

Research Article,

Accuracy of Intraoperative Frozen Section Analysis in Borderline Ovarian Tumor and the Factors Affecting It.

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Abstract:

Objective: To analyze the accuracy of frozen section (FS) examination of a borderline ovarian tumor (BOT) and the factors affecting it.

Methods: We retrospectively evaluated 132 patients who were operated on in our clinic for ovarian mass between 1996 and 2016, who underwent FS examination and who had a BOT as a result of the final pathology. We investigated the frozen accuracy, overdiagnosis and underdiagnosis rates and the factors affecting the accuracy of the diagnosis.

Results: The mean age of the sample group was 44.6 ± 15.2 years. 50.8% of our patients were serous, 34.8% were mucinous and 14.4% were sero-mucinous in histology. Our Frozen Section accuracy rate was 75%, and underdiagnosis and overdiagnosis rates were 20.5% and 4.5%, respectively. The factors affecting the accuracy of the frozen section were histological type ($p = 0.003$), presence of solid component ($p = 0.002$) and preoperative CA 125 value ($p = 0.001$).

Conclusion: Frozen examination has a low accuracy rate that affects the correct selection of surgical treatment for bots. FS should be performed by experienced gynecopathologists and it is necessary to consider carefully the factors that may cause misdiagnosis of the pathology.

Key words: Borderline tumor Remove Borderline tumor Ovary Remove Ovary Frozen section analysis Remove Frozen section analysis Overdiagnosis Remove Overdiagnosis Underdiagnosis Remove Underdiagnosis

Introduction:

BOTs constitute approximately 15% of all ovarian neoplasia and show a behavioral pattern between benign cystadenoma and invasive carcinoma [1,2]. When compared with invasive carcinomas, BOTs are more commonly diagnosed at a young age and during fertility. One-third of cases are under 40 years of age [3,4]. Surgery is the standard treatment for BOTs, and the age of the patient, the

stage of the disease, the desire for fertility, and the histopathological character of the tumor determine the extent of surgery. Priority should be given to conservative treatment for patients of a young age who wish to preserve fertility. BOTs are often initially diagnosed as tumors with benign characteristics in preoperative evaluations, so intraoperative FS examination becomes a critical point for the appropriate operative method.

In pathology, the frozen examination is referred to as ‘Frozen Section’, or ‘Intraoperative Consultation’. As there is no normal follow-up procedure, technical artifacts are inevitable and determine the accuracy of the procedure. Further investigations (histochemistry, immunohistochemistry, molecular, etc.) applied in routine diagnosis cannot be performed or have limitations in the frozen section. Frozen section is crucial for the surgeon to determine the appropriate surgical method for the patient. Decisions on complete surgical staging and radicality of surgery (especially fertility-sparing surgery) all depend on the results of FS. FS examination prevents unnecessary surgical procedures and reduces perioperative complications. However, Medeiros described the ‘Frozen section’ examination as a moderately useful diagnostic method in differentiating between benign and malignant tumors with a high accuracy rate but with relatively moderate efficiency in the discrimination of BOTs [5]. In this study, we wanted to investigate the diagnostic accuracy of FS in our clinic and the factors that may affect results.

Materials and Methods:

A total of 132 patients with the diagnosis of an adnexal mass, who were operated on between October 1996 and April 2016, were included in the study. Ethics committee approval was obtained from Çanakkale 18 Mart University (date:11.03.2020/number:2020-05) prior to the study. The patients whose frozen examination was not performed, who had another primary malignancy and whose final pathology result was reported as ‘invasive ovarian tumor’ were excluded from the study. Histological subtypes of BOTs were classified as serous, mucinous and sero-mucinous. The clinical characteristics of the tumors, in terms of the presence of solid compounds, were evaluated preoperatively by ultrasonography and/or computed tomography. The mass lesion was classified according to the uni/multi-cystic character and whether it included a solid area. The tumor diameter of the specimen, which was sent to the pathology laboratory without being fixed, was measured. The pathologist then made two to five cuts, depending on the size of the tumor. Frozen section examination was done based on the solid, papillary or necrotic areas of the mass lesion. Frozen section examination was done for both ovaries if the tumor was bilateral. In all cases, a minimum of 1 section per 1 cm of maximal tumor diameter was examined for

