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RESEARCH

Accuracy of Intraoperative Frozen Section in the Evaluation of Patients with Adnexal Mass: Retrospective Analysis of 748 Cases with Multivariate Regression Analysis

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Abstract
Objective To evaluate the accuracy of intraoperative frozen section in the evaluation of patients with adnexal mass and to define the clinicopathological factors associated with misdiagnosis during frozen section evaluation.
Methods The clinicopathological data of patients who underwent exploratory laparotomy for adnexal mass were reviewed. Results of the intraoperative frozen section and permanent histology reports were compared. Univariate and multivariate analyses were performed to reveal factors associated with misdiagnosis.
Results The study group consisted of 748 patients. Of these patients, 509 (68.0 %) had benign, 43 (5.7 %) had borderline, 196 (26.2 %) had malignant histological diagnosis at permanent section. The overall agreement between intraoperative frozen section and permanent pathology was 96.8 %. Twenty four out of 745 cases (3.8 %) were misdiagnosed by frozen section. Univariate analysis showed that borderline histology ($p<0.0001$) and tumor size larger than 10 cm ($p=0.012$) were associated with misdiagnosis. According to multivariate analysis, borderline histology (OR: 22.6, $p<0.0001$) was the only independent predictor for misdiagnosis during frozen examination.
Conclusion The frozen section evaluation of the adnexal mass is highly accurate. However, tumor size greater than 10 cm and borderline histology are the factors that adversely influence the accuracy of intraoperative frozen section. Clinicians must be aware of these pitfalls during intraoperative decision making following frozen section report.

Keywords Frozen section · Ovarian tumor · Adnexal mass · Ovarian cancer · Borderline ovarian tumor

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Introduction

Adnexal mass is a very common gynecologic problem and excluding a possible malignancy is the principle objective of the gynecologists when dealing with this condition. The most important tools for determining the preoperative risk of malignancy are radiological imaging studies and serum tumor markers. However both sensitivity and specificity of these techniques are limited [1]. Although these studies help clinicians to counsel their patients and to make preoperative preparations, frozen section evaluation is the preferred method for assessment of suspicious adnexal mass and for decision making during surgery [2–4].

Accuracy of frozen section analysis had been the subject of many studies and investigators reported various sensitivities and specificities ranging from 62.7 to 100 % and 97.1 to 100 %, respectively [2, 3, 5, 6]. Nonetheless, studies evaluating the impact of clinical and pathological factors on the accuracy of frozen section are limited and only a few of these studies had adequate number of patients to allow them to perform a multivariate analysis [3, 7–13]. Therefore, we conducted this study to evaluate the accuracy of intraoperative frozen section in the evaluation of patients with adnexal mass and to define the factors for associated with misdiagnosis.

Materials and Methods

The clinical and histopathological data of the patients who underwent exploratory laparotomy for adnexal mass between January 2007 and January 2013 at Hacettepe University Hospital were retrospectively reviewed. Cases with a previous history of ovarian tumors, including benign neoplasms, malignant tumors and borderline tumors were excluded. Referred cases with incomplete surgery and patients who underwent interval cytoreductive surgery after neoadjuvant chemotherapy were also excluded. Patients in whom intraoperative frozen section assessment had been performed during the study period were included. For the purposes of this study, the permanent pathological diagnoses were assumed to be correct. Cases who were accurately identified as malignant but in which the origin of tumor could not be set as primary or metastatic by frozen section were described separately and were not included in the study group. Study flowchart is presented in Fig. 1.

During surgery, it was the senior gynecologic surgeon's decision to request frozen section consultation or not. Whenever the senior surgeon required a frozen section consultation, the specimens were delivered immediately to the frozen section room located next to the operation theatre. An attending pathologist analyzed all frozen section specimens. Moreover, consultation with an expert gynecologic pathologist was available via the telepathology system if required. At least one representative part was sampled for frozen section after macroscopic examination of the specimen. The gynecologic pathologist who was not blinded to frozen section results examined both the frozen section slides and the rest of the specimens to report the permanent histopathology.

