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Evaluation of a step-by-step approach to frozen section diagnosis in ovarian masses

Ashumi Gupta[1], Neelam Jain[2]

[1]Associate Professor, [2]Assistant Professor, Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India

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ABSTRACT

Background: Ovarian cancer forms a significant proportion of cancer-related mortality in females. It is often detected late due to non-specific clinical presentation. Radiology and tumor markers may indicate an ovarian mass. However, exact diagnosis requires pathological evaluation, which may not be possible before surgery. Intraoperative frozen section (FS) is, therefore, an important modality for the diagnosis of ovarian masses. **Aims and Objectives:** This study was conducted to study step-by-step approach along with diagnostic utility and accuracy of intraoperative FS in diagnosis of ovarian masses. **Materials and Methods:** Retrospective comparative analysis was done to determine the diagnostic accuracy of FS as compared to routine histopathology in the pathology department of a tertiary care hospital. Diagnostic categorization was done into benign, borderline, and malignant. Overall accuracy, sensitivity, and specificity of FS technique were calculated. **Results:** Out of 51 cases, FS analysis yielded accurate diagnosis in 94.1% of ovarian masses. Intraoperative FS had a sensitivity of 94.7%, specificity of 96.9%, 3.1% false-positive rate, and 5.3% false-negative rate in malignant tumors. In benign lesions, FS had 91.7% sensitivity and 100% specificity. FS had 75% sensitivity and 96.4% specificity in cases of borderline tumors. **Conclusion:** FS is a fairly accurate technique for intraoperative evaluation of ovarian masses. It can help in deciding the extent of surgery. It distinguishes benign and malignant tumors in most cases with high sensitivity and specificity. A methodical approach is useful in determining accurate diagnosis on FS diagnosis.

Key words: Accuracy; Frozen section; Ovarian tumors

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INTRODUCTION

Ovarian cancers account for 3.4% of all malignancies in women worldwide. It is one of the most lethal malignancies in females and presents a high burden of mortality.[1] Following breast and cervix, ovary is the third most common site for cancer in India, accounting for around 6% of all cancers in Indian women. It occurs more frequently in women aged between 45 and 65 years.[2] The patients may be asymptomatic or have non-specific symptoms such as abdominal fullness, bloating sensation, weight loss, and urinary frequency. Uncommonly, ovarian tumors may be accompanied by paraneoplastic syndromes such as recurrent venous thrombosis, seborrheic keratosis, or subacute cerebellar degeneration. Sex cord stromal tumors may manifest as hormone effects such as virilization.[3] Variable presentation and non-specific symptoms, may lead to late detection of ovarian cancer at an advanced stage, contributing to poor outcome.

Genetic and familial risk factors have been implicated in the development of ovarian cancers, and importance of careful clinical assessment including personal and family history cannot be emphasized more. Ultrasonography is usually the first line of investigation that may point toward the ovarian origin of mass and its cystic and/or solid nature. CA-125 is the most commonly used tumor marker in cases of suspected ovarian malignancy. However, it is neither very sensitive nor specific in distinguishing malignant ovarian tumors from benign lesions. Other tumor markers include serum alpha-fetoprotein, beta-human chorionic

Address for Correspondence:
Dr. Neelam Jain, Assistant Professor, Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan - 313 001, India. **Mobile:** +91-9950325218. **E-mail:** neeljain05@gmail.com

gonadotropin in germ cell tumors, and inhibin in sex cord stromal tumors.[3]

Further workup includes computerized tomography and/or magnetic resonance imaging.[4] In early stage ovarian cancer, surgery is potentially curative. Chemotherapy may be have to be added in advanced stage.[3] Intraoperative staging is done for malignant and borderline tumors with omentectomy, peritoneal washings, peritoneal biopsy, abdominal hysterectomy and bilateral salpingo-oophorectomy, and biopsy from retroperitoneal lymph nodes.[4] Frozen section (FS) can provide important information intraoperatively so that patients with benign ovarian lesions are spared from the morbidity associated with surgical staging.[5] Furthermore, fertility preservation may be valuable, particularly in younger patients, and extent of surgery can be decided with the help of FS.[5] At the same time, optimal staging may be performed once the diagnosis of borderline/malignant tumor is given on FS.[4] Subsequent histopathological examination (HPE) of the resected tissues is the diagnostic gold standard and guides the clinician in deciding further patient management.[4] FS has been used for head and neck, thyroid, and gynecological malignancies for intraoperative pathological assessment with reasonable accuracy.[6,7]

This study was conducted to study step-by-step approach and to determine the overall diagnostic accuracy and utility of intraoperative FS in ovarian masses, in a tertiary care hospital in Southwest Rajasthan.

