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Original Article

Diagnostic Accuracy of Frozen Section Analysis and Factors Associated with Discordance of Final Histopathology in Mucinous Ovarian Tumor

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Abstract

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Aim and Objective This article determines the diagnostic accuracy of frozen section (FS) in case of mucinous ovarian tumor (MOT) and tailoring of intraoperative treatment decision.

Material and Methods This was an observational study in which retrospective data was analyzed prospectively from January 2008 to December 2015 at the Regional Cancer Center. This study included 158 patients with MOT who underwent FS analysis during staging laparotomy at our institute. FS's sensitivity, specificity, and diagnostic accuracy were calculated and compared with final paraffin histopathological examination (HPE). Univariate and multivariate analyses were done to decide factors associated with changes in final HPE.

Results FS analysis and final HPE report were concordant in 77.8% (123/158) of the cases and discordant in 22.1% (35/158). Out of 35 discordant cases, 29 (18.3%) were upgraded and 06 (5.6%) were downgraded. Out of 33 borderline cases, 16 (48.4%) were upgraded to malignant MOT and 6 (18.1%) were downgraded to benign MOT on final HPE. Out of 40 malignant MOT, 40 (100%) showed malignancy on final HPE. In the case of benign MOT on FS, 13 out of 85 (15.2%) upgraded to borderline or malignant. Sensitivity and specificity of FS were 76.60 and 55.17%, respectively, for benign MOT, 55.17 and 86.96% for borderline MOT, and 86.96 and 100% for malignant MOT.

Conclusion In MOT, due to its large size and heterogeneous nature, it displays spectrum of appearance ranging from benign cyst adenoma, and borderline tumor to adenocarcinoma. Our study showed significant discordance between FS and final histopathological diagnosis in borderline MOT.

Keywords

- mucinous ovarian tumor
- frozen section
- sensitivity
- specificity

Introduction

Ovarian cancer is the third most frequent type of gynecological cancer, accounting for 4% of all female cancers and 31% of all gynecological cancers.[1] The most frequent subtype of ovarian cancer is epithelial ovarian cancer (EOC), which has the highest mortality rate of all gynecological cancers.[2] Mucinous ovarian tumors (MOTs) account for 12% of all

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EOC, but their true incidence is less than 3%.[3] The most common treatment for ovarian tumors is surgical debulking. Preoperative diagnosis of MOT is extremely difficult due to the limited diagnostic accuracy of imaging and serum tumor markers.[4,5] Frozen section (FS) analysis during primary staging laparotomy may be useful in tailoring the scope of surgery. FS diagnosis during staging laparotomy is considered an acceptable diagnostic approach in the case of EOC (diagnostic accuracy, 86–97%).[6] Inaccuracy of FS rises in case of MOT due to incorporation of benign, borderline, and malignant components in the same specimen. The final histology (histopathological examination [HPE]) report may change the FS diagnosis of MOT, leading to a change in the patient's therapeutic approach. This study was conducted to determine the diagnostic accuracy of FS in case of MOT.

Materials and Methods

This was an observational study in which retrospective data was analyzed prospectively, with the approval of the Institutional Research Committee. Data was obtained from the Medical Record Section of the Regional Cancer Center of the Government of India. A total of 158 patients, from January 2008 to December 2015 were included in this study. Patients who underwent primary staging laparotomy with FS analysis were included in the study. Patients who had received any other form of treatment before were excluded. Data was collected and analyzed as a result of comparing the FS analysis report to the final HPE report.

The FS analysis was performed by a specialist gyne-oncopathologist at our institute. After meticulous grossing, one to four slices were obtained from the most suspicious portion of the specimens, depending on the size of the tumor. The results of the hematoxylin and eosin stain on the frozen specimen's imprint slide were conveyed to the surgical team. After the FS report, the tissue was processed for paraffin blocks. At least one paraffin section per centimeter was developed for the final paraffin HPE. The final HPE report was compared to the FS report to see if it had been upgraded, downgraded, or remained the same. The data was analyzed in terms of age, size of tumor, laterality of tumor, presence of solid component and extensive disease, FS report, and final HPE.

Statistical Analysis

The final analysis was performed using IBM Statistical Package for Social Science (IBM SPSS [Statistical Package for Social Science] software [v 21.0]) and a Microsoft Excel spreadsheet. The diagnostic accuracy, sensitivity, and specificity of FS were determined and compared to the final HPE. Univariate logistic regression was done to determine factors associated with change in final HPE.

Results

A total of 158 patients with MOT who met the inclusion criteria were studied. The average tumor size was 19.7 cm and the median age of the patients was 43.9 years. Tumor was found to be bilateral in 12 (7.5%) patients. In 47 (29.7%) patients, there was extensive upper abdominal disease. When the FS report and the final HPE were compared, the overall concordance rate of the study was 77.8% (123/158). While in malignant MOT it was 100% (40/40), in benign MOT 84.5% (72/85), and in borderline tumor 33.3% (11/33).

