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Diagnostic accuracy of intraoperative frozen section in endometrial cancer: Correlation with final histopathology

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ABSTRACT

Purpose: Accurate intraoperative assessment of tumor characteristics for endometrial cancer, including histological type, grade, and depth of myometrial invasion (MI), is essential for determining the extent of surgery, particularly lymphadenectomy. This study aims to evaluate the concordance between intra-operative frozen section analysis (IFS) and final histopathology (FH) in endometrial cancer cases.

Methods: This retrospective analysis included 100 patients who underwent laparoscopic staging surgery for endometrial carcinoma between March 2018 and September 2024. Data on histological type, tumor grade, MI, lymph node involvement, and cervical/adnexal metastases were extracted from medical records. The diagnostic accuracy of IFS was assessed by comparing findings with FH. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen's kappa (κ) statistics were used to determine agreement levels.

Results: IFS demonstrated high concordance with FH for malignancy detection (97%, $\kappa = 0.56$). Sensitivity, specificity, PPV, and NPV were 96.9%, 100%, 100%, and 40%, respectively. Tumor grading agreement was 78.2% ($\kappa = 0.67$), with the highest accuracy in Grade 3 tumors (sensitivity 85.0%, specificity 98.3%). MI assessment showed strong agreement ($\kappa = 0.851$) with 93.7% overall accuracy. Lymph node evaluation by IFS exhibited excellent agreement ($\kappa = 0.942$), with 98.3% accuracy.

Conclusion: IFS is a reliable tool for intraoperative decision-making in endometrial cancer, particularly for malignancy detection, MI assessment, and lymph node evaluation. However, moderate concordance in tumor grading suggests caution in surgical decision-making based solely on IFS results. Future research should focus on optimizing frozen section protocols to improve diagnostic accuracy and streamline intraoperative management.

Introduction

Endometrial cancer is among the most frequently diagnosed malignancies in women across both high-income and low- to middle-income countries.[1] The standard treatment for endometrial cancer is a definitive surgical approach involving total hysterectomy along with bilateral salpingo-oophorectomy, which ensures the removal of the uterus, fallopian tubes, and ovaries.

Additionally, lymphadenectomy, involving the removal of pelvic and/or para-aortic lymph nodes, may be performed depending on

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the disease stage. However, its extent and impact on survival outcomes remain a subject of ongoing research, particularly in early-stage cases.[2] While some clinicians advocate for routine lymph node removal in all patients, others prefer a selective approach based on individual risk factors.[3]

In the majority of cases, tumor grade and histological subtype are initially assessed preoperatively through endometrial curettage or biopsy. However, intraoperative pathological evaluation, particularly frozen section analysis, has been shown to exhibit high sensitivity and specificity, significantly influencing surgical decision-making. Research suggests that frozen section assessments of endometrial tissue provide a reliable prediction of the final histopathological diagnosis, aiding in determining the appropriate extent of surgical intervention for each patient.[4]

While several studies have assessed the diagnostic accuracy of frozen section analysis, data from laparoscopic staging cohorts remain limited, especially in the Indian subcontinent. This study aims to bridge this gap by evaluating the concordance of frozen section and final histopathology in a tertiary care endoscopy centre.

Material and methods

This retrospective study included patients who underwent laparoscopic staging surgery at our institution for carcinoma endometrium from March 2018 to September 2024. Cases in which intraoperative frozen section analysis was not conducted, as well as those with incomplete medical records, were excluded from the study. Medical records were obtained from the hospital database and the baseline data was extracted. The frozen section and final histopathology records were noted. Although all cases had an endometrial biopsy preoperatively showing diagnosis of malignancy, preoperative imaging and biopsy studies have not been analyzed in the current study and the pathologists were blinded to the preoperative biopsy results.

The frozen-section examination data included histological type, tumor grade (categorized using a three-tier grading system for endometrial carcinoma, while serous carcinoma, clear cell carcinoma, and carcinosarcoma were all classified as grade 3), depth of myometrial invasion (MI), and assessment of cervical or adnexal involvement. The final histopathological diagnosis, including tumor grade, MI, and overall pathological findings, was analyzed and compared with intraoperative frozen section data. In cases where surgical staging involved lymphadenectomy, the pathological findings of the resected lymph nodes were also documented.

Pathology protocol: When the hysterectomy specimen was received for frozen section analysis, it was carefully inspected, measured, weighed, and then bivalved longitudinally through the cervical canal and endometrial cavity. Any ulcerative, polypoid, poorly defined, hemorrhagic, necrotic, solid, or infiltrative masses within the endometrial cavity were considered "suspicious for malignancy," and sections from these areas were taken for further evaluation. The uterine corpus was typically sectioned horizontally at approximately 5-mm intervals from the endometrial surface toward the serosa. Tumor size, location and depth of MI, were recorded. At least one full-thickness section from the area with the deepest grossly observed MI was submitted for frozen-section examination. One or two slides containing tissue sections were prepared and stained using a rapid H&E stain for microscopic analysis. In cases where no gross lesions were identified, a random section was submitted for IFS. In selected cases, frozen section analysis was performed on retroperitoneal lymph nodes, including pelvic and para-aortic nodes, to guide intraoperative decision-making. The decision to proceed with lymph node evaluation was based on multiple factors, including the intraoperative frozen section findings of the primary tumor,

Table 1
Baseline characteristics of study population.

