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Genitourinary Cancer

Concordance of Frozen Section Diagnosis of Epithelial Ovarian Neoplasm and Discussing the Diagnostic Pitfalls: An Institutional Experience

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Abstract

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Background Ovarian neoplasm is the third most common malignancy in Indian women. Intraoperative diagnosis becomes the critical guiding tool for the surgeons to take the decisions on the extent of surgery specially when preserving fertility has to be considered.

Aims and Objective The aim of this study is to evaluate the concordance of intraoperative diagnosis of frozen section (IFS) of ovarian epithelial neoplasm at our institute and to review and discuss the diagnostic pitfalls along with the review of literature.

Materials and Methods Data were archived from departmental record and the detailed clinical data of the patients were retrieved from hospital record system. The discordant cases were reviewed again in an attempt to address the pitfalls.

Statistical Analysis Diagnostic accuracy, sensitivity, specificity, and positive and negative predictive value of IFS of ovarian neoplasm were analyzed.

Results The overall frozen section diagnosis was concordant with final histopathology in 36 out of 44 cases (81%). The sensitivity of IFS diagnosis was found to be 100% for benign and borderline tumors, whereas 88.9% for malignant epithelial tumors, but the correctness of diagnosis is high only for benign and malignant tumors (high positive predictive value) in compared with borderline ones. The diagnostic pitfalls were identified individually in discordant cases.

Conclusion An accurate interpretation of IFS in ovarian epithelial malignancy can be achieved in benign and malignant cases, but limited in borderline tumors. Awareness of the artifacts and the limitations in mind and the IFS diagnosis can be of great help for proper management of the ovarian neoplasm.

Keywords

- frozen
- intraoperative
- ovarian
- neoplasm
- pitfalls
- accuracy

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Introduction

Ovarian neoplasm is one of the most common gynecological causes of women morbidity and mortality worldwide and they comprise a dynamic spectrum of histologic subtypes with varying prognosis. It is the third leading cause of malignancy in Indian women and the second most common female genital tract malignancy in Kamrup urban registry.[1] Since the preoperative diagnosis of subcategorization of ovarian mass is difficult because of various factors like their anatomical location, limited accuracy of imaging, and nonspecific rise of serum tumor marker, the decision on the management also becomes difficult. So, the intraoperative diagnosis becomes the critical guiding tool for the surgeons to decide the extent of surgery. As we know, in general, that benign and borderline tumor are adequately managed by conservative surgery, whereas malignant tumors require an extensive radical surgery with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy along with pelvic and retroperitoneal lymphadenectomy and sampling from many peritoneal sites.[2,3] Therefore, the accuracy of the intraoperative frozen section (IFS) diagnosis is one of the deciding factor for the management of ovarian neoplasm. It has been reported in the literature that IFS diagnosis of ovarian neoplasm has a better diagnostic accuracy in benign and malignant tumors than the borderline tumors.[4]

Aims and Objective

The aim of the present study is to evaluate the concordance of intraoperative diagnosis of frozen section of ovarian neoplasm at our institute and to review the discordant cases to discuss the diagnostic pitfalls along with the review of literature.

Materials and Methods

We have collected 3 years data of IFS diagnosis of ovarian epithelial neoplasm for a period of 3 years from departmental record and the detailed clinical data of the patients were retrieved from hospital record system. Data regarding their clinicopathological data like histological subtype, tumor size, age of the patients, menopausal status, laterality of the mass, preoperative Ca-125 level, and the final paraffin section diagnosis were obtained from these records. The slides for discordant cases (between frozen sections and histopathology diagnosis) were further reviewed and an attempt to address the cause of error was made.

The following are the indications for patients undergoing IFS diagnosis similar to many other institutes[3]:

1. Raised CA-125 in clinically benign looking adnexal mass.
2. Patient with adnexal mass who has a past history of malignancy at another site.
3. Young patients with ovarian mass, intending to retain the fertility.

During laparotomy, the tumor was used to be removed and was sent immediately to the pathology department in unfixed state putting it in normal saline. After grossing thoroughly, representative tumor sections were used to be taken from various areas, the number of sections being 3 to 5 depending on the size and nature of the specimen. The tissue then put in cryostat instrument to section at around 4 to 5 µm. The slides were stained with hematoxylin and eosin and viewed under microscope for results. The slides were reviewed and results were recorded in the department. The average time taken from the receiving of specimen to reporting was 15 to 20 minutes.

