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Diagnostic Accuracy of Intraoperative Frozen Section and Causes of Error in Ovarian Epithelial Tumors: An Institutional Experience

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Abstract

Background: Ovarian cancer is the second most common type of female genital tract malignancy. Treatment planning differs for benign, borderline, and malignant subtypes of surface epithelial tumors and depends on accurate histopathological diagnosis. The aim of this study is to determine the accuracy and causes for error in intraoperative diagnosis of ovarian surface epithelial tumors.

Methods: In this retrospective study, we analyzed all cases of ovarian surface epithelial tumors referred to the Pathology Department of our hospital from April 2010 to December 2015. We considered the final diagnosis as the gold standard and determined the accuracy, sensitivity, specificity, positive predictive value, negative predictive value, underdiagnosis and overdiagnosis for each group of benign, borderline, and malignant tumors. An expert pathologist blinded to the diagnosis reviewed patients' frozen and permanent slides and categorized causes of error into misinterpretation, sampling, and technical errors.

Results: We assessed 220 patients' slides (96 benign, 66 borderline, and 58 malignant tumors). The accuracy of the frozen section was: 98% in benign, 80.3% in borderline and 67.2% in malignant tumors. The frozen sections had a sensitivity of 97.9% for benign tumors and a sensitivity of 67.2% and specificity of 100% for malignant tumors. Borderline tumors had a sensitivity of 91% and specificity of 88.4%. Mucinous borderline tumors comprised the more frequent uncertain and underdiagnosed cases. The main cause for error in this group was sampling error. In malignant neoplasms, 15.5% were reported to be at least borderline. Technical issues were the cause of difficulty in interpretation. In the benign category, cystadenofibroma could be misinterpreted as a borderline malignancy.

Conclusion: Frozen section is an accurate, specific method for diagnosis of benign and malignant tumors. In the borderline category, the results should be interpreted with caution.

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Introduction

Ovarian cancer is the second most common type of female genital tract malignancy and the most frequent cause of death in this group.[1] Surface epithelial tumors are subdivided into benign, borderline and malignant subtypes. They are the most frequent type of ovarian cancers. Treatment planning differs in these subtypes and depends on an accurate histopathologic diagnosis. While conservative surgery can be considered for benign tumors, complete staging and radical surgery are recommended for borderline and malignant subtypes, respectively.[2] Preoperative diagnosis of ovarian masses based on clinical, laboratory, and radiologic findings is not accurate and histologic examination is difficult. The accuracy of frozen sections as an intraoperative guide for decision making by the surgeons has been evaluated in several studies. The aim of this study is to determine the cause and frequency of different errors which can lead to an incorrect diagnosis. We report the accuracy of this method in our referral gynecology oncology center.

Materials and Methods

This retrospective cross-sectional study included all cases of ovarian surface epithelial tumors referred to the Pathology Department for frozen section study at our hospital from April 2010 to December 2015. We reviewed the pathology reports of the patients. Demographic and clinical data, findings on gross examination, intraoperative diagnosis, and final histopathologic diagnosis on permanent sections were analyzed. In the cases of incorrect or uncertain diagnosis, an expert pathologist blinded to the diagnosis reviewed the prepared slides for frozen section and related permanent sections.

We categorized types of errors into the following subgroups: (A) technical error defined as any problem in the quality of the frozen slides such as thick sections, poor staining, etc.; (B) sampling error when the frozen sections were not representative of the pathologic findings, necessary for correct diagnosis. These findings were discovered over extensive sampling after overnight fixation; and (C) misinterpretation defined as any problem in the interpretation of appropriate and representative frozen section slides by the pathologist.

We considered the permanent section diagnosis as the gold standard method for the true diagnosis. We used 2 × 2 tables to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) as well as the overall accuracy for each group of benign, borderline, and malignant tumors. Frequency of different causes of error was also calculated in the different subcategories.

Results

In this study, we investigated 220 patients' pathology reports for 58 malignant, 66 borderline and 96 benign epithelial tumors. Table 1 lists the age, size, rate of bilaterality, and histologic subtype for each of the groups. Approximately 77.2% of malignant tumors were correctly reported, 15.5% were reported as "at least borderline", 12% "borderline', and 3.4% "sex-cord stromal tumor". Also, 1.7% of the samples were deferred. Overall accuracy in definite diagnosis of malignant tumors was 67.2%. Table 2 shows the comparison between frozen and permanent section reports for different subgroups of malignant tumors. Diagnostic accuracy of frozen sections was 100% for poorly differentiated carcinomas, 80% in metastases and 77.2% in papillary serous carcinomas. Most of misdiagnosed cases belonged to the endometrioid and clear cell type tumors.

