

Challenges of Frozen Section in Borderline Ovarian Tumors: A 10-Year Retrospective Analysis from a Tertiary Gynecological Cancer Center: Retrospective Analysis

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ABSTRACT Objective: Frozen section procedure gives a great advantage of fertility preserving in young women with borderline ovarian tumors (BOTs). However diagnostic accuracy of frozen section in BOTs is not as high as the other ovarian lesions. In the present study, we aimed to evaluate the comparison of frozen section results and final pathology results in patients with BOTs. **Material and Methods:** A total of 97 patients who had BOTs, either on the frozen section or final paraffin section in our clinic between 2007 and 2017 were included in the study. Frozen section and final pathology were compared with medical records of the patients such as age, menstruation, preoperative serum CA-125 and CA 19-9 values, histological diagnosis, subtype, size, localization, and capsule involvement. **Results:** In BOTs, the diagnostic accuracy of the frozen section was 67%. Frozen section has 74% sensitivity, 40% specificity, 83% positive predictive value and 29% negative predictive value. In the present study, the only factor that affects the accordance between the frozen section and the final paraffin section was the papillarity of the tumor, and it was observed that when the tumor was more papillary, the results had been more compatible. **Conclusion:** In BOTs, surgical management should be performed with caution depending on the frozen section to avoid overtreatment, especially in young women.

Keywords: Borderline ovarian tumors; frozen section; ovarian tumors

Borderline ovarian tumors (BOTs) are characterized by atypical epithelial proliferation without stromal invasion.¹ BOTs constitute 14-15% of epithelial ovarian tumors and the incidence of BOTs is 1.8 to 5.5 in every 100,000 women per year.²⁻⁴ BOTs have a better prognosis due to diagnosis in early stage of disease in a great majority of patients.^{2,5,6} Approximately one third of the women with BOT are under the age of 40.^{2,7} Therefore, ovarian preservation is important. In young women to determine the surgical approach intraoperatively gives a great advantage of fertility preserving. Histopathological examination is the only method to diagnose BOTs. It might be possible to diagnose BOTs intraoperatively by frozen section. Diagnostic accuracy of frozen section in benign and malignant ovarian lesions except in BOTs shows a good sensitivity (65-100%) and an excellent

specificity (>99%).⁸ According to the literature, the diagnostic accuracy of frozen section is varying between 48% and 79% in BOTs.⁹⁻¹⁵ In this study we aimed to present our experiences on frozen section in BOTs.

Frozen section procedure gives a great advantage of fertility preserving in young women with BOT. However, diagnostic accuracy of frozen section in BOTs is not as high as the other ovarian lesions. In present study, we aimed to compare frozen section and final pathology results in BOTs.

MATERIAL AND METHODS

This is a single institutional retrospective cohort study conducted at a tertiary cancer center. Institutional review board approval was received from

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Zeynep Kamil Women's and Children's Disease Training and Research Hospital Ethics Committee (approval date/number: 26.05.2017/109). One hundred four patients operated with preoperative diagnosis of BOT in our clinic between January 2007 and January 2017 were evaluated. Three patients diagnosed with mixed ovarian tumors were excluded from the study. Three patients diagnosed in different clinics and one patient who was not able to be performed a frozen section procedure were excluded from our study. Medical records, operation details, and the data of 97 patients (including age, menstruation, preoperative serum CA-125 and CA19-9 values, frozen section results, histologic subtypes, tumor sizes, tumor lateralization, capsule involvement and final pathologic diagnosis) were collected from our electronic database. Both frozen sections and final paraffin sections of all patients were examined by the same gynecopathologist. After the macroscopic examination, frozen section was performed by taking a 1 cm tissue from the suspicious area of tumor and the materials were frozen until -22°C and sliced into 5 micrometer sections. Frozen sections were reported as benign, borderline, at least borderline, or malignant. Final paraffin sections were reported as benign, borderline or malignant. Each frozen section and final paraffin section results were compared and the agreement was evaluated. When calculating the sensitivity, specificity, positive predictive value, and negative predictive value, malignant and benign results were counted as negative test results at the final pathology, while benign and 'at least borderline' results were counted as negative test results at the frozen section examination.

