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Integration of Biomarkers, Sonographical Findings, Frozen Section with Histopathological Analysis in Ovarian Neoplasms: A Tertiary Care Center Perspective

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ABSTRACT
Ovarian cancer, the third most common malignancy among women in India, presents with high mortality rates due to late diagnosis. Intraoperative frozen section analysis plays a pivotal role in surgical management by providing a rapid histopathological diagnosis. This study evaluates the accuracy of frozen section diagnosis in comparison to final histopathological diagnoses and its role in guiding surgical decisions for ovarian lesions. Aim of the study was to assess the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of frozen section diagnosis for ovarian tumors. Additionally, the study aims to correlate frozen section findings with preoperative biomarkers and imaging results. This retrospective study was conducted at the Department of Pathology, Vydehi Institute of Medical Sciences and Research Center, Bangalore, over 18 months (January 2023 to June 2024). A total of 57 cases of ovarian lesions underwent frozen section analysis. Relevant clinical, biomarker and radiological data were collected. Frozen sections were compared to final diagnoses made from formalin-fixed paraffin-embedded (FFPE) sections. Diagnostic accuracy measures, including sensitivity, specificity, PPV and NPV, were calculated. The study found that frozen section diagnosis had a sensitivity of 94%, specificity of 96%, PPV of 95% and NPV of 97%. A concordance rate of 96.5% was observed between frozen section diagnoses and final histopathological diagnoses. The most common ovarian lesions diagnosed were serous borderline tumors (14.04%) and mucinous cystadenomas (12.28%). Two cases were discordant, including one of lymph angiomatous vascular proliferation and another of a follicular cyst. Biomarker analysis showed wide variation in CA-125 levels, with a mean value of 140.05U/ml, but this was not always correlated with malignancy. Frozen section diagnosis is a highly reliable tool for the intraoperative assessment of ovarian lesions, with high sensitivity and specificity. While it plays a crucial role in surgical management, especially for real-time decision-making, diagnostic limitations exist, particularly for complex lesions like mucinous and borderline tumors. Further research with larger sample sizes is recommended to refine diagnostic accuracy in these challenging cases.

INTRODUCTION

Ovarian cancer is the third most common malignancy among women in India, contributing to 6.7% of all cancer cases in women[1]. The disease is associated with a high mortality rate, largely because it is often diagnosed at an advanced stage. Ovarian neoplasms are highly heterogeneous and include a broad range of tumor types. According to the 2020 World Health Organization (WHO) classification, ovarian tumors are categorized into surface epithelial tumors, germ cell tumors, sex cord-stromal tumors and other carcinomas[2]. Due to this wide range of pathologies, accurate diagnosis and timely intervention are critical for improving patient outcomes in ovarian cancer management. Surgical intervention remains the cornerstone of ovarian cancer treatment, and intraoperative frozen section analysis is a valuable tool used during surgery to provide a rapid histopathological diagnosis[3]. This technique allows surgeons to make informed, real-time decisions about the extent of surgery by determining whether an ovarian lesion is benign, borderline, or malignant. Frozen section analysis plays a vital role in ensuring comprehensive surgical staging, particularly when malignancy is suspected but unconfirmed. For younger women, it can also guide decisions regarding conservative, fertility-sparing surgeries[4]. Intraoperative frozen section analysis helps minimize the risks of both over treatment and under treatment. If a lesion is found to be benign, unnecessary radical surgeries can be avoided, preserving fertility when possible[5]. Conversely, if a lesion is malignant, more extensive procedures, such as comprehensive staging or debulking, can be performed to ensure complete treatment. This approach prevents the need for additional surgeries, reducing morbidity and improving patient outcomes. Despite the high accuracy of frozen section diagnosis, discrepancies between frozen section results and final histopathological diagnoses are reported in some studies, particularly in mucinous and borderline tumors[6]. Mucinous ovarian tumors are challenging due to their large size, heterogeneity and the frequent presence of benign, borderline and malignant components within the same tumor. This can lead to sampling errors and misinterpretation. Similarly, borderline ovarian tumors, which show increased cellular atypia but lack stromal invasion, are difficult to classify accurately during frozen section analysis[7]. These diagnostic challenges are clinically significant, as under-diagnosis may lead to suboptimal surgery, while over-diagnosis could result in unnecessarily radical procedures, potentially compromising fertility. In addition to frozen section analysis, preoperative diagnostic tools like serum CA-125 levels and radiological imaging are crucial for the early diagnosis of ovarian neoplasms. Elevated CA-125 levels are commonly associated with epithelial ovarian cancers, particularly in advanced stages and are used to monitor disease progression and response to treatment. However, CA-125 alone is not definitive for diagnosis, as it can be elevated in benign conditions such as endometriosis[8]. Radiological imaging techniques, including transvaginal ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), are essential for evaluating ovarian masses. These imaging modalities, used in conjunction with serum biomarkers, aid in assessing tumor size, morphology and characteristics such as solid or cystic components, papillary projections and internal septations. This comprehensive approach supports preoperative planning and helps differentiate between benign and malignant lesions[9]. The primary aim of this study is to evaluate the accuracy, sensitivity, specificity, and predictive values of intraoperative frozen section analysis for ovarian tumors by comparing it with final histopathological diagnoses from paraffin-embedded sections. Additionally, the study seeks to correlate frozen section findings with preoperative biomarkers and imaging results, wherever feasible, to enhance the overall diagnostic process and improve patient management.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Pathology at Vydehi Institute of Medical Sciences and Research Center, Bangalore. Over a period of one and a half years, from January 2023 to June 2024, we analyzed frozen sections and corresponding paraffin-embedded sections of ovarian lesions. A total of 57 cases were included in this analysis.