Aims and objectives

This study aims to study step-by-step approach and to determine accuracy and diagnostic utility of intraoperative FS in ovarian masses.

MATERIALS AND METHODS

It was a retrospective study conducted in the Department of Pathology, Geetanjali Medical College and Hospital, Udaipur in Southern Rajasthan, India, after approval of the Institutional Ethical Committee. Cases of ovarian masses that were received for FS from May 2017 to April 2021, over a period of 4 years, were included in the study. HPE of formalin-fixed paraffin-embedded (FFPE) sections was taken as gold standard for diagnosis. Records of FS and FFPE reports were retrieved. Clinical information, demographic details, radiological findings, and tumor marker levels including CA-125 and cytology findings were included from previous records as and when available.

The specimens sent intraoperatively were sampled for FS. Gross specimen was examined in detail. Representative tissue bits were taken varying in number from 2 to 6 were taken, and frozen immediately using optimal cutting temperature compound – Leica Tissue Freezing Medium. Sectioning was done using Cryostat Leica CM 1860UV at 3–6 μm thickness. Hematoxylin and eosin (H and E) staining by the rapid method was performed and the sections were examined under microscope. The cell type (epithelial, stromal, germ cell, or sex cord), presence or absence of invasion, and growth pattern were studied in detail to determine the categories as benign, borderline, and malignant categories. After FS diagnosis was completed, the tissue samples for FS and rest of the specimen were fixed in 10% formalin and complete grossing was done the next day after fixation. These sections were processed in automatic tissue processor Leica TP 1020 as routine FFPE sections and stained with H and E staining using autostainer Thermo Scientific Gemini AS. Reporting was done as per routine protocol after FFPE sections were submitted after processing. Diagnosis on FFPE sections was considered as the gold standard with which diagnosis on FS was compared. Overall accuracy, sensitivity, specificity, false-positive rate, false-negative rate, positive predictive value, and negative predictive value were calculated. Concordant diagnostic categorization was considered true positive. In benign tumors, diagnosis of borderline or malignant tumor on FS was taken as false positive. In borderline tumors, diagnosis of benign tumor on FS was taken as false negative. In malignant tumors, benign or borderline categorization on FS was taken as false negative.[8]

RESULTS

A total of 51 cases were included in the study, with age ranging between 16 and 84 years. Mean age at presentation was 44.5 years. A large proportion of patients (47.1%) presented in the age ranging from 40 to 60 years followed by 21–40 years (37.3%). Few patients presented in <20 years and >60 years of age. Age distribution in benign, malignant, and borderline tumors showed wide variability (Table 1). Ascites was present in 12 out of 19 cases of malignant ovarian tumors and in 11 cases of benign lesions. The size ranged from 3.2–48 cm (Table 1).

On gross examination, the appearance of ovarian tumors varied from cystic uniloculated or multiloculated, solid cystic tumors, and solid tumors. Among malignant tumors, maximum cases (94.7%) had a solid component with or without cystic areas, whereas some tumors were largely cystic (5.3%). Solid cystic appearance of a malignant ovarian mass is shown in Figure 1. Borderline epithelial tumors on gross examination were solid-cystic (40%) and cystic (60%). Appearance of benign ovarian lesions showed varied gross appearance. Benign epithelial tumors were predominantly cystic. Fibromas and fibrothecomas had

a predominantly solid yellowish to whitish homogenous cut surface, while teratomas had a solid cystic cut surface. Size of the mass more than 10 cm did not show significant correlation with the presence of malignancy, as many of benign tumors were also large in size.