In 96 benign tumors, 94 cases were diagnosed precisely. Only 2 cases of papillary serous cystadenofibroma were incorrectly diagnosed as borderline malignancy. Diagnostic accuracy of the benign tumors was 98%.

In the borderline category, 12.5% of the samples were deferred. In these, 5 cases belonged to the mucinous tumors and 2 cases to the serous subtype. A total of 9.5% mucinous and 7.1% serous tumors were diagnosed as benign tumors. No malignant tumor was reported in any sample. Overall diagnostic accuracy in the borderline category was 80.3% (66.6% in mucinous, 88% in

Table 1. Frequency of surface epithelial tumors of the ovaries based on histologic subtype, mean size, mean age and rate of bilaterality.

Ovarian epithelial tumor		Number (%)	Mean size (cm)	Bilateral	Mean age (years)
Benign N=96 (43.6%)	Serous	46 (48)	14.2	2	54.7
Mucinous		50 (52)	17.5	1	50.6
Borderline N=66 (30%)	Serous	42 (63.6)	9	3	38.9
Mucinous		21 (31.8)	18.5	0	44.4
Seromucinous		3 (4.5)	9.5	0	63
Malignant N=58 (26.4%)	Metastasis	10 (17.2)	11.9	6	45.7
Endometrioid		9 (15.5)	11.7	2	50.7
Serous		22 (38)	11.09	11	51.7
Mucinous		1 (1.7)	16	0	62
Seromucinous		3 (5.1)	15.3	1	47.3
Poorly differentiated		10 (17.2)	13	6	42.8
Total		220	12.67	32	48.1

papillary serous, and 66.6% in seromucinous tumors; Table 3).

Table 4 lists the diagnostic accuracy, sensitivity, specificity, PPV and NPV, overdiagnosis, underdiagnosis, and uncertain diagnosis of intraoperative consultation in benign, borderline and malignant epithelial tumors. A review of frozen section slides and permanent paraffin block prepared slides in misdiagnosed or unknown cases showed the following results. In both benign cases which were reported as borderline, the final diagnosis was papillary cystadenofibroma. There were errors in interpretation. Interpretation error was the cause for tumors of borderline malignancy that were deferred or had uncertain diagnosis. We noted that two cases of papillary serous tumors were misdiagnosed because of interpretation error. In 5 mucinous neoplasms, sampling error was noted. In malignant tumors, slides of 4 cases with discrepant answers were lost in our archives and excluded. A review of frozen section slides in all specimens that had reports of at least borderline tumor showed high nuclear atypia, mitoses, and architectural complexity without definite evidence of stromal invasion. We attributed the cause for discrepancy to the combination of technical and interpretation errors. However in all cases with borderline reports, there were errors in misinterpretation.

Discussion

Surface ovarian epithelial tumors are categorized as benign and borderline tumors based on the presence or absence of epithelial atypia, pseudostratification, mitoses, and structural complexity in more than 10% of the neoplasms. In malignant tumors, there is stromal invasion by atypical epithelial cells in more than a 10 mm^2 area.[3,4] While benign epithelial tumors can only be treated with cystectomy, optimal surgical staging is recommended for borderline and malignant tumors. Optimal surgical staging includes total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, peritoneal washing, peritoneal biopsies, and pelvic and para-aortic lymph node sampling. In young patients diagnosed with borderline tumors who want to preserve their fertility, salpingo-oophorectomy of the involved ovary without hysterectomy can be performed. As a result, the correct diagnosis at the time of surgery is crucial for management of ovarian tumors.

The accuracy of intraoperative frozen section for diagnosis of ovarian neoplasms has been evaluated in different studies. The largest recent review assessed 38 studies that included 11181 patients (3200 malignant, 1055 borderline, and 6926 benign tumors).[5] In this study, the researchers used two thresholds to assess frozen section performance. First, they defined invasive cancers as positive, whereas borderline and benign tumors were defined as negative. The researchers reported an average sensitivity of 90% [95% confidence interval (CI): 87.6%-92%] and average specificity of 99.5% (95% CI: 99.2%-99.7%). They considered invasive and borderline tumors as

Table 2. Comparison of frozen and permanent section diagnosis in malignant epithelial tumors of the ovaries.