The overall discordance rate of the study was 22.1% (35/158). Twenty-nine of the 35 discordant cases (18.3%) were upgraded, while 6 (5.6%) were downgraded. On subgroup analysis, the highest discordance rate (67%) was found in borderline MOT (22/33). On final HPE, 16 (48.4%) of the 33 borderline cases were upgraded to malignant MOT and 6 (18.1%) were downgraded to benign MOT. In the case of benign MOT (85/158) on FS, 13 of 85 (15.2%) patients were upgraded to either borderline or malignant MOT. No discordance rate was observed in malignant MOT (►**Table 1**).

For benign MOT, the sensitivity and specificity of FSs were 76.60 and 55.17%, respectively, 55.17 and 86.8% for borderline MOT, and 86.96 and 100% for malignant MOT (►**Table 2**).

Table 1 Comparison of frozen section report with final histopathology report

	$n = 158$						
FS report	Malignant (M) 40	Benign (B) 85			Borderline (BL) 33		
Final HPE	M (40) 100%	B (72) 84.5%	BL (8) 9.4%	M (5) 5.8%	B (6) 18.6%	BL (11) 33.3%	M (16) 48.4%

Abbreviations: FS, frozen section; HPE, histopathological examination.

Table 2 Sensitivity, specificity, positive predictive value, and negative predictive value of FS diagnosis of MOT

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Benign	76.60	55.17	84.7	42.1
Borderline	55.17	86.8	48.4	89.6
Malignant	86.9	100	100	94.9

Abbreviations: FS, frozen section; MOT, mucinous ovarian tumor.

Table 3 Univariate analysis of outcome variables

Frozen section analysis compared with final HPE				
Variables	**Same diagnosis ($n=123$)**	**Upstages ($n=29$)**	**Downstages ($n=06$)**	**Overall *p*-value**
Age (y)				
≤ 35	41	09	1	0.687
> 35	82	20	5	
Size (cm)				
< 10	8	0	1	0.226
10–20	49	13	4	
> 20	66	16	1	
Laterality				
Unilateral	113	27	6	0.754
Bilateral	12	2	0	
Extensive disease				
Present	36	10	1	0.665
Absent	87	19	5	
Solid component				
Present	37	14	1	0.119
Absent	86	15	5	
Septations				
Present	115	29	5	0.197
Absent	08	0	1	

Abbreviation: HPE, histopathological examination.

Malignancy has the highest diagnostic accuracy, while borderline MOT has the lowest.

The existence of a solid component, extensive upper abdomen disease, bilateral tumor, tumor size, and septation were not significantly linked with discordance rate of the final HPE in univariate analysis (►**Table 3**).

Discussion

FS diagnosis is a reliable intraoperative approach when imaging and tumor markers are unable to distinguish between benign, borderline, and malignant tumor. FS analysis allowed us to tailor the extent of the surgery. MOT is difficult to identify even on FS analysis, due to its heterogeneous nature. We observed that the total concordance rate between FS and final HPE in MOT was 77.8% in our retrospective analysis of 158 patients. With a sample size of 414 EOC and 107 MOT, Brun et al observed 79% concordance rate between FS and final HPE.[7]

The proportion of borderline MOT had a significant impact on the concordance rate of the study. Houck et al discovered a 60% concordant rate with 47 borderline MOT out of 140 EOC.[8] In our study, 22 were discordant borderline MOT out of 158 MOT. As the number of borderline MOT rises, the discordance rate of the study rises in proportion to the sample size. In our study, the discordance rate was 22.1% (35/158). Maximum discordance was with borderline MOT, 67% (22/35). Sixteen borderline MOTs were upgraded as malignant, while six were downgraded as benign with focal atypia (►**Fig. 1**). The reason for the upgrade was the extensive sampling of specimen to evaluate invasive foci in paraffin sections. The permanent paraffin sections revealed stromal invasion with areas of benign and borderline tumor in the same specimen. Because of the large tumor size and the fast sampling intraoperatively, well-differentiated invasive foci are unlikely to be detected during the FS. Final histopathology was downgraded in cases where frozen was equivocal for benign or borderline MOT and final HPE confirmed benign MOT with focal atypia.

Eight out of the 85 benign MOTs (8/85) were upgraded to borderline MOTs and 5 (5/85) to malignant and metastatic MOTs. Only one of the five upgraded malignant cases was related to the primary ovary, while the other four were related to the gastrointestinal tract primary (low grade mucinous appendiceal tumor) that appeared as benign ovarian masses on FS reports. The upgrades to borderline or malignant were due to the detection of a microinvasion or an invasive nodule on the permanent paraffin HPE by extensive sampling to evaluate invasion. Adding immunohistochemistry (IHC) markers to the permanent paraffin section makes it possible to confirm the primary origin of MOT (ovarian or gastrointestinal) but does not differentiate between benign and borderline MOT. When a morphological variation between the primary and metastasis was found, an IHC panel was used to confirm the origin of the tumor. The risk of upstaging in our study was 18.3% (29/35), which is in the range of 12–40% in other studies.