Study Population: All patients who underwent frozen section analysis for ovarian lesions during the study period were included. Relevant details such as age, clinical history, baseline laboratory findings (biomarkers) and radiological investigations were collected from the medical records department.

Intraoperative Procedure: During intraoperative consultation, once the ovarian specimen was excised, it was immediately transported to the histology laboratory. In the lab, the specimen was grossly examined for parameters such as size, capsule integrity and consistency. Based on these gross findings, representative sections were chosen for further analysis.

Frozen Section Analysis: The selected tissue samples were frozen using an Epredia HM 525 NX cryostat machine at a temperature of -24°C. Sections with a thickness of 6-7µm were prepared and stained with hematoxylin and eosin (HandE). These stained slides were then examined under a light microscope by one

or more pathologists. During this process, relevant clinical data, biomarkers and radiological findings were collected and documented for each case.

Formalin-Fixed Paraffin-Embedded (FFPE) Analysis: After the initial frozen section analysis, the specimens were fixed in formalin. Additional representative sections were taken for routine tissue processing, paraffin embedding and subsequent HandE staining. The definitive diagnosis was made following a detailed microscopic examination of all the slides by one or more pathologists.

Diagnostic Criteria and Classification: Final histopathological diagnoses were made in accordance with the College of American Pathologists (CAP) protocol. Tumors were classified based on the 2020 World Health Organization (WHO) classification of ovarian neoplasms.

Comparative Analysis: The results from the intraoperative frozen section diagnosis were compared with the final histopathological diagnoses made from the paraffin-embedded sections. Discrepancies or agreements between the two diagnostic methods were documented.

Statistical Analysis: Cases were categorized as either concordant or discordant based on the comparison between frozen section and final histopathological diagnoses. The diagnostic accuracy of the frozen section analysis was calculated by determining sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in relation to the final histopathological diagnoses.

RESULTS AND DISCUSSIONS

Table 1: Demographics and Clinical History Table

Parameter	Count
Age Range (Years)	19 - 78
Mean Age (Years)	40.64
Symptoms	**Count**
Pain abdomen	16
Ascites	1
Menorrhagia	1
Bleeding PV	1
Pelvic Mass	1
Abdominal distension	3

The data presented in the (Table 1) show that the age of the patients ranged from 19-78 years, with a mean age of 40.64 years. The most common symptom reported was abdominal pain, seen in 16 patients. Other symptoms were less frequent, with ascites, menorrhagia, bleeding per vaginum (PV) and the presence of a pelvic mass, each being observed in only one patient. Additionally, 3 patients experienced abdominal distension. Ca 125 levels vary in different types of ovarian neoplasms. Serous ovarian tumors generally show higher levels than mucinous ones. In