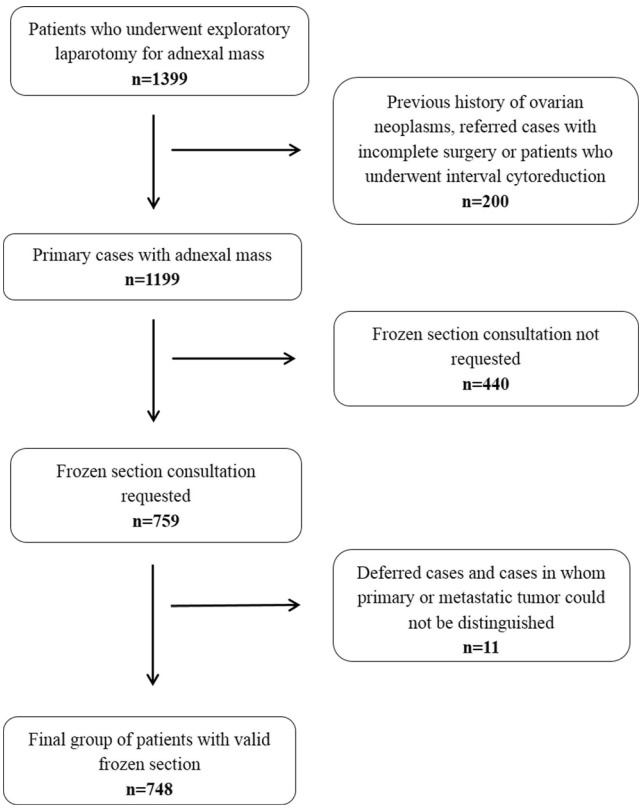

Fig. 1 Study flowchart

The frozen section analysis results and the permanent pathological diagnoses were categorized as benign, borderline, and malignant. The overall agreement between frozen section diagnosis and permanent histopathology reports was determined. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of frozen section analysis for benign tumors, borderline ovarian tumors (BOT) and malignant neoplasms were evaluated by 3×3 contingency tables. Malignant tumors reported as borderline and BOTs reported as benign by frozen section were defined as "underdiagnosis" and benign lesions diagnosed as borderline or malignant and BOTs diagnosed as malignant tumors by frozen section were defined as "overdiagnosis". Both underdiagnoses and over diagnoses were interpreted as "misdiagnosis". Data regarding patients' demographic characteristics, intraoperative findings of tumor size, presence of bilateral tumors, ascites, permanent tumor histopathology and performance of frozen section examination by general pathologist or gynecologic pathologist were recorded from patients' files and pathology reports. The pathological slide reviews of the misdiagnosed cases were not performed. However, data for suspected causes of misdiagnosis was obtained from the comments of gynecologic pathologists in the permanent histological report.

The association between misdiagnosis (overdiagnosis or underdiagnosis) and each clinicopathological factor was determined with univariate analysis via Chi-square or Fisher's exact test for categorical variables and *t*-test or Mann–Whitney-*U* test for continuous variables. The clinicopathological factors which were found to be significantly associated with misdiagnosis in univariate analyses were subjected to multivariate analysis via logistic regression. A p-value less than 0.05 was set for statistical significance. SPSS 11.5 (SPSS Inc., Chicago, IL, USA) was used for the data management and statistical analysis.

This study was approved by the Local Ethical Committee of Hacettepe University Faculty of Medicine.

Results

In total, 1,399 patients were subjected to surgery during the study period and 1,199 were subjected to primary surgery. Among them, frozen section examinations were performed in 759. Diagnoses of 4 patients could not be identified by frozen section, and the results were deferred for paraffin section. One of these patients had tubo-ovarian abscess complex and diagnosis was deferred due to massive tissue necrosis and inflammation. Another patient had metastatic hepatocellular

