FS bulguları ile final histopatoloji arasında pozitif uyum olan hastalardan oluşurken, grup 2'ye iki inceleme sonucu arasında negatif uyum olan hastalar dahil edildi. Bu çalışmada her iki grup temel özellikler, tümör belirteçleri, tümör boyutu, bilateralite, menopozal durum ve asit varlığı açısından karşılaştırıldı.
Bulgular: İki grup arasında yaş, vücut kitle indeksi, tümör belirteçleri (CA125, CA19-9, CEA, AFP, CA15-3, β-HCG) ve tümör boyutu açısından istatistiksel olarak anlamlı fark yoktu (sırasıyla $P=0,74$, $P=0,55$, $P=0,87$, $P=0,55$, $P=0,24$, $P=0,33$, $P=0,70$, $P=0,32$ ve $P=0,98$). Üstelik bilateral BOT ve asit varlığının yanı sıra menopozal durum açısından da her iki grup arasında fark görülmedi ($P=0.11$, $P=0.60$, $P=0.69$, sırasıyla).
Sonuç: Çalışma bulgularına dayanarak, hastaların intraoperatif FS bulgularıyla final histopatolojileri arasındaki uyum ve uyumsuzlukta temel özellikler ve tümör belirteçleri açısından farklılık olmadığını belirledik.
Anahtar kelimeler: Borderline over tümörleri, Frozen histopatoloji, Uyum

Introduction

Borderline ovarian tumors (BOTs) are epithelial ovarian tumors that differ from both benign and malignant neoplasms of the ovaries [1]. Although the exact incidence of BOTs has not yet determined, approximately 15–20% of serious tumors are considered to be as borderline [1]. BOTs have the pathological features of both benign and malignant neoplasms, thereby making a diagnostic challenge for pathologists. Until recently, several microscopic, macroscopic, and clinical parameters have been defined to differentiate the BOTs from malignant carcinomas. BOTs can spread to the peritoneum or to the lymph nodes, and they may relapse, as similar to malignant carcinomas. Additionally, BOTs have higher rate of proliferation and nuclear atypia that includes protuberances formation [2]. However, in contrast to malign carcinomas, stromal invasion is not seen in BOTs, and the incidence rate of BOT is higher in younger patients. On the other hand, in differential diagnosis, the gray zone still appears broad.

Even though the diagnosis in other gynecologic neoplasms can be set prior to surgery, the exact diagnosis of ovarian tumors mostly cannot be made until surgery. Frozen sections (FS) are commonly used in the intraoperative treatment of adnexal masses, and it helps in selecting the most appropriate surgical treatment method. In the course of ovarian tumors surgery, the objectives of FS are to identify patients who require a more extensive operation, to separate a group that can be treated with a more limited surgery, and to separate the group that can perform fertility preserving surgery [3,4]. Considering the vast majority of patients with BOT are at reproductive age at the time of diagnosis [5], it can be said that the intraoperative FS examination becomes more important. However, BOTs constitute a subgroup of ovarian tumors with a lower accuracy for FS [3,4]. It has been reported that the sensitivity of FS examination for ovarian tumors varies from 56 to 89% [3,6].

Although several parameters have been identified to show the consistency between the FS and the final histopathological diagnosis, the role of the demographic, clinical and biochemical characteristics on the consistency remain unknown. In this study, we aimed to analyze the characteristics of patients with BOT and to demonstrate the effect of the demographic, clinical and biochemical characteristics, on the consistency of intraoperative FS findings with the final histopathological diagnosis.

Materials and methods

Study Population

This retrospective study is related to the clinical data of 31 BOT patients who underwent perioperative frozen histopathological examination between 2010 and 2017 in the obstetrics and gynecology clinics of Kafkas University Medical Faculty Hospital and Fırat University Medical Faculty Hospital. Baseline characteristics, obstetric and clinical features, pathologic reports, and operation notes were obtained from the electronic files of patients who were surgically treated due to BOTs. The approval of the local institutional review board (2019/80576354-050-99/52) has been obtained prior to the study. The types of surgical intervention included the total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, myomectomy, cystectomy, appendectomy and bilateral pelvic paraaortic lymph node dissection.

Data collection

Baseline clinical and demographic characteristics, and patients' medical data (age, body-mass index and obstetric features [gravidity, parity, menopausal status, the number of previous abortions and dilatation & curettage interventions]) were obtained from the hospital's electronic record. All blood biochemical parameters including cancer antigen-125 (CA-125), cancer antigen-19-9 (CA-19-9), carcinoembryonic antigen (CEA), alfa feta protein (AFP), cancer antigen 15-3 (CA-15-3), and βeta-human chorionic gonadotropin (β-HCG) were measured upon admission to the hospital.