Statistical analysis was done taking histopathology of the same specimen as gold standard. Sensitivity, specificity, and predictive value were calculated using the standard 2×2 methods.

Results

A sum of 53 cases of ovarian neoplasm had undergone IFS diagnosis during the period of 3 years, out of which 44 were ovarian epithelial neoplasm. The mean age of our patients was 44 year and left-sided laterality was most commonly seen (►Table 1).

The overall frozen section diagnosis was concordant with final histopathology in 36 out of 44 cases (81%) (►Table 2) Among the total eight discordant cases, four were major error in classifying into benign, borderline, and malignant category and four were minor error in subtyping in the same category. The major diagnostic error was made in three borderline cases and in one case of benign frozen diagnosis, which were turned out to be microinvasive and invasive carcinoma. This was specially seen in borderline mucinous tumors (3 cases) and one case of serous cystadenoma. But minor diagnostic errors were seen in subtyping of two benign and two malignant cases.

Among the benign category, there were two cases misinterpreted as seromucinous cyst that on histopathology showed features of endometriotic cyst. One case of serous cystadenoma was turned out to be clear cell carcinoma (CCC).

In three cases of discordant borderline cases, three were mucinous carcinoma with expansile growth pattern of invasion.

Except one case, no other malignant cases were misdiagnosed as nonmalignant category in IFS, but there were two cases with subtyping error in malignant category. One IFS diagnosis of poorly differentiated serous carcinoma turned

Table 1 Demographic and clinical data of patients ($n = 44$)

Age	< 40 years	16
	>40 years	28
Menopausal status	Premenopausal	24
	Postmenopausal	20
Laterality of tumor	Right	16
	Left	19
	Bilateral	09

Table 2 The results of frozen and paraffin sections in various categories of epithelial ovarian neoplasms ($n = 44$)

Category of ovarian tumor	Frozen diagnosis	Histopathology concordance	Types of error
Benign	26	23	1 major error as benign vs. malignant, 2 minor error in subtyping
Borderline	08	05	3 major error as borderline vs. invasive
Malignant	10	08	2 minor error in subtyping

Table 3 Sensitivity, specificity, PPV, and NPV of frozen section

Category	Sensitivity	Specificity	PPV	NPV
Benign	100%	87.5%	88.5%	100%
Borderline	100%	92.3	62.5	100%
Malignant	88.9%	94.3%	80%	97.1%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

out to be B cell lymphoma and one case of CCC was mistaken as high-grade serous carcinoma in IFS (►Table 3).

Discussions

Internal quality assurance of IFS diagnosis can be achieved by the concordance of frozen-histopathological correlation. The reported accuracy rate of IFS diagnosis of ovarian neoplasm was 70 to 97%.[5,6] The current study showed overall accuracy rate of IFS diagnosis as 81%, but if we consider only the major error, the accuracy rate is 90.9%. The sensitivity of IFS diagnosis in our study was 100% for benign and borderline tumors, whereas 88.9% for malignant epithelial tumors. In our retrospective analysis, IFS did not miss the categorization into benign, borderline, and malignant ovarian tumors (high sensitivity), but the correctness of diagnosis is high only for benign and malignant tumors (high positive predictive value) in compared with borderline ones. The major diagnostic error was misdiagnosing the case of CCC as the benign serous cystadenoma. The CCC is characterized by tubulocystic, papillary growth, and solid pattern with characteristic hyalinized fibrovascular cores. The degree of nuclear atypia may also vary greatly among different areas of the same tumor.[7] While reviewing the case, we came across that the number of sections taken was only two and the sections showed multiple cystic spaces with attenuated epithelial lining (►Fig. 1A) and foci showing the hob nailed hyperchromatic nuclei (►Fig. 1B) that had been overlooked by the reporting pathologist. The cystic spaces with overgrown fibromatous ovarian stroma had misled the diagnosis of serous cystadenofibroma. In this case since the patient was elderly and on the discretion of clinical ground, the total hysterectomy with salpingo-oophorectomy and presumptive staging was performed.