carcinoma, which was first presumed to be lipomatosis or fat necrosis and then deferred for paraffin section. The remaining two of four deferred cases had adult type granulosa cell tumor and clear cell carcinoma of the ovary, respectively. In 7 cases, frozen section identified the mass as malignant, but could not differentiate whether the lesion was a primary ovarian malignancy or a metastatic lesion. After excluding these 11 cases, 748 patients with valid frozen section reports constituted the study group. Of these patients 509 (68.0 %) had benign, 43 (5.8 %) had borderline, 196 (26.2 %) had malignant histological diagnosis at permanent section (Table 1). The malignant group was significantly older and had higher levels of preoperative CA-125 level compared to the benign and borderline groups ($p<0.0001$). The mean tumor size of the borderline histology group was significantly larger compared to the benign and malignant tumors ($p=0.001$). The histological diagnoses of ovarian tumors were grouped as non-neoplastic lesions ($n=245$, 32.8 %), epithelial ovarian tumors ($n=344$, 46.0 %), germ cell tumors ($n=84$, 11.2 %), sex-cord stromal tumors ($n=42$, 5.6 %) and metastatic tumors ($n=33$, 4.4 %).

The correlation between intraoperative frozen section and the permanent diagnoses is summarized in Table 2. The overall agreement between frozen section analysis and permanent section was 724/748 (96.8 %). The accuracy rates for benign, borderline and malignant tumors were 97.7, 97.6, and 98.3 %, respectively. Twenty four out of 748 cases (3.2 %) showed discrepancies (misdiagnosis) between the intraoperative frozen section reports and the permanent diagnoses. There were 9 (1.2 %) cases of overdiagnosis (false positives) and 15 (2.0 %) cases of underdiagnosis (false negatives). Table 3 shows the summary of the misdiagnosed cases. One of the most common causes of overdiagnosis, which was observed in one third of the cases, was the misinterpretation of benign mucinous ($n=2$) or serous ($n=1$) cystic neoplasms as borderline tumors. Both mucinous tumors had localized borderline histology. However, these focal borderline regions were found to be less than 10 % after sampling whole tumor in permanent pathology. 8 of 15 (53.3 %) underdiagnosed cases were reported as benign in frozen section, but during the examination of permanent sections, atypical epithelial proliferations were noticed and final diagnoses of these tumors were reported as BOT. Univariate analysis showed that borderline histology ($p<0.0001$) and tumor size larger than 10 cm ($p=0.012$) were associated with misdiagnosis of ovarian tumors by frozen section analysis. Based on multivariate analysis, borderline histology (OR: 22.6, $p<0.0001$) was the only independent factor of misdiagnosis (Table 4).

Discussion

Accurate intraoperative histological diagnosis by frozen section consultation constitutes the most crucial step of surgical treatment in patients with adnexal masses. According to the literature, frozen section analysis of ovarian neoplasms has a high accuracy rate which was reported to be more than 90 % in many studies [8, 14–16]. In the current series, the overall accuracy of frozen section was 96.8 %. The sensitivity for benign and malignant ovarian tumors was 98.8 and 96.4 %, respectively and these results were similar to the other published series [2–4, 14, 15, 17]. However, in case of borderline ovarian tumors the sensitivity of frozen section was only 74.1 %. In the related literature, the sensitivity of intraoperative frozen section for BOTs was also presented to be low (between 64.6 and 88.5 %) [11–13, 18].

Although our results show that frozen section consultation is a reliable tool for intraoperative decision making, there were 24 misdiagnosed cases (3.2 %) which significantly differed from permanent histological diagnoses. We analyzed the clinical and pathological factors which could potentially influence the accuracy of intraoperative frozen section and found that the significant predictors of misdiagnosis in univariate analyses were tumor size and borderline histology.

In the current series, univariate analysis showed that tumors larger than 10 cm were more likely to be misdiagnosed by frozen section however this finding was not supported by the regression analysis as an independent factor. The influence of tumor size on the accuracy of frozen section diagnosis has been evaluated by several investigators. Geomini et al. [7] evaluated frozen section results of 257 patients and observed only one underdiagnosed case in 50 patients with tumors less than 10 cm. The risk of false negative diagnosis was more than 10.0 % (11/97) in patients with tumors larger than 10 cm. Taskiran et al. [9] showed that discordance rate between frozen section and permanent pathology was 3.1 % in patients with adnexal mass smaller than 15 cm while this rate was 14.3 % in patients with tumors larger than 15 cm. Interestingly, Brun et al. [3] reported a contradictory result demonstrating that tumor size smaller than 10 cm was associated with a risk of misdiagnosis. They proposed that this