Table 2: Biomarkers Table (CA-125 and Others)

Biomarker	Mean	Standard Deviation	Range
CA-125 (U/ml)	140.05	179.43	10 - 600
Other Biomarkers			
LDH (U/L)	534	N/A	Single Case
B-HCG (IU/L)	286	N/A	Single Case

our study the mean CA 125 levels was 140.05 with levels ranging from 10-600U/ml seen mostly in serous lesions with highest levels of 600U/ml observed in serous carcinomas. Mucinous neoplasms showed only mild elevation of CA 125 levels.Markers like LDH and HCG levels were elevated in Germ cell tumors like Dysgerminoma. On Ultrasound benign lesions showed thin walls, anechoic appearance and lack of solid components or septation. Borderline ones showed features like complex lesions with thick septations and solid areas. Whereas malignant ones showed complex multiloculated lesions, solid areas extending into pelvic cavity with ascites. Sexcord stromal tumors showed lobulated heterogenous mass of soft tissue(Table 2). This (Table 3) provides a detailed breakdown of the various ovarian lesions diagnosed histopathologically in the study. The ovarian lesions are classified by their tumor type (benign, borderline, malignant) across different categories, such as epithelial tumors, sex cord stromal tumors, germ cell tumors, mesenchymal tumors, metastatic tumors and non-neoplastic cysts. The number of cases and their corresponding percentage out of the total sample size (57 cases) are also listed. The majority of the lesions belong to the epithelial tumor group, where serous borderline tumors represent the most common subtype (14.04%), followed by mucinous cystadenomas (12.28%). Sex cord stromal tumors were dominated by fibromas, comprising 8.77% of the cases. Among germ cell tumors, mature teratomas were the most frequent. The presence of non-neoplastic cysts and lesions such as endometriosis cysts was also significant, making up 8.77% of the cases. The (Table 4) compares frozen section diagnoses with final histopathological diagnoses in 57 cases of ovarian lesions. A high concordance rate of approximately 96.5% was observed, indicating that in the majority of cases, the frozen section diagnosis matched the final diagnosis made from formalin-fixed paraffin-embedded (FFPE) sections. The most frequent diagnoses were serous borderline tumors (14.04%) and mucinous cystadenomas (12.28%), both showing concordance. Other commonly concordant diagnoses included benign sex cord stromal tumors (8.77%), endometriosis cysts (8.77%) and serous cystadenomas (3.51%). Out of the 57 cases, two were discordant: one frozen diagnosis of lymph angiomatous vascular proliferation, which differed from the final histopathology and a case of follicular cyst. Overall, the study confirms the reliability of frozen section analysis for intraoperative diagnosis of ovarian lesions, with only minor discrepancies. This table calculates the sensitivity,

Table 3: Histopathological Diagnosis of Ovarian Lesions

Histopathological Diagnosis	Tumor Type	No. of Cases	Percentage (%)
Epithelial Tumors			
Serous Cystadenoma	Benign	2	3.5%
Serous Borderline	Borderline	8	14.04%
Serous Carcinoma	Malignant	2	3.5%
Mucinous Cystadenoma	Benign	7	12.28%
Mucinous Borderline	Borderline	3	5.26%
Mucinous Carcinoma	Malignant	3	5.26%
Seromucinous Cystadenoma	Benign	4	7.02%
Endometrioid Carcinoma	Malignant	2	3.5%
Sex Cord Stromal Tumors			
Fibroma	Benign	5	8.77%
Germ Cell Tumors			
Mature Teratoma	Benign	3	5.26%
Immature Teratoma	Malignant	1	1.75%
Dysgerminoma	Malignant	1	1.75%
Mesenchymal Tumors			
Leiomyoma	Benign	3	5.26%
Metastatic Tumors			
Krukenberg Tumor	Malignant	1	1.75%
Non-Neoplastic Cysts and Lesions			
Follicular Cyst	Benign	1	1.75%
Simple Cyst	Benign	3	5.26%
Corpus Luteal Cyst	Benign	2	3.5%
Endometriotic Cyst	Benign	5	8.77%
Lymphangiomatous Vascular Proliferation	Benign	1	1.75%