Permanent section (N)	Frozen section				
	Deferred	At least borderline	Borderline	Malignant	Sex cord stromal tumor
	N (%)	N (%)	N (%)	N (%)	N (%)
Papillary serous carcinoma (22)	0	3 (13.6)	2 (9.1)	17 (77.2)	0
Mucinous carcinoma (1)	0	0	1 (100)	0	0
Endometrioid carcinoma (9)	0	3 (33.3)	1 (11.1)	3 (33.3)	2 (22.2)
Clear cell carcinoma (3)	1 (33.3)	1 (33.3)	0	1 (33.3)	0
Poorly differentiated carcinoma (10)	0	0	0	10 (100)	0
Metastasis (10)	0	1 (10)	1 (10)	8 (80)	0
Seromucinous carcinoma (3)	0	1 (33.3)	2 (66.6)	0	0
Total (58)	1 (1.7)	9 (15.5)	7 (12)	39 (67.2)	2 (3.4)

positive and benign tumors were defined as negative. In this case, the average sensitivity was 96.5% (95% CI: 95.5%-97.3%) with an average specificity of 89.5% (95% CI: 86.6%-91.9%). If the frozen section diagnoses were benign and malignant tumors, the final permanent diagnosis would be the same in 94% of benign and 98% of malignant cases. However in borderline tumors, 21% of the cases would have the final diagnosis changed to malignant neoplasm.[5]

The overall accuracy of frozen section diagnosis in our institute was 84.5% which agreed with a study by Wootipoom et al. in Thailand participating 229 patients. They reported an accuracy of 89.7%.[6] A high sensitivity, specificity, PPV and NPV of frozen section in diagnosis of benign epithelial tumors was reported, as with numerous other investigations. There were only two cases of serous cystadenofibroma misinterpreted as borderline neoplasms due to their structural complexity. Another study reported the same results.[7]

In borderline tumors, the average accuracy of frozen section was approximately 60% (27%-82.9%).[8] We reported an average accuracy of 80.3% which supported the results by Song et al. They evaluated 76 patients and found 82.9% agreement between frozen sections and final permanent diagnosis.[9] The frequency of underdiagnosis (24.5%) was more than overdiagnosis (4.9%).[8] We have observed a frequency of 7.5% for underdiagnosis and 0% for overdiagnosis. Sampling error in mucinous tumors is the most frequent cause of underdiagnosis in the borderline category while misinterpretation can lead to misdiagnosis in serous borderline tumors. Diagnostic difficulty in borderline mucinous tumors has been reported in other studies and attributed to their larger size and increased tumor heterogeneity.[10] Most severe lesions and malignant areas might not be sampled when there are a limited number of sections for frozen study. There is no agreement about the effectiveness of additional sampling in these tumor types.[11,12]

In malignant neoplasms, numerous studies reported greater than 95% specificity and PPV for frozen sections.[13] We determined this to be 100% in our study. However our institute had lower sensitivity and NPV in the frozen section diagnosis of invasive cancers. A total of 47.3% of discrepant cases were reported to be at least borderline

Table 3. Comparison of frozen section and permanent diagnosis in borderline tumors of the ovaries.

Permanent sections (N)	Frozen section		
Borderline N (%)	Benign N (%)	Borderline N (%)	Deferred
Serous (42)	3 (7.1)	38 (88)	1 (4.7)
Mucinous (21)	2 (9.5)	14 (66.6)	5 (23)
Seromucinous (3)	0	2 (66.6)	1 (33.3)
Total (66)	5 (7.5)	53 (80.3)	8 (12)

Table 4. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), overall accuracy, frequency of uncertain, and over and under diagnosis of frozen sections in diagnosis of benign, borderline and malignant epithelial tumors of the ovaries.

Ovarian epithelial tumor	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)	Uncertain diagnosis N (%)	Under-diagnosis N (%)	Over-diagnosis N (%)
Benign (96)	97.9	95	95	98.3	98	0	0	2 (2)
Borderline (66)	91	88.4	74.8	96.5	80.3	8 (12)	5 (7.5)	0
Malignant (58)	67.2	100	100	89.5	67.2	1 (1.7)	16 (27.5)	0
Total (220)	85.4	94.5	89.9	94.7	84.5	9 (4)	21 (9.5)	2 (0.9)

tumors. A review of the frozen section slides showed high nuclear atypia, mitoses, and architectural complexity without definite evidence of stromal invasion in all of these slides. This result could suggest that the presence of these morphologic findings was highly predictive of malignant diagnosis. All patients with this type of report have undergone optimal surgical staging for malignant tumors. While poorly differentiated, high grade papillary serous, and metastatic carcinomas are easier to diagnose, mucinous, endometrioid and clear cell carcinomas are more frequent intraoperative misinterpretations. We noted that on final diagnosis, 12% of tumors diagnosed as borderline were changed to malignant.

In conclusion, intraoperative pathological investigations with the frozen section method are an efficient way to evaluate benign tumors and high grade carcinomas. However it is more difficult to interpret borderline, malignant mucinous, endometrioid, and clear cell carcinomas. Sampling error is the main cause of underdiagnosis in borderline mucinous tumors and technical issues that lead to difficulty in interpretation of stromal invasion in some malignant carcinomas. Considering these limitations, surgeons should consult with pathologists in problematic cases in order to obtain the appropriate treatment decision.

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Conflict of interest

No conflict of interest is declared.

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