Neoplastic masses (78.4%) constituted the maximum number of cases (Table 2), while non-neoplastic lesions such as endometriosis, benign hemorrhagic cyst, and stromal edema were seen in 11 cases (21.6%). Eleven cases (27.5%) were bilateral and 29 (72.5%) were unilateral (72.5%). Histopathological features were studied in detail and categorization of tumors was done accordingly (Figure 2).

Epithelial tumors were the most common category (56.8%) including serous tumors (35.3%), mucinous tumors (13.7%), Brenner tumors (3.9%), and clear cell carcinoma (3.9%).

Table 1: Age and size of ovarian lesions at presentation

	Benign	Borderline	Malignant
Age (years)			
Range	18–71	16–54	23–84
Mean±SD	46.0±14.6	27.6±15.8	47.1±14.7
Size (cm)			
Range	3.2–25	16–48	4–27.5
Mean±SD	11.7±6.5	25.8±13.9	13.2±7.0

Table 2: Diagnostic categorization of ovarian masses

Category	N	%
Neoplastic		
Epithelial tumors		
Serous cystadenoma	5	9.8
Papillary serous cyst adenofibroma	1	2.0
Serous borderline tumor	3	5.9
Serous cystadenocarcinoma	9	17.6
Mucinous cystadenoma	3	5.9
Borderline mucinous tumor	2	3.9
Mucinous cystadenocarcinoma	2	3.9
Brenner tumor	2	3.9
Clear cell carcinoma	2	3.9
Germ cell tumors		
Teratoma	3	5.9
Sex cord stromal tumor		
Fibrothecoma	3	5.9
Granulosa cell tumor	3	5.9
Metastases		
Endometrial adenocarcinoma	1	2.0
Poorly differentiated carcinoma	1	2.0
Non-neoplastic		
Tuberculosis	1	2.0
Endometriosis	3	5.9
Hemorrhagic corpus luteum	1	2.0
Stromal edema and HGE	1	2.0
Stromal edema	1	2.0
Hemorrhagic cyst with torsion	1	2.0
Negative for malignancy	3	5.9
Total	51	100.0

Second most common group was sex cord stromal tumors (11.8%) followed by teratomas (5.9%) and metastases. Sub-categorization of ovarian masses is shown in Table 2.

Diagnoses of FS were compared with that of FFPE sections (Table 3). Out of 51 cases, on FS, 29 were diagnosed as benign lesions, three as borderline tumors, and 19 as malignant tumors. HPE of FFPE tissue sections revealed 27 benign lesions, five borderline tumors, and 19 malignant tumors. Out of 29 cases diagnosed benign on FS, 27 were benign on FFPE sections and two cases was underreported on FS. Out of 19 cases reported as malignant on FS, 18 were reported as malignant tumors on FFPE sections, while one was reported as borderline tumor. Out of five cases of borderline tumors on FFPE, three were diagnosed correctly on FS. One case was underreported as benign and one was overreported as malignant on FS.

Overall accuracy of FS for correct categorization of ovarian masses was 94.1%, with 94.7% sensitivity and 96.9% specificity in diagnosing malignant tumors, and 91.7% sensitivity and 100% specificity in diagnosing benign lesions (Table 4). For borderline tumors, FS had slightly lower sensitivity at 75%.

A methodical approach (Figure 3) by integrating the clinical and radiological details and other important investigations with the gross and histopathological features yielded accurate characterization in most cases.

DISCUSSION

Ovarian tumors can be classified into surface epithelial tumors, sex cord stromal tumors, and germ cell tumors.