Table 4: Frozen Section Diagnosis vs. Final Histopathological Diagnosis

Frozen Diagnosis	Final Histopathological Diagnosis	No. of Cases	Percentage (%)	Concordance
Mucinous Cystadenoma	Mucinous Cystadenoma	7	12.28%	Concordant
Benign Sex Cord Stromal	Fibroma	5	8.77%	Concordant
Serous Borderline	Serous Borderline	8	14.04%	Concordant
Benign Cyst	Simple Ovarian Cyst	4	7.02%	Concordant
Serous Cystadenoma	Serous Cystadenoma	2	3.51%	Concordant
Serous Carcinoma	Serous Carcinoma	2	3.51%	Concordant
Mature Teratoma	Mature Teratoma	3	5.26%	Concordant
Positive for Malignancy	Krukenberg Tumor / Mucinous Carcinoma / Endometrioid Carcinoma	5	8.77%	Concordant
Endometriotic Cyst	Endometriotic Cyst	5	8.77%	Concordant
Mucinous Borderline	Mucinous Borderline	3	5.26%	Concordant
Seromucinous Cystadenoma	Seromucinous Cystadenoma	4	7.02%	Concordant
Immature Teratoma	Immature Teratoma	1	1.75%	Concordant
Dysgerminoma	Dysgerminoma	1	1.75%	Concordant
Stromal Tumor	Leiomyoma	2	3.51%	Concordant
Benign Dermoid	Mature Teratoma	1	1.75%	Concordant
Benign Ovarian Tumor	Seromucinous Cystadenoma	2	3.51%	Concordant
Positive for Malignancy	Lymphangiomatous Vascular Proliferation	1	1.75%	Discordant
Mucinous borderline	Follicular Cyst	1	1.75%	Discordant
	Total	57	100%	

Table 5: Diagnostic Accuracy of Frozen Section Compared to Final Histopathology

Accuracy Measure	Value (%)
Sensitivity	94%
Specificity	96%
Positive Predictive Value	95%
Negative Predictive Value	97%

specificity, PPV and NPV of the frozen section diagnosis compared to the final histopathological diagnosis. The (Table 5) presents the accuracy measures of the frozen section diagnosis in comparison to the final histopathological diagnosis. The sensitivity of the frozen section diagnosis is 94%, indicating its ability to correctly identify positive cases. The specificity is 96%, reflecting its accuracy in ruling out negative cases. The positive predictive value (PPV) is 95%, meaning that 95% of the positive diagnoses made by the frozen section were accurate. Meanwhile, the negative predictive value (NPV) is 97%, showing that 97% of the negative diagnoses were correct. These values suggest a high level of accuracy and reliability in using frozen section diagnosis for identifying ovarian pathologies.

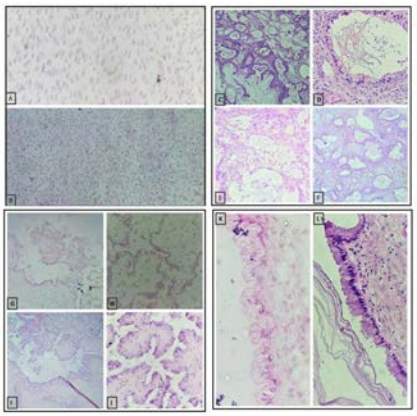

Fig. 1: Histopathological and Frozen Section Photomicrographs of Ovarian Lesions
Photomicrographs: **A-**Fibroma (Frozen section, 40×), **B**-Fibroma (Paraffin-embedded HandE section, 20×)., **C-F-**Mucinous Adenocarcinoma (Paraffin-embedded HandE sections)., **G-H-**Serous Borderline Tumor (Frozen section, 20× and 40X),

I-J-Serous Borderline Tumor (Paraffin-embedded HandE sections, 20× and 40×).,
K-Mucinous Cystadenoma (Frozen section, 40×),
L-Mucinous Cystadenoma (Paraffin-embedded HandE section, 40×) (Fig. 1).