In another one case of histologically proven CCC that was misdiagnosed as high-grade serous cystadenocarcinoma, the frozen section review revealed that there was extensive papillary growth with high nuclear grade and lack of clearing in the cytoplasm (►Fig. 2A and B). Literature also mentions that occasional ovarian CCCs might have a pronounced papillary architecture that mimics a serous borderline tumor at frozen section on low power examination.[7]

Both being aggressive in nature with high nuclear grade, the different morphologic clue to the distinguish CCC from HGSC may be tubulo-cystic pattern along with papillary fronds, hyalinized fibrovascular core and presence of adjacent endometriosis (generally seen in 25% of cases). Having high nuclear grade in both the conditions, the diagnostic clue of CCC could be tubule-cystic pattern, hyaline fibro vascular core along with adjacent areas of endometriosis if present, hyaline bodies, present in 25% of cases can be of great help. CCC shows lesser mitoses than other high-grade ovarian carcinomas (usually <5/10 high-power fields [HPFs]). High-grade serous carcinoma shows papillary and solid growth

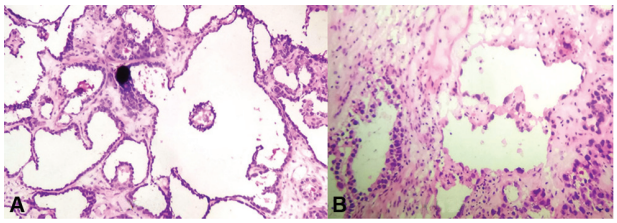

Fig. 1 **A** Multiple cystic spaces lined by cells with very minimal atypia in clear cell carcinoma lead to misdiagnosis of serous cystadenoma. **B** Review slide shows cystic spaces lined by hobnailed cells under diagnosed by pathologist.

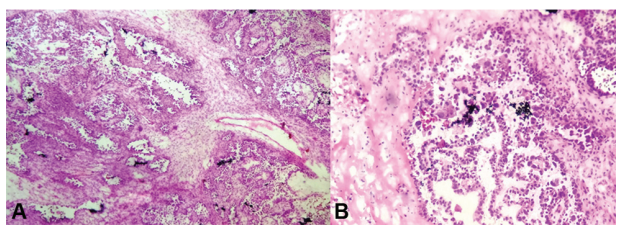

Fig. 2 **A** and **B** Tubular and papillary pattern misinterpreted as high-grade serous adenocarcinoma.

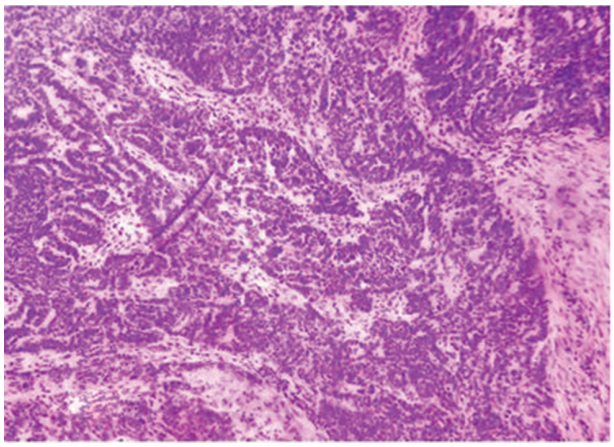

Fig. 3 Fused and long papillae of high-grade serous adenocarcinoma.

with slit-like glandular spaces and high mitotic activity (greater than 12/10 HPF)[8] (►Fig. 3).

Having high nuclear grade in both the conditions, the diagnostic clue of CCC could be tubule-cystic pattern, hyaline fibro vascular core along with adjacent areas of endometriosis if present, hyaline bodies, present in 25% of cases can be of great help. CCC shows lesser mitoses than other high-grade ovarian carcinomas (usually <5/10 high-power fields [HPFs]). High-grade serous carcinoma shows papillary and solid growth with slit-like glandular spaces and high mitotic activity (greater than 12/10 HPF)[8] (►Fig. 3).

The other major discordance was seen in three cases of mucinous borderline tumors that on histopathology were mucinous carcinoma. As literature also mentioned borderline tumor has got low sensitivity due to sampling error because of their unproportionately large size,[9] we also have missed out invasive components in these three cases. It would worth mentioning that expansile type of growth pattern under microscopy may sometimes leads to misdiagnosis (►Fig. 4).