All statistical analyses were performed using Number Cruncher Statistical System 2007, Statistical Software (Utah, USA). One-way ANOVA test and independent t-test were used to compare the groups. Kruskal-Wallis test for intergroup comparisons of variables without normal distribution. Dunn's multiple comparison test and Mann-Whitney U test were used for the comparison of paired groups, and chi-square test for categorical variables. Sensitivity, specificity, positive predictive value, negative predictive value and odds ratio were calculated to show the compatibility of the final paraffin section and

frozen section results. A p-value <0.05 was used as the cut-off for significance.

RESULTS

Mean age of the patients was 41.61 ± 13.35 years. Sixty-eight patients (70.10%) were premenopausal and 29 patients (29.90%) were postmenopausal. The comparison of frozen section and final paraffin section results were shown in [Table 1](#). Diagnosis of 57 (82.60%) patients with BOT on frozen section did not change on final pathology report. All of the patients with at least BOT in the frozen section ($n=8$) were diagnosed with malignant ovarian tumor at the final pathology. The accuracy of frozen section was calculated as 67%. Comparisons of histologic subtypes of the tumors on frozen section and final pathology were shown in [Table 2](#). Histologic subtypes were not reported in 15 (15.46%) patients with benign ovarian tumors. Factors affecting the agreement of the frozen section and the final pathology were shown in [Table 3](#). There was a statistically significant difference between mucinous, endometrioid and serous tumors in terms of mean tumor sizes ($p=0.001$). Mean size of mucinous tumors was significantly higher than endometrioid and serous tumors ($p=0.046$ and $p=0.001$, respectively). CA-125 values of the patients with malignant ovarian tumor were higher than the patients with BOT ($p=0.005$). Mean CA-125 values of the patients with serous and mucinous BOTs on final paraffin section were 277 IU/mL and 20 IU/mL, respectively and CA-125 values were significantly higher in patients with serous BOT ($p=0.0001$). Seven of 77 patients (9.09%) with BOT on final paraffin section had micro-invasion. Five patients with serous BOT and 2 patients with mucinous BOT had micro-invasion on the final paraffin section. Fertility sparing surgery was performed in 68 (70.11%) patients and complete staging surgery was performed in 29 (29.89%) patients. Fifteen patients (15.46%) underwent laparoscopic surgery and 79 (81.44%) patients underwent laparotomy. Appendectomy was performed in 32 (32.98%) patients and involvement of appendix was detected in one (3.12%) patient. Lymph node dissection was performed in 50 (51.54%) patients and involvement of lymph node

TABLE 1: Comparison of final paraffin section and frozen section results

		n	Final paraffin section					
			Malignant		Borderline		Benign	
Frozen section	At least borderline [†]	8	8	100%	0	0.00%	0	0.00%
	Borderline [‡]	69	9	13.04%	57	82.60%	3	4.36%
	Benign [§]	20	0	0.00%	20	100%	0	0.00%

[†]: Row includes 8 patients had at least borderline ovarian pathology on frozen section and all of them was interpreted as malignant on final paraffin section; [‡]: Row includes 69 patients were interpreted as borderline on frozen section and only 57 of them was reported as borderline on final pathology, 12 of them was misinterpreted on frozen section; [§]: Row includes 20 patient who had benign ovarian lesion according to frozen section but it was reported as borderline on final paraffin section.

TABLE 2: Comparison of histologic subtypes of the tumors on final pathology and frozen section.

		n	Final pathology results			
			Serous	Mucinous	Endometrioid	Transitional
Frozen section	Serous [†]	45 (54.88%)	44 (97.77%)	-	1 (2.23%)	-
	Mucinous [‡]	32 (39.02%)	5 (15.63%)	27 (84.37%)	-	-
	Endometrioid [§]	4 (4.88%)	-	-	4 (100.00%)	-
	Transitional [§]	1 (1.03%)	-	-	-	1 (100.00%)

[†]: Serous ovarian lesion was the most common diagnosis on frozen section and only 1 of them reinterpreted as endometrioid on final pathology;

[‡]: Mucinous tumors were more likely misinterpreted on frozen section than the other histologic subtypes;

[§]: Endometrioid and transitional tumors were rarely seen but they had 100.00% compliance both on frozen section and final paraffin section in our study.

TABLE 3: Factors affecting the compatibility of the frozen section and the final pathology results.