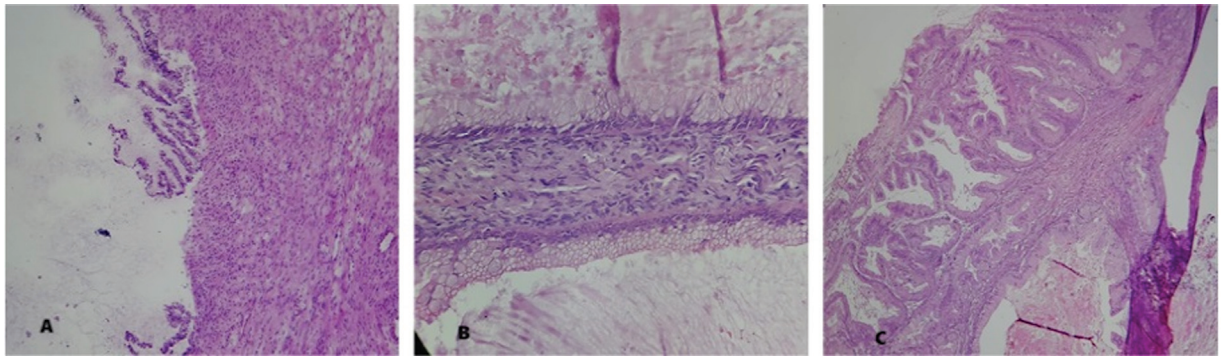

Fig. 1 (**A**) Borderline tumor. (**B**) Single line of epithelium with maintained stoma. (**C**) Crowding of glands with high nuclear-to-cytoplasmic ratio.

Studies in the literature suggest that FS report in MOT has a wide range of diagnostic accuracy due to their heterogeneous nature, nonovarian origin, and larger size. Storms et al discovered that malignancy had a sensitivity of 28.6%, borderline had 91.6%, and benign had 71.4%, while specificity was 100, 55.1, and 93.3% for malignancy, borderline, and benign, respectively.[9] Another study by Pongsuvareeyakul et al reported that FS in MOT has a sensitivity and specificity of 99 and 78.5% for benign MOT, 67 and 95% for borderline MOT, and 56 and 99% for malignant MOT, respectively.[10] In our study, FS analysis had the highest sensitivity and specificity with malignancy (86.9 and 100%), followed by benign (76.6 and 55.1%) and the lowest with borderline MOT (55.1 and 86.8%). The positive predictive value of borderline MOT is the lowest (48.4%). Based on these results, it was determined that borderline and benign MOTs were more likely to be misdiagnosed on FS analysis. Ratnavelu et al published a Cochrane review in 2016 that found borderline tumor to be a major risk factor for discordancy.[11] More FS cuts, as well as clear communication of intraoperative findings with the pathologist, are required to improve FS accuracy.

In the case of carcinoma on the final HPE, inadequate surgery may necessitate additional surgery, whereas extensive surgery in the case of benign histology may result in unnecessary postoperative morbidity. Staging that is adequate and appropriate can help in avoiding postoperative complications and increase the chances of survival. That is why studies on the accuracy of FS are much required for determining the extent of surgery based on FS. It is important to establish a relationship between a variety of parameters associated with FS diagnosis and subsequent HPE discordance. In our study, solid component, septation, and extensive upper abdomen disease were found to be independent predictors of malignancy at FS diagnosis. While no parameter was shown to be significantly related to the discrepancy between the FS and the final HPE (►Table 3).

Storms et al looked at the factors that influence FS accuracy and found that age, tumor size, bilateral tumor, and extensive upper abdomen disease was not significantly linked to upstaging of FS diagnosis.[9] Pongsuvareeyakul et al discovered that tumor size greater than 13 cm was associated with FS inaccuracy, in study of 164 patients of MOT, but no independent discrepancy predictor was found.[10] Preoperative and intraoperative findings, as well as adequate collaboration with the pathologist, may all aid in the reduction of discrepancies between FS diagnosis and final HPE.

Conclusion

MOT being heterogeneous, larger size, and limited time available for FS analysis, there is lack of accuracy of FS. Our study concluded that FS has high sensitivity and specificity in both malignancy and benign varieties of MOT. However, it is less in borderline subtype of MOT. To minimize clinical inconsistency based on FS analysis, our institute's protocol is to do a thorough preoperative counseling and informed consent regarding the chance for a second operation if final HPE gets upstaged, in young patients. While we prefer to do comprehensive staging in patients who had completed their family, the surgeon and the pathologist must coordinate intraoperatively to increase diagnostic accuracy of FSs in MOTs.

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Conflict of Interest
None declared.

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