Table 1 Patients' characteristics and histological types according to permanent pathology

Characteristics	Benign $n=509$	Borderline $n=43$	Malignant $n=196$
Mean age, years (range)	47.0 (13–85)	39.0 (19–84)	53.5 (12–80)
Mean tumor size, cm (range)	7.0 (2–48)	11 (2–26)	9.0 (1–30)
Mean CA-125 level, IU/ml (range)	19 (1–1,445)	28 (9–802)	272 (5–15,985)

Table 2 Comparison of frozen section diagnosis with permanent paraffin diagnosis

Frozen section diagnosis	Permanent section diagnosis			
	Benign	Borderline	Malignant	Total
Benign	503	8	3	514
Borderline	3	32	4	39
Malignant	3	3	189	195
Sensitivity (%)	98.8	74.1	96.4	
Specificity (%)	95.4	99.0	98.9	
PPV (%)	97.9	82.1	96.9	
NPV (%)	97.4	98.4	98.5	

discrepancy could be related to higher frequency of unilocular cysts smaller than 10 cm which exhibit small foci of atypia whereas larger tumors were more frequently associated with gross morphological malignancy features like vegetation, solid components and septations. Nonetheless, it is obvious that compared to permanent pathologic evaluation, there is not enough time to take too many slices during frozen section procedure and large tumors may require multiple slices which is not always feasible in limited time settings [7]. In addition, most of the published studies demonstrated that accuracy of frozen section diagnosis is negatively influenced by large tumor size [7, 9, 10, 19]. In our view, tumor size is not an independent factor for misdiagnosis per se but it is actually dependent on the histopathological features of the tumors. Therefore, we think that misdiagnosed cases due to larger size tumors are reflections of the diagnostic errors that result from the intrinsic histological features of the tumors. This is supported by the fact that BOT's in our study group were significantly larger than benign and malignant tumors. Histopathological feature of the ovarian tumor is important parameter for the success of frozen section diagnosis as well. In the current study, we found that frozen section diagnosis has a lower sensitivity for BOTs (74.1 %) compared to benign lesions (98.8 %) and malignant tumors (96.4 %). As in univariate analysis, multivariate logistic regression analysis also showed that borderline histology was significantly associated with misdiagnosis (OR: 22.6; 95 % CI: 6.2–81.4, $p<0.0001$). In a recent pooled analysis of 1,104 patients, Song et al. [11] showed that frozen section diagnosis was correlated with permanent pathology in only 741 of 1,104 patients (67.1 %). The problems presented by BOTs are said to be mainly related to sampling errors due to large tumor size and histopathological heterogeneity [15]. We also found that BOTs were significantly larger than benign and malignant tumors. While some authors suggested examination of multiple frozen sections to overcome sampling problems, others resisted this approach and stated that it could impair the permanent section results [10, 15, 19, 20]. Future studies should aim to increase the accuracy of frozen section for BOTs without altering paraffin section results.

Another result of our study which is worth mentioning is the relation of pathologist's experience with frozen section accuracy. In our study, only 108 of 745 frozen section consultations (14.4 %) were evaluated by gynecologic pathologists. Although, the overall accuracy of gynecologic pathologists was higher than that of general pathologists, the difference was not statistically significant (98.1 % and 96.6 %, respectively, $p=0.56$). In our view, reaching a conclusion of no significant relationship between pathologist's experience and

Table 3 Summary of misdiagnosed cases

	Frozen section diagnosis	Final diagnosis	*n*
Overdiagnosis ($n=9$)	Borderline ovarian tumor	Mucinous cystadenoma	2
	Borderline ovarian tumor	Serous cystadenofibroma	1
	Primary carcinoma	Serous borderline tumor	2
	Primary carcinoma	Endometrioid borderline	1
	Primary carcinoma	Stromal luteoma	1
	Primary carcinoma	Simple cyst	1
	Metastatic tumor	Thecofibroma	1
Underdiagnosis ($n=15$)	Benign	Mucinous borderline tumor	4
	Benign	Serous borderline tumor	2
	Benign	Endometrioid borderline tumor	1
	Benign	Clear cell borderline tumor	1
	Benign	Carcinoid tumor	1
	Benign	Metastatic tumor	2
	Borderline ovarian tumor	Endometrioid ovarian carcinoma	1
	Borderline ovarian tumor	Serous ovarian carcinoma	2
	Borderline ovarian tumor	Metastatic tumor	1