		Concordant		Discordant		p value
		n	%	n	%	
Age		41.74±13.9		41.31±12.3		0.883
Cystic/ solid [†]	Cystic	46	73.02%	23	74.19%	0.991
	Solid	2	3.17%	1	3.23%	
	Semi-solid	15	23.81%	7	22.58%	
Macroscopy [‡]	Papillary [§]	40	71.43%	9	39.13%	0.005*
	Multicystic	6	10.71%	9	39.13%	
	Multicystic-papillary	7	12.50%	1	4.35%	
	Polypoid	2	3.57%	1	4.35%	
	Other (Necrosis etc.)	1	1.79%	3	13.04%	
Size		11.92±6.59		12.97±7.42		0.480
Laterality	Unilateral	52	80.00%	27	84.38%	0.602
	Bilateral	13	20.00%	5	15.63%	
Capsule [§]	Intact	38	60.32%	26	81.25%	0.068
	Unintact	25	39.68%	6	18.75%	
CA-125		240.64±713.44		201.81±426.77		0.447
CA 19-9		77.84±241.82		996.55±3000.85		0.912

[†]: Row excludes 3 patients that did not interpret solid, cystic or semi solid on frozen section result;

[‡]: Row excludes 18 patients that had no macroscopic definition on frozen section result;

[§]: Row excludes 2 patients that had no information about capsule involvement on frozen section result;

[§]: Papillarity is the most important factor that effecting the compliance when it is compared to other macroscopic features.

* In this study macroscopic features are the factors that affecting compliance between frozen section and final paraffin section significantly (p<0.005).

was detected in 5 (10%) of them. The final pathology reports of these 5 patients were invasive ovarian cancer.

Five (7.25%) patients with BOT on frozen section were underdiagnosed and fertility sparing surgery were performed, but they had invasive ovarian cancer

on the final pathology. Three of them underwent complete surgical staging surgery and other 2 patients refused follow-up in our clinic. One (1.45%) patient who was overdiagnosed as BOT on frozen section and had complete staging surgery was reported as benign on final paraffin section. One patient with 18 weeks of pregnancy underwent laparotomy because of an ovarian lesion and fertility sparing surgery was performed depending on frozen section report. The frozen section and the final paraffin section were concordant and reported as serous BOT. One patient who underwent cystectomy during cesarean section had benign lesion at frozen section, the final pathology report was serous BOT. But this patient had no further follow-up data in our clinic. During the cesarean section, one patient was diagnosed with serous BOT on frozen section and underwent unilateral salpingo-oophorectomy with lymph node dissection. The final pathology was BOT in this case. Endometriosis was accompanied by at least endometrioid BOT on frozen section in 3 patients and 2 of them underwent complete staging surgery. However, one of them underwent fertility sparing surgery due to communication problems between the pathologists and the surgeons. The final diagnosis of 3 patients were invasive endometrioid ovarian tumor. The patient who was performed fertility sparing surgery refused follow-up. One patient was overdiagnosed as mucinous BOT on frozen section and the final pathology was benign on paraffin section. BOT was reported in one patient with adnexal torsion on frozen section and underwent salpingo-oophorectomy. However, the final pathology of this patient was benign.

DISCUSSION

The aim of frozen section in ovarian tumors is to identify patients who require complete staging surgery or to determine the conditions for a conservative surgery intraoperatively. A meta-analysis of 18 studies which compare the diagnostic accuracy of frozen section and the final paraffin section results in ovarian pathologies shows that frozen section has a good sensitivity (65-100%) and excellent specificity (>99%).⁷ Intraoperative frozen section analysis of large tumors, mucinous tumors and borderline tumors has a low sensitivity. Because these tumors require a

large sampling area to exclude the invasive disease. In the literature, the accuracy of frozen section on BOTs was reported between 48% and 79%.⁹⁻¹⁵ This variability might depend on increased knowledge and experience over time on frozen section procedure. Low sensitivity of frozen section may misdirect the surgeon when the patient underdiagnosed with BOTs. Patients with epithelial ovarian carcinoma should be performed complete surgical staging due to the 25% possibility of subclinical metastases.¹⁶ Another concern of the low sensitivity of frozen section in BOTs is overdiagnosis that may lead to increased morbidity and mortality due to overtreatment.