permanent section diagnosis. All the clinicopathological characteristics, FS and final pathology results of the persistent paraffin sections were examined for possible factors that may affect FS (age, histological type, tumor diameter, localization, tumor characteristics, presence of acid, preoperative CA 125 value). The presence of paraffin in the results was defined as the correct diagnosis (borderline). The results of the frozen section other than ‘BOT’ were considered as the wrong diagnosis. The term ‘underdiagnosis’ was used for benign frozen results and ‘overdiagnosis’ was used for a malignant frozen section result. Two pathologists experienced in gynecologic pathology evaluated two cases of frozen paraffin.

Statistical Analysis:

The data were analyzed using SPSS version 20.0. For the presentation of the data, number, percentage, mean, standard deviation, median, minimum and maximum values were used. The Chi-square test was used for the analysis of categorical data. $P < 0.05$ was accepted for statistical significance.

Results:

The mean age of our 132 patients was 44.6 ± 15.2 (median 44.0) and 39.4% of the patients were 40 years or older. On histological examination, 67 (50.8%) serous BOTs were found, 46 (34.8%) mucinous and 19 (14.4%) sero-mucinous. Only 9 (6.9%) of our cases were bilateral and 7 of them had serous histology.

When the tumor diameter was examined, it was found to be 10.5 ± 5.7 cm (median 9) in serous type, 21.0 ± 10.1 cm (median 20) in mucinous type, and 10.7 ± 6.2 cm (median 8) in sero-mucinous type. Preoperative CA 125 levels were: 120.6 ± 198.6 U / ml (median 56.1 minimum (min) - maximal (max) 3-983) for serous BOTs; 49.9 ± 70.3 U / ml (median 23.8 min-max 2-375) for mucinous BOTs and 94.1 ± 104.9 U / ml (median 55.3 min-max 7.9-358) for sero-mucinous BOTs. No solid content was evident in 43.3% of our patients (42/97) who were evaluated by imaging methods in our records. The frequency of the mass lesion showed a homogenous distribution with regard to its uni/multi-cystic structure and including solid areas or not (Table 1).

Table 1. Radiologic (computed tomography/ultrasonography) features of the study group

	n (%)
Purecystic/solidarea (-)	18 (19,6)
Multi cystic/solidarea (-)	22 (23,9)
Purecystic/solidarea (+)	31 (33,7)
Multi cystic/solidarea (+)	21 (22,8)

When FS results were examined, 20.5% (27/132) of tumor masses were diagnosed as 'benign' and 4.5% (6/132) were diagnosed as 'malignant'. As a

result, our correct FS diagnosis rate is 75%. When the factors which influenced diagnostic accuracy of FS was analyzed, while histological type of the tumor (p=0,003), presence of a solid component (p=0,002) and pre-operative CA125 value (p=0,001) were found to be significant, an association was not found between misdiagnosis and age, mass diameter, bilateral location and presence of acid (Table 2).

Table 2. The factors affecting the accuracy of the frozen section examination.

		Underdiagnosis		True diagnosis		Overdiagnosis		p
		n=27	%20,5	n= 99	%75	n=6	%4,5	
Age	< 40	9	33,3%	41	41,4%	2	%33,3	0.709
	≥40	18	66,7%	58	58,6%	4	%66,7	
Histology	Serous	7	25,9%	57	57,6%	3	50,0%	0.003
	Mucinous	18	66,7%	27	27,3%	1	16,7%	
	Serous-mucinous	2	7,4%	15	15,2%	2	33,3%	
Tumordiameter	<5cm	4	15,4%	16	16,2%	1	20,0%	0.969
	≥5cm	22	84,6%	83	83,8%	4	80,0%	
Solid compound	No	13	76,5%	26	34,2%	3	75,0%	0.002
	Yes	4	23,5%	50	65,8%	1	25,0%	
Bilaterality	No	26	100,0%	90	90,9%	5	100,0%	0.078
	Yes	0	0,0%	9	9,1%	0	0,0%	
Ascite	No	22	95,7%	81	90,0%	5	100,0%	0.417
	Yes	1	4,3%	9	10,0%	0	0,0%	
Preop.CA125 serumlevel	<35 IU/ml	18	81,8%	35	39,3%	1	20,0%	0.001
	≥35 IU/ml	4	18,2%	54	60,7%	4	80,0%	