Table 4 Univariate and multivariate analyses of the clinicopathological factors for misdiagnosis during frozen section

Variable	Accurate diagnosis n (%)	Misdiagnosis n (%)	*p*	*p*-value (OR; 95 % CI) of multivariate analysis for misdiagnosis	
Menopausal status					
Premenopausal	405 (55.9)	13 (46.4)	0.863	–	
Postmenopausal	319 (44.1)	11 (45.8)			
Age (years)					
<60	578 (79.8)	20 (83.3)	0.801		–
≥60	146 (20.2)	4 (16.7)			
Preoperative CA-125 (IU/mL)					
<35	390 (57.8)	16 (66.7)	0.386		–
≥35	285 (42.2)	8 (33.3)			
Tumor histology					
Borderline tumors	32 (4.4)	11 (45.8)	<0.0001	<0.0001	(22.6; 6.2–81.4)
Others	692 (95.6)	13 (54.2)			
Bilateral disease					
Yes	167 (23.1)	6 (25.0)	1.0	–	
No	556 (76.9)	18 (75.0)			
Gynecologic pathologist					
Yes	106 (14.6)	2 (8.3)	0.559	–	
No	618 (85.4)	22 (91.7)			
Intraoperative ascites					
Present	114 (15.8 %)	2 (8.3 %)	0.564	–	
Absent	609 (84.2 %)	22 (91.7 %)			
Tumor size					
<10 cm	453 (62.8 %)	9 (37.5 %)	0.012	0.416	(1.6; 0.483–5.811)
≥10 cm	268 (37.2 %)	15 (62.5 %)			
Epithelial tumors					
Mucinous	78 (23.9 %)	7 (41.2 %)	0.145	–	
Non-mucinous	249 (76.1 %)	10 (58.8 %)			

frozen section accuracy in ovarian lesions could be a misleading message with a retrospective study design because most of the challenging cases could have been consulted to the gynecopathologists without recording to the pathology reports. In our study, the only two misdiagnosed cases by gynecopathologists were large mucinous tumors which have the inevitable risk of inadequate sampling in the frozen section room. In the literature, many authors proposed that accuracy and success of intraoperative frozen section is strictly related to pathologist's familiarity with gynecologic pathology [14, 21]. Brun et al. [3] reviewed the frozen section results of 414 patients with epithelial tumors and showed that frozen section diagnosis of borderline ovarian tumors depended mainly on the pathologist's experience. Bige et al. [8] compared the results of frozen section diagnoses according to the expertise of pathologists on gynecologic tumors. The sensitivity, specificity and predictive values of the subspecialist pathologists were higher in all types of tumors. Stewart et al. [15] reviewed 914 consecutive ovarian frozen sections performed in 2 laboratories; one of which provides a general pathology service and the other a specialist gynecologic pathology service. In the general pathology laboratory, misinterpretation and misdiagnosis rates were more common. Indeed, none of the published studies including the present study were perfect for evaluating the subspecialist effect on frozen section accuracy because of blinding bias. We agree with Brun et al. [3] that only a prospective study involving both general and gynecologic pathologists to analyze the frozen section specimens simultaneously could adequately assess the impact of expertise on the accuracy of frozen section. Until such a prospective study is accomplished it would be a prudent conclusion to underline the importance of gynecologic pathologists' effect on accuracy of frozen section.

In conclusion, our review of a large number of cases confirms that frozen section evaluation of the adnexal masses provides high accuracy, high sensitivity and specificity. Tumor size larger than 10 cm and borderline histology adversely influence the accuracy of frozen section diagnosis and borderline histology is the only independent factor for misdiagnosis. Clinicians must understand both beneficial points and

the potential pitfalls of this procedure when they have to make an intraoperative surgical decision. Patients should also be counseled about the possibilities of false positive and false negative results before the surgery.

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