In two cases, frozen section diagnosis was given as benign cyst but the exact typing was inconclusive due to the loss of

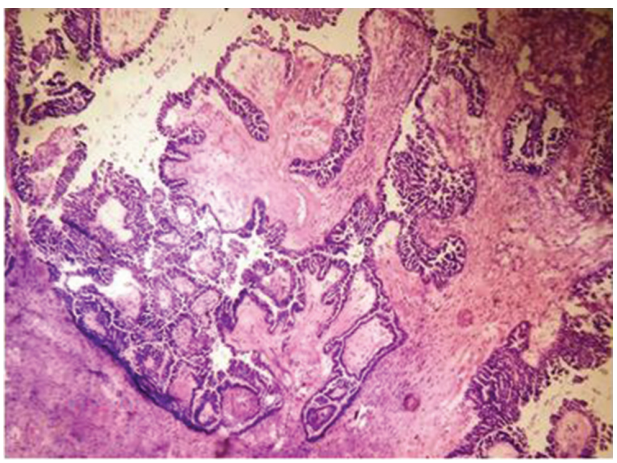

Fig. 4 Borderline ovarian tumor with missed microinvasion due to sampling error.

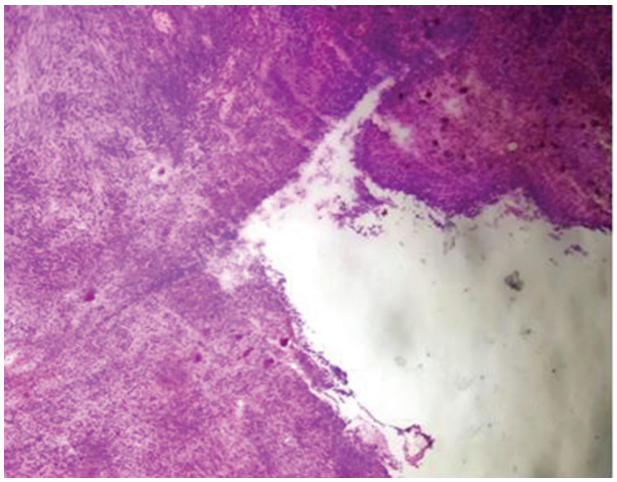

Fig. 5 Endometriotic cyst without proper lining epithelium and missed foci of endometrial glands due to inflammation.

lining epithelium because of the freezing artifacts and the histopathological diagnosis of the same was given as endometriotic cyst (►Fig. 5).

Many studies mentioned that several factors could influence the accuracy of frozen section diagnosis, such as histologic type, tumor size, patient characteristics, and the reporting pathologist's experience.[5,10–12] This held true for borderline tumors especially mucinous neoplasms in which we have seen a low positive predictive value in our study.

A multivariate analysis also reports the poor predictors of misdiagnosis in borderline tumors are such as mucinous subtypes, smaller tumor size (< 10 cm), borderline component less than 10%, and the pathologist's experience.[13]

Houck et al found that age > 35 years, histologic type, tumor size >20 cm, and unilateral tumors were the main predictors of misdiagnosis of borderline ovarian tumors.[14] However, study done by Brun et al found that the pathologist's experience was a major determinant of diagnostic accuracy or inaccuracy.[13]

To lessen the chances of sampling error, performing multiple sections of at least one section for every 8 to 10 cm size of the mass is recommended in the frozen section diagnosis of mucinous ovarian tumors.[15–17]

The recommended minimum number of sections for IFS diagnosis was 2 to 3 and for borderline, it was little more in numbers for their unusually bigger size. Sampling for frozen section analysis must include any solid, papillary excrescences or thickened cyst wall or thickened septa areas that are grossly suspicious. One should not overlook the area of hemorrhage and necrosis as just hemorrhagic cyst, because there may be clue to CCC or seromucinous carcinoma. In such cases, extra one to two sections are reasonable and justifiable.[18]

Lastly, while reporting borderline tumor in IPS, a note stating that invasion would be ruled out in permanent sections only after additional extensive sampling. Lastly, while reporting borderline tumor in IPS, a note to be mentioned ,stating that invasion would be ruled out in permanent sections only after additional extensive sampling.

Conclusion

IFS plays a vital role in the management of patients with ovarian neoplasm. An accurate interpretation of IFS in ovarian epithelial malignancy specially in benign and malignant case can be achieved, but limited in borderline tumors. In such cases, a definitive diagnosis should be awaited until the evaluation of permanent sections after communicating the difficulties with the operating surgeon. In addition, alteration of certain cytological and architectural features in frozen sections might lead to erroneous diagnosis. So, with the awareness of the artifacts and the limitations in mind, the IFS diagnosis can be of great help for proper management of the ovarian neoplasm.

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Conflict of Interest
None declared.

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