Discussion:

FS examination first applied in 1816 is widely used for suspected ovarian masses [6]. The sensitivity and specificity of FS in differentiating benign and malignant neoplasms is 65-9% and 97-100%. On the other hand sensitivity and specificity for BOTS were found to be as follows: 25-92%, and 60-99% [7,8,9,10]. The FS accuracy for mucinous BOT is the lowest. Cross et al. described the case of the 267 mucinous borderlines, where the FS accuracy rate was given as 79% [11]. Brunve et al described another of the 107 mucinous BOTs, where the accuracy rate was 79% [12]. The low incidence of overdiagnosis in the literature and in our series is directly related to the experience of the pathologists, who play an important place in ensuring the correct diagnosis. Other factors such as imaging findings, clinical findings, tumor

markers, and intraoperative findings and communication with pathologists may also contribute to increased intraoperative FS accuracy [13]. While Gültekin et al. emphasized that underdiagnosis was 3.3 fold greater in the subjects whose CA125 value was below 35 IU, CA125 level was below 35 IU in 18 out of 22 underdiagnosis cases. Another similarity with that study and ours is the fact that the frozen accuracy rate is high in the mass lesions which include a solid component and pure cystic mass morphology is more frequent in the underdiagnosis group [14]. In the Houck series, the rate of overdiagnosis was 10.7% and the rate of underdiagnosis was 29.3%. The non-serous histologic type was the determinant of false FS [15]. Tempfer et al. found that the rates of underdiagnosis and overdiagnosis were 28% and 0% respectively. They

stated that the only independent risk factor was tumor diameter and that the tumor diameter of < 20 cm was the sole factor of underdiagnosis [16]. Li et al. concluded that tumor size and histology are the causative factors of underdiagnosis [17]. Bilateral / unilateral existence of BOTs was not

significant in our study and could not be demonstrated in the related literature [15,18]. A review of the literature, including rates of accuracy, overdiagnosis, and underdiagnosis of BOTs is given in Table 3.

Table 3. Summary of studies in the literature

	Country	Year	Number	Accuracy %	Underdiagnosis %	Overdiagnosis
Houck	Usa	2000	140	60,84(140)	29,3(41/140)	10,7(15/140)
Kayıkcioglu	Turkey	2000	33	69,7(23/33)	30(7/23)	13(3/23)
Tempfer	Austuria	2007	96	71,9(69/96)	28(27/96)	0(0/96)
Kim K.	S.Korea	2009	181	60,2(109/181)	6(11/181)	34(61/181)
Kim JH.	S.Korea	2009	101	62,4(63/101)	32(32/101)	6(6/101)
Li	China	2009	73	75,3(55/73)	25(18/73)	0(0/73)
Shih KK.	Usa	2011	120	86,7(104/120)	0,8(1/120)	13(15/120)
Song T	S.Korea	2011	354	64,4(228/354)	31(108/354)	5(18/354)
Basaran D.	Turkey	2014	59	62,7(37/59)	31(18/59)	7(4/59)
Huang Z.	China	2018	155	81,9(127/155)	14(22/155)	4(6/155)
Ourstudy	Turkey	2019	132	75(99/132)	20,5(27/132)	4,5(6/132)

The FS accuracy rate obtained in our study was in accordance with data in the literature. Although literature data supported that frozen section number is a factor that influences the accuracy rate, unfortunately, we could not find data to confirm this in pathology records [19, 20]. As a result, BOT s in FS examination have low accuracy, low sensitivity, and low positive predictive value. Experienced gynecopathology experts are needed in order to reduce the rate of misdiagnosis rate. In any case, it is essential that surgeons and pathologists are fully aware of the potential risk factors for misdiagnosis.

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