Table 3: Diagnosis of benign, borderline, and malignant tumors on FS and FFPE sections

FS diagnosis	FFPE diagnosis			
	Benign	Borderline	Malignant	Total
Benign	27	1	1	29
Borderline	0	3	0	3
Malignant	0	1	18	19
Total	27	5	19	51

FS: Frozen section, FFPE: Formalin-fixed paraffin embedded

Table 4: Sensitivity, specificity, FPR, and FNR of frozen section in diagnosis of ovarian masses

	Benign	Borderline	Malignant
Sensitivity	91.7%	75%	94.7%
Specificity	100%	96.4%	96.9%
FPR	0	3.6%	3.1%
FNR	8.3%	25%	5.3%

FPR: False-positive rate, FNR: False-negative rate

Surface epithelial tumors are further categorized into benign, borderline, and malignant tumors. Germ cell tumors and sex cord stromal tumors can be benign or malignant. The distinction between benign, borderline, and malignant ovarian tumors is important to predict the prognosis as well as decide the management of the patient. Radiology can help in determining site and extent of tumor, but has limited value in exact characterization of ovarian neoplasms.[9]

Estimation of CA-125 is a part of routine workup of patients with suspected ovarian tumors. However, it has low specificity and sensitivity in differentiating benign lesions from malignant ovarian tumors.[10,11] CA-125 can be raised in non-neoplastic conditions such as adenomyosis and endometriosis, and in benign tumors such as leiomyoma of uterus.[11]

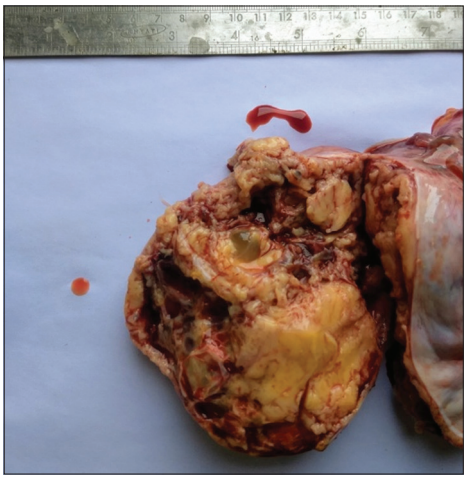

Figure 1: Gross appearance of malignant ovarian mass with solid cystic cut surface and areas of hemorrhage

Gross evaluation constitutes an important part of pathological examination of ovarian masses. Most of malignant tumors in our study showed a solid component with or without cystic areas, and few were cystic on gross appearance. Solid component can be detected in most of the malignant ovarian tumors.[12] and adequate sampling from solid areas or thickened areas may yield representative histopathology facilitating and accurate diagnosis on FS. Benign surface epithelial tumors are largely cystic, whereas stromal tumors such as fibrothecomas are solid with homogenous firm whitish to yellowish cut surface. Granulosa cell tumors are usually solid cystic. Germ cells tumors such as teratomas are usually cystic with or without solid areas, and the latter should be sampled to rule out immature component. Borderline tumors may are usually cystic, with or without solid areas, and thorough sampling needs to be done to rule out invasion. Presence of hemorrhage and necrosis may be seen in some of the malignant tumors. Sometimes, large ovarian tumors may undergo torsion with hemorrhagic infarction.

HPE of the resected tumor is the ultimate tool in diagnosis of ovarian tumors and additional investigations such as immunohistochemistry (IHC) may be required in some cases. However, FS can provide useful information intraoperatively for determining extent of surgery. FS technique is indicated intraoperatively for tumor diagnosis to decide the surgical management and evaluation of margins. It has been used widely in head-and-neck cancer. In cases where the site of origin is not clear in cytology, FS may be useful. It may be valuable for intraoperative confirmation of malignancy in cases where a pre-operative biopsy is unavailable.[6] FS is indicated where pre-operative diagnosis is not clear to determine the nature and malignant