Baseline parameters	N=100	
Age (years) (mean±SD)	58.50±8.86	
BMI (mean±SD)	30.8±6.16	
Parity [median (IQR)]	2 (2-2.5)	
Post menopausal	81	
Previous surgeries		
Appendectomy	3	
Cesarean section	21	
Cholecystectomy	2	
Comorbidities		
Diabetes	27	
Hypertension	41	
Hypothyroidism	10	
Previous history of malignancy	2	
Breast	2	
Thyroid	1	
Histopathology	Frozen section diagnosis N=100	Final histopathology N=100
Endometrioid adenocarcinoma	71	80
Adenocarcinoma	18	0
Serous	3	10
Endometrial hyperplasia	3	0
Poorly differentiated	1	3
Clear cell	0	4
Carcinosarcoma	2	1
No evidence of malignancy	2	2

the depth of myometrial invasion observed, and the surgeon's clinical assessment of lymph node involvement.

Statistical analysis: Cohen's unweighted κ statistic, along with 95% confidence intervals (CIs), was utilized to evaluate the level of agreement between frozen section analysis and the final histopathological diagnosis. Cohen's weighted and unweighted κ statistic, along with 95% CIs, was used to evaluate the level of agreement for tumour grade between the two groups. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of frozen section analysis in detecting malignancy, MI, and tumor grade were calculated, with the final histopathological interpretation serving as the gold standard. The data analysis was performed using the free web-based calculator: https://www.graphpad.com/quickcalcs/kappa1.

Results

Case records of 156 cases with a diagnosis of uterine neoplasm, operated at our centre were analysed. A total of 100 cases were included and 56 were excluded due to the absence of intraoperative frozen section evaluation (n = 28), incomplete clinical or histopathological data (n = 10), or a diagnosis of sarcoma (n = 12).

The mean age of study population was 58.50±8.86 (range: 40-83) years and a median (IQR) of 52 (58.5-65) years with a mean BMI of 30.8±6.16 kg/m^2. A majority of women were postmenopausal (81%). Twenty-six cases had history of previous abdominal surgery (Table 1). The most common histology noted in both the intra-operative frozen section analysis (IFS) and final histopathology (FH) was endometrioid adenocarcinoma (71% vs. 80%). The overall frozen section and histopathology results are shown in Table 1.

There was high concordance (97%) between IFS and FH for detection of malignancy with κ = 0.56, 95% CI, 0.12-1.00, suggesting moderate agreement (Table 2). Thus, the sensitivity of IFS was 96.9%, specificity of 100%, positive predictive value of 100% and negative predictive value of 40%. There were 3 cases of endometrioid adenocarcinoma which was reported as endometrial hyperplasia on IFS.

Tumour grade

The correlation between tumor grade for cases with a final diagnosis of carcinoma according to tumor grade interpretation by IFS is summarized in Table 3. A total of 74.0% cases were graded on IFS. The agreement rate for grading endometrial carcinomas between IFS and FH was 78.2% (Weighted κ = 0.72; κ = 0.67, 95% CI: 0.52–0.81). The diagnostic performance of frozen section evaluation in grading endometrial carcinoma varied across different tumor grades. For Grade 1 tumors, the sensitivity and specificity were 81.3% and 80.4%, respectively, with a PPV of 74.3% and a NPV of 86.0%. Grade 2 tumors demonstrated a sensitivity of 69.2% and specificity of 86.5%, with a PPV of 72.0% and an NPV of 84.9%. For Grade 3 tumors, frozen section showed the highest accuracy, with a sensitivity of 85.0%, specificity of 98.3%, PPV of 94.4%, and NPV of 95.0%. These findings indicate that frozen section evaluation is most reliable for identifying high-grade tumors while showing moderate concordance for lower grades.

Myometrial invasion

Table 3 presents the correlation between MI in cases with a final diagnosis of carcinoma and its assessment using IFS. The MI evaluation via IFS was performed in 95% cases, as three cases were diagnosed with endometrial hyperplasia and two cases showed no evidence of malignancy. Frozen section evaluation showed a strong agreement with FH for assessing myometrial invasion (κ = 0.851). The overall accuracy was 93.7%, with a sensitivity of 92.9% and specificity of 94.0% for detecting ≥50% invasion. The PPV and NPV were 86.7% and 96.9%, respectively.

Lymph nodal evaluation

Table 3 compares the concordance of the IFS in retroperitoneal nodal evaluation including pelvic and para-aortic lymph nodes with FH. In 60 cases lymph nodes were sent for IFS. This decision was based on surgeon discretion considering IFS histology, depth of invasion and intra-operative nodal assessment. IFS demonstrated excellent agreement with FH for detecting nodal metastasis (κ = 0.942), with an overall accuracy of 98.3%. The sensitivity and specificity were 100% and 98.8%, respectively, while the PPV and NPV were 90.9% and 100%, respectively. These results highlight the high reliability of frozen section analysis