The current study highlights the accuracy and utility of intraoperative frozen section diagnosis in the management of ovarian lesions. With a sensitivity of 94%, specificity of 96%, positive predictive value (PPV) of 95% and negative predictive value (NPV) of 97%, these findings suggest a high level of diagnostic reliability. This aligns well with previous studies which also emphasize the accuracy of frozen section analysis, particularly in identifying benign and malignant ovarian lesions[10]. However, as seen in prior research, challenges remain, especially in diagnosing mucinous and borderline ovarian tumors, where discrepancies are more common due to sampling limitations and tumor heterogeneity. The concordance rate of 96.5% observed in this study is consistent with earlier research, where concordance rates between frozen section diagnoses and final histopathological findings range from 85-97% depending on the study and type of tumor analyzed. Studies such as by De Decker *et al.* (2021) and Houck *et al.* (2000) report similar high concordance, especially for serous and mucinous cystadenomas and borderline tumors, where frozen section diagnosis can reliably match the final diagnosis[11,12]. However, the discordant cases in the present study lymph angiomatous vascular proliferation and a follicular cyst highlight the limitations of frozen section diagnosis in cases where the lesion presents with unusual his to logical features or is difficult to classify intra operatively. This study confirms the difficulties faced in diagnosing certain types of ovarian tumors, especially mucinous and borderline tumors. Earlier literature has pointed out that mucinous tumors, due to their large size, heterogeneous nature and presence of both benign and malignant components within the same tumor, often lead to discrepancies in frozen section diagnosis[13]. The current study supports this observation, suggesting that the diagnostic challenges of mucinous tumors remain a relevant concern. Similar findings have been reported by Storms *et al.* (2012), who noted that mucinous and borderline tumors are prone to under-or over-diagnosis during intraoperative consultation[14]. The present study also examined biomarkers such as CA-125, LDH and B-HCG. While CA-125 levels were elevated in several cases, they were not always directly correlated with malignancy, reflecting the limitations of CA-125 as a standalone diagnostic marker. This is consistent with studies like Charkhchi *et al.* (2020), which noted that while CA-125 is useful for monitoring ovarian cancers, it lacks specificity and can be elevated in benign conditions such as endometriosis[15]. The single measurements of LDH and B-HCG in this study were not statistically significant, likely due to the small number of cases in which these biomarkers were evaluated. Frozen section diagnosis plays a pivotal role in guiding intraoperative surgical decisions, particularly regarding the extent of surgery[16]. The current study confirms that accurate frozen section diagnosis can reduce the need for secondary surgeries, prevent over treatment, and aid in comprehensive surgical staging. This finding is supported by earlier studies, such as one by Zaiem[17], which demonstrated that intraoperative frozen section diagnoses reduce surgical morbidity by guiding immediate surgical decisions. Several studies have documented the accuracy and reliability of frozen section diagnosis in ovarian tumors. A study by Kennedy[18] reported sensitivity and specificity rates for frozen section diagnoses of 89% and 98%, respectively, in a large cohort of 1,000 ovarian tumor cases, which closely aligns with the current study's sensitivity (94%) and specificity (96%). Other studies, such as by Sukumaran[19], have pointed out the inherent challenges of diagnosing borderline and mucinous ovarian tumors using frozen section analysis. This study's findings echo those of Park *et al.* (2019) and Geomini *et al.,* (2005), who also observed a higher rate of diagnostic discrepancies in mucinous and borderline tumors, largely due to sampling issues and tumor heterogeneity[20,21].

CONCLUSION

The current study demonstrates the high diagnostic accuracy of frozen section analysis in ovarian lesions, with sensitivity, specificity, PPV and NPV values reflecting a high level of reliability. However, diagnostic discrepancies, particularly in mucinous and borderline tumors, remain a challenge, as supported by earlier research. The role of frozen section analysis in guiding intraoperative decision-making is invaluable, especially for ensuring appropriate surgical intervention and preventing unnecessary procedures. Although this study contributes to the growing body of evidence supporting the utility of frozen section diagnosis in ovarian pathology, further research with larger cohorts is needed to fully address the limitations observed, particularly in diagnosing complex tumors like mucinous and borderline lesions. A combined approach using biomarkers with structured ultrasound assessment helps guide clinical decision making such as need for surgical intervention and the extent of surgery required.

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