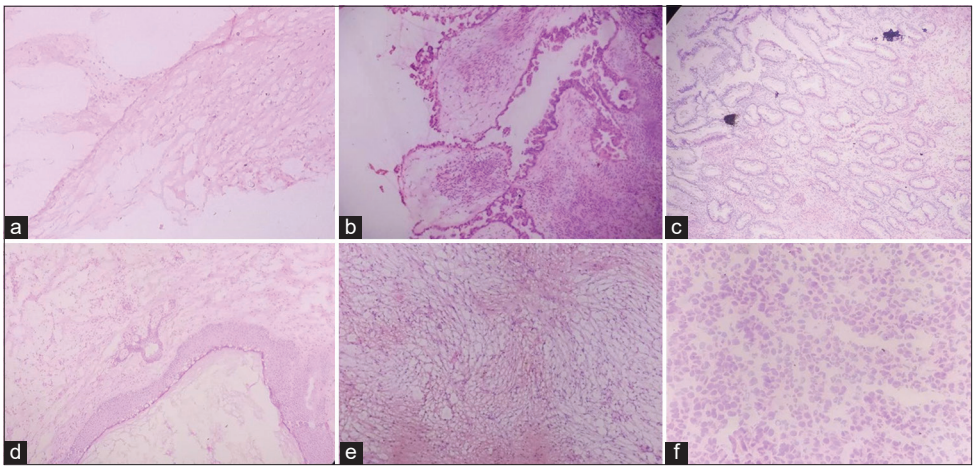

Figure 2: Histopathological features of ovarian tumors on FS; (a) serous cystadenoma: Cyst lined by flattened to cuboidal benign epithelium (H & E ×40); (b) serous borderline tumor: Lined by stratified epithelium with tufting and micropapillary architecture (H & E, ×10); (c) mucinous carcinoma: Neoplastic glands lined by mucinous epithelium with low-grade nuclear features (H & E, ×10); (d) teratoma: Stratified squamous epithelium and sebaceous glands (H & E, ×20); (e) fibrothecoma: Fascicular pattern with spindle cells and bland nuclei (H & E, ×10); (f) granulosa cell tumor: Uniform cells with bland appearing nuclei arranged diffusely and in cords (H & E, ×40)