Sampling of tissues and pathological examination

Medical records indicated that different specimens of FS were sampled from the surgical field. All specimens were assessed by a senior pathologist who experienced in the gynecological pathology. Medical records indicated that the excised and unfixed specimens were firstly examined macroscopically. The solid, papillary, and necrotic areas that causing suspicion of malignancy were chosen for FS analysis. At least one sample was received for each centimeter excised material to be fixed into formalin and dipped into paraffin. All samples were frozen at -25°C, and they were sliced into a thickness of 8 mm. Hematoxylin and eosin staining was carried manually out. The FS results and the final histopathological evaluation were performed by the same pathologist. Eventually, the FS results that performed on the peri-operative period were compared with the final histopathological diagnosis whether the findings were concordant or discordant (The discrepancy between an initial FS result of BOT and the final histopathological diagnosis was categorized as "discordant"). According to the FS result, a staging surgery with or without lymphadenectomy was performed depending on the histological subtype of the tumor. Patients who had a concordant (grouped as the group 1) or discordant (grouped as the group 2) results between the FS and final histopathology were compared in terms of abovementioned variables.

Statistical analysis

The statistical analysis of the data was performed by IBM Statistical Package for Social Sciences (SPSS) Statistics 20 software (SPSS Inc., Chicago, IL, USA). The normality of distribution for variables was assessed with Shapiro Wilk test. The comparison of variables with normal distribution was assessed with Student-t test, whereas variables without normal distribution were analyzed using Mann Whitney-U test and Chi-Square test. The quantitative data was expressed as the mean (standard deviation) or median (interquartile range: 25-75). The data for bilaterally and menopause were analyzed with Fisher's chi square test. P value less than 0.05 in confidence interval of 95% was considered as statistically significant.

Results

The study population consisted of 31 BOT patients (mean age: 47 years) who underwent peri-operative FS examination. The number of patients who had a concordance between the results of intraoperative FS and the final

histopathology was twenty (n=20, 64.5%) (defined as the group 1), while the number of patients with discordance were eleven (n=11, 35.5%) (defined as the group 2). Demographic and laboratory characteristics of all patients are listed in Table 1. There were no statistically significant differences between the two groups in terms of age (*P*=0.74), body-mass index (*P*=0.55), levels of CA 125 (*P*=0.87), CA 19-9 (*P*=0.55), CEA (*P*=0.24), AFP (*P*=0.33), CEA 15-3 (*P*=0.70) and β-HCG (*P*=0.32). The tumor size determined during the intraoperative exploration did not differ between the two groups (*P*=0.98) (Table 1).

Table 2 demonstrates the comparison between the obstetric profiles of both groups. There were no differences between the two groups with respect to numbers of gravidity (*P*=0.26), parity (*P*=0.40), abortion (*P*=0.32), and dilatation & curettage (*P*=0.44) (Table 2). Furthermore, there was no significant difference between the groups in terms of bilateral involvement (*P*=0.11), menopausal status (*P*=0.70), and presence of ascites (*P*=0.60) (Table 3).

Table 1: Comparison of data derived from groups with concordant and discordant results of frozen section and definite histopathological diagnosis

Variable	Group		*P*-value
	Concordant (n=20)	Discordant (n=11)	
Age (years)	46.3 (15.2)	44.5 (11.9)	0.74*
BMI (kg/m^2)	26.5 (2.8)	27.2 (2.5)	0.55*
CA 125 (U/ml)	61.3 (71.2)	72.5 (109.7)	0.87**
CA 19-9 (U/ml)	26.3 (67.4)	16.6 (15.8)	0.55**
CEA (ng/ml)	1.9 (1.5)	1.2 (0.5)	0.24**
AFP (ng/ml)	2.2 (1.7)	2.0 (1.8)	0.33**
CA 15-3 (U/ml)	24.1 (9.7)	20.8 (29.7)	0.70**
β-hCG (mIU/mL)	0.9 (1.9)	1.1 (1.8)	0.32**
Tumor size‡ (cm)	14.1 (9.4)	13.4 (10.6)	0.98**

Data are expressed as mean (standard deviation), * Student t test, ** Mann Whitney U test, ‡ determined via intraoperative exploration

Table 2: Comparative analysis of discrete variables in groups with concordant and discordant results of frozen section and definite histopathological diagnosis