In present study, mean age of the patients with BOT on final paraffin section was 40.9 years and 70.1% of the patients were premenopausal. These findings are consistent with the literature.¹⁰⁻¹² The surgical procedures should be considered depending on the fact that BOTs are mostly seen in premenopausal women. In the present study, frozen section and final paraffin section results were compared and the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of frozen section procedure were 74%, 40%, 83%, 29%, and 67%, respectively. According to histological subtype compatibility, the frozen section had 97% sensitivity, 90% specificity, 86% positive predictive value, 98% negative predictive value, and accuracy of frozen section on histologic diagnosis was 93%. Compatibility on serous tumors was higher than mucinous tumors (97.77% versus 84.37%). This diminished compliance of frozen section in mucinous tumors might be attributable to the size of tumors which requires more sampling. In addition, sampling errors of the pathologist may lead to discrepancies. We observed that age, CA-125 and CA 19-9 values, size, cystic or solid characteristics of tumor, and laterality did not affect compliance. Our study showed that the most important factor affecting the agreement between frozen section and final pathology is the papillarity of the tumor. Papillary structures are more likely seen in tumors with compatible diagnosis on frozen section and the final pathology. Papillary structures may provide pathologist to determine the sampling areas on tumor.

Even though there are studies suggesting that the pathologist's experiences are related to frozen section

compatibility, there are some contrary studies.^{13,17} In our study, frozen sections and paraffin sections were evaluated by pathologists who had many years of experience in gynecopathology and the compatibility was similar to the literature.

In the present study, a statistically significant difference was found between the mean sizes of mucinous, endometrioid and serous tumors ($p=0.001$). Mean tumor size of the mucinous tumors was significantly higher than the endometrioid and serous tumors ($p=0.046$, $p=0.001$, respectively). Our findings are consistent with the literature. In the literature, tumor sizes were variable for increased misdiagnosis in frozen section of BOTs. For example, in a study, misinterpretation on frozen section was more common in tumors greater than 20 cm (25.2% versus 44.8%).¹⁰ There are also studies that limit the sizes as 8 cm, 10 cm and 15 cm.¹¹⁻¹³ In our study, the accuracy of frozen section was lower in mucinous tumors depending on greater sizes than serous tumors. Results of 17 patients were malignant on the final pathology in present study. In 5 (7.25%) of 17 patients, the frozen sections were misinterpreted as BOT and fertility sparing surgery was performed, but they were reclassified as invasive tumors on the final pathology and lead us to perform a second surgery. Misinterpretation of frozen section in 1 (1.45%) patient was due to communication problems between the pathologist and the surgeons. This case shows that in frozen section, it is not the only difficulty to diagnose. Also, the communication between pathologist and surgeon is one of the key points. One patient who had complete surgical staging depending on the frozen section had been overtreated and the final pathology was benign. In our opinion these two cases showed the negative consequences of using frozen section on BOTs. On the other hand, 91 of 97 (93.81%) patients underwent adequate surgical management.

There are some limitations in our study. Number of the cases and retrospective design of the study might be one of the limitations. In our clinic frozen section is used very often because it is one of the main centers of women's health in Turkey. Therefore, we have a significant number of patients with BOT who is performed frozen section although they

are relatively rare tumors. In additional, our pathology department has gynecopathologists who are specified in gynecologic oncology and therefore frozen section sensitivity in this study may not reflect overall. Our study also has strengths. This is a single center study and frozen sections are interpreted by the same specified gynecopathologists. Furthermore, our study is designed to include all the BOTs, diagnosed either by frozen section or final paraffin section.

CONCLUSION

Frozen section is a critical step in the management of BOTs, which are usually diagnosed in premenopausal patients. To reduce the risk of misdiagnosis, frozen section should be performed by experienced pathologists specialized in gynecology. Sampling of the tissue and also consultation of the patient should be performed properly to prevent possible communication problems between the pathologist and the surgeon. In BOTs, the surgeon should be aware that the histologic diagnosis may be reinterpreted on final paraffin section and intraoperative management should be performed with caution.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Münip Akalın, Canan Kabaca Kocakuşak; **Design:** Münip Akalın; **Control/Supervision:** Burak Giray; **Data Collection and/or Processing:** Emine Eda Akalın; **Analysis and/or Interpretation:** Emine Eda Akalın; **Literature Review:** Münip Akalın, Emine Eda Akalın; **Writing the Article:** Münip Akalın, Burak Giray; **Critical Review:** Canan Kabaca Kocakuşak, Burak Giray; **References and Fundings:** Münip Akalın; **Materials:** Münip Akalın.

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