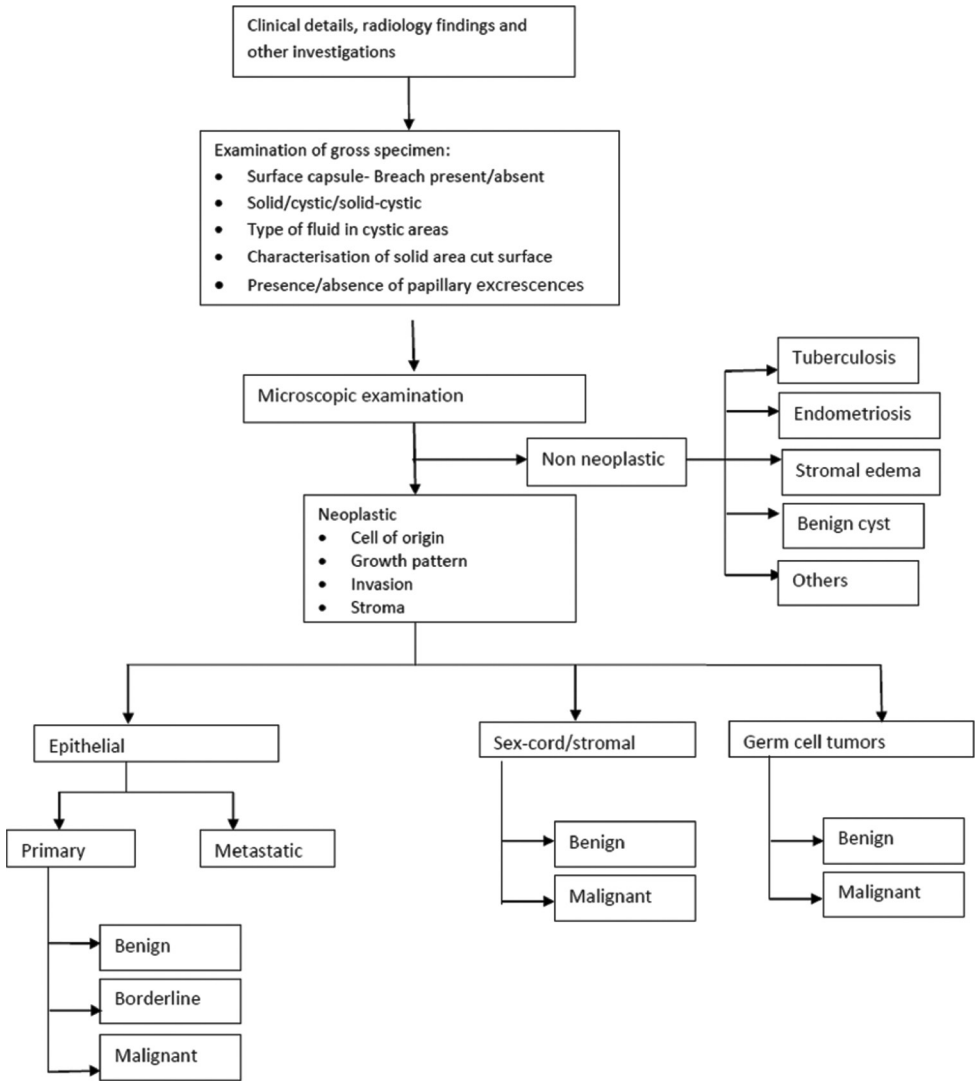

Figure 3: Step-by-step approach to frozen section diagnosis of ovarian masses

potential of ovarian masses.[8] FS has been found to be a reliable technique in gynecological neoplasms including endometrial and cervical cancer. In ovarian tumors, the diagnosis may not be established before surgery in many cases, and therefore, FS may provide important diagnostic information, which may guide the extent of surgery.[7]

FS allows microscopic examination of tissue in minimum time. In ovarian neoplasms, usually the excision specimen is sent for FS. Gross examination of tumor is available to the pathologist, and it can provide important clue to the diagnosis of ovarian masses. Frozen artifact may at times alter the morphology and make tissue interpretation difficult. In cases where large numbers of sections need to be sampled, final diagnosis may be made on the FFPE sections.

Incorporation of clinical data with available investigations, radiology findings, and operative findings can provide useful information. Proper gross evaluation with representative sampling by an experienced pathologist cannot be emphasized more. The microscopic examination should be done with the evaluation of architectural pattern, cytological features, and stromal characteristics. Methodical approach can guide the pathologist in interpretation of the histopathological features. First and foremost, categorization into neoplastic or non-neoplastic lesions needs to be done, followed by further subtyping. Non-neoplastic cases can be given appropriate diagnoses as per their morphological features. In neoplastic lesions, tumor architecture, pattern of growth, cellular and nuclear features, mitotic activity, presence or absence of invasion, and stromal characteristics should be examined in detail. Neoplasms can be subdivided as per their cell of origin, followed by further categorization into benign and malignant, as that is the most important piece of information a surgeon needs at an intraoperative stage to decide plan of immediate surgical management.

Borderline epithelial neoplasms may be difficult to accurately categorize on FS section in some cases. Such cases may be reported as at least borderline if invasion cannot be categorically commented on FS.[8] In some cases, particularly if suspicious areas are equivocal for malignancy, the diagnosis may have to be deferred for further sampling after fixation and routine tissue processing for a conclusive diagnosis.[5]

FS is a fairly sensitive and accurate technique for categorization of ovarian masses.[4] Various studies have reported the accuracy of FS in ovarian neoplasms ranging from 83% to 94.3% with high sensitivity and specificity.[5,12-15] During our study, accurate diagnostic categorization was possible in most cases (94.1%). For benign cases, FS was fairly sensitive (91.7%) and specific (100%). For malignant lesions, FS has a high sensitivity (94.7%) and specificity (96.9%) with low false-positive rate (3.1%) and false-negative rate (5.3%). These results are similar to the previous studies.[5,12-14] There were five cases of borderline ovarian tumors, out of which three were diagnosed correctly on FS. Borderline epithelial tumors can be difficult to diagnose on FS. Gross specimen is usually cystic with multiple loculations. As the nuclear atypia may be mild in benign and borderline tumors, multiple tissue sections may be required for definite diagnosis. Limited sampling in FS may pose a challenge in diagnosing such cases and definite categorization relies on FFPE sections. Underdiagnosis of malignancy may be a concern in borderline tumors, as mucinous tumors of the ovary are often heterogeneous, and further sampling may yield tissue sections with invasive component.[5,12] Large mucinous tumors with borderline component may be problematic.[13] Microscopic invasion may be difficult to assess on FS, due to artefactual aberrations. Any solid areas should be sampled and examined microscopically to rule out malignancy. The number of borderline tumors in our study was less and a larger study may help determine the exact accuracy of FS in cases of borderline epithelial tumors of the ovary.