Variable	Group		*P*-value
	Concordant (n=20)	Discordant (n=11)	
Gravidity	3 (0-9)	4 (0-14)	0.26*
Parity	2 (0-9)	3 (0-14)	0.40*
Abortion	0 (0-2)	0 (0-3)	0.32*
Dilatation & curettage	0 (0-1)	0 (0-2)	0.44*

Data are expressed as median (interquartile range), * Mann Whitney U test

Table 3: Comparative analysis of discrete variables in groups with concordant and discordant results of frozen section and definite histopathological diagnosis

Variable		Group			
		Concordant (n=20)		Discordant (n=11)	
		n	%	n	%
Bilaterality	Yes	1	5	3	27.3
	No	19	95	8	72.7
	P-value*	0.11			
Menopause	Yes	8	40	3	27.3
	No	12	60	8	72.3
	P-value*	0.69			
Ascites	Yes	2	10	2	18.2
	No	18	90	9	81.8
	P-value*	0.60			

* Fisher's Exact test

Discussion

In the present study, we focused on the potential effect of the demographic, obstetric and biochemical characteristics on the consistency of intraoperative FS results with the final histopathological diagnosis in patients with BOT. Our study demonstrated that baseline demographic, obstetric, and biochemical features of patients are not effective on the discrepancy between the FS evaluation and the final histopathological diagnosis.

Most of the adnexal masses have a diagnostic challenge in the preoperative period. Therefore, intraoperative histopathological examination has a pivotal role both in the identification of the masses and the determination of the surgical

modality. FS examination has a high overall accuracy for the diagnosis of ovarian cancers; however, the diagnostic sensitivity of FS may reduce up to below 60% in BOTs surgeries [3,6]. Similar the results of previous studies, a consistent finding were found in our study as the concordance between the results of intraoperative FS and the final histopathology was 64.5%. The diagnostic difficulty in BOT patients may frequently lead the surgeon to postpone the appropriate surgical staging until the definite pathology is obtained. Nevertheless, this delay may increase the rate of re-intervention, facilitate the postsurgical tumor spread, interrupt the adjuvant treatment, and increase the psychological distress, particularly in young women with high desire for fertility [7]. Similarly, in our study, 64.5% of the patients were not in menopause, but in fertile age.

The sensitivity of FS for patients with BOT may be attributed to several parameter including pathologist experience [8,9], the mucinous histopathology and size of the tumor [1,10]. It has been established that the cut-off tumor size for increased discrepancy of FS for ovarian tumors ranges from 10 to 20 cm [11,12]. The vast majority of cases (94%) of discordant diagnosis occur in tumors with a size of more than 13 cm [13]. In our study, the FS evaluation was performed by senior pathologists experienced in gynecological pathology, and the mean size of the tumors was 13.83 cm. Although the experience of pathologists seems to be satisfactory, the concordance between the results of intraoperative FS and final histopathology was 64.5 % in the study.

There are contradictory data in the literature regarding the association between the consistency of intraoperative FS results with the final histopathological diagnosis and demographic and biochemical characteristics in patients with BOT. In a study conducted by Tempfer et al. [8] reported that there was no relationship between age, the presence of bilateral tumor, and CA 125 level with the concordance of FS analysis. In another study, a good correlation was observed between serum CA 125 level and FS accuracy, especially in patients with an advanced stage of BOTs [2]. On the other hand, CEA and CA 15.3 were not found to be correlated with BOTs, but CA 19-9 was partially associated with the mucinous subtype of BOTs [2]. However, we did not found any association between the consistency of intraoperative FS results with the final histopathological diagnosis and any biochemical marker including CA 125, CA 19-9, CEA, AFP, CA 15-3 and β-HCG.

There is a limited data regarding the relationship between obstetric features and the concordance of intraoperative FS results. The present study showed that the obstetric profile was not associated with the consistency between intraoperative FS results and the final pathological diagnosis. Bilaterality of the tumor, or ascites in the abdomen, which are easily detectable by the diagnostic tools, does not seem to aid the accuracy of FS.

Limitations

Our study has certain limitations. Our study had a retrospective design, and it was based on the patient file analyses. The sample size is a quite small; hence the prognostic data could not be introduced due to low number of patients

Conclusion

In patients with BOT, an unsatisfactory examination finding of FS may result in a repeated surgical intervention,

which probably leads to worse outcomes, especially in vulnerable or morbid subjects. Reducing the discrepancy between the peri-operative FS and the final histopathological diagnosis could assist to choose a suitable surgery method. This study, investigating the effects of obstetric history, demographic characteristics, and biochemical characteristics on the FS discordance, revealed that the abovementioned parameters did not effect on the discordance between the FS evaluation and the final histopathological diagnosis.

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