In one case, differential diagnosis of primary ovarian versus metastatic carcinoma was kept. The ovaries were bilaterally enlarged with gray-white firm cut surface. Serum CA-125 and carcinoembryonic antigen levels were both raised. Final histopathology revealed a poorly differentiated adenocarcinoma. Careful gross and microscopic examination may indicate the origin of epithelial malignancy whether primary or metastatic. Bilateral involvement, multinodularity, surface involvement, and signet ring morphology of tumor cells are known to favor metastatic origin rather than primary ovarian carcinoma.[16] In some cases, the primary site of origin may not be ascertained radiologically, and IHC may be required for confirmation. IHC may help in distinguishing between primary ovarian carcinomas and adenocarcinomas of gastrointestinal origin.[17]

Teratomas are another group of tumors that may have different morphology in different areas. We came across a case of ovarian mass wherein the sections on frozen showed areas of mature teratoma with stratified squamous epithelium, skin adnexal structures, respiratory type epithelium, islands of mature cartilage, adipose tissue, and bone. However, on gross examination, the tumor was largely solid and a high suspicion for immature component was kept. After fixation, extensive sampling was done and subsequent FFPE sections revealed few areas with immature neuroepithelium indicating a Grade-I immature teratoma. The previous studies have reported discrepancies in FS results of teratoma, similar to our study. The area with immature component may not be sampled during FS and may be missed. Diagnosis in these cases requires adequate sampling, and final histopathological evaluation may be required for accuracy.[5]

Sometimes, the ovarian tumors can undergo necrosis or infarction that may be extensive and viable areas may be difficult to obtain on FS.[5] There may be hemorrhage and sometimes torsion in large masses, which may prevent accurate interpretation on FS, when extensive. Such cases may need more than adequate number of sections after fixation, to detect viable tumor areas, if present.

Apart from sampling error, other difficulties encountered by the pathologist during FS analysis includes frozen artifact. The tissue should be frozen immediately, as soon as it is received in the laboratory. Formation of ice crystals during frozen technique may result in suboptimal sections with morphological artifact and interpretation may be difficult.[5] Furthermore, time poses a constraint in FS diagnosis, particularly in cases that need extensive sampling.

In spite of multiple limitations and challenges, FS technique is a fairly sensitive tool to detect ovarian malignancy. Intraoperative FS gives the pathologist the opportunity for gross examination, and quick HPE of tissue, with determination of the nature of ovarian mass. The extent of surgery can thus be limited to an adequate excision, at the same time preventing overtreatment.

Limitations of the study

Further studies with a larger sample size would enhance the current understanding, particularly with regard to borderline tumors. Borderline epithelial tumors are one of the challenging areas in frozen section diagnosis. We encountered 5 cases of borderline tumors which is a small number. Also, inclusion of another pathologist for HPE reporting, blinded to the FS diagnosis could have removed the element of bias.

CONCLUSION

FS is a sensitive and specific technique for intraoperative evaluation of ovarian masses and accurate categorization is possible in most cases by following a step-by-step approach. Intraoperative FS allows correct categorization of ovarian masses in most cases and may provide important information to the surgeon, allowing him to take appropriate surgical decision. Borderline tumors and teratomas are a potential diagnostic pitfall in FS assessment of ovarian masses and final diagnosis may require FFPE sections in some cases.

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Authors Contribution:
AG – Concept and design of the study and manuscript preparation and revision; **NJ –** Statistical analysis, result interpretation, and manuscript preparation.

Work attributed to:
Geetanjali Medical College and Hospital, Udaipur - 313 001, Rajasthan, India.

Orcid ID:
Dr. Ashumi Gupta - https://orcid.org/0000-0003-4207-502X
Dr. Neelam Jain - https://orcid.org/0000-0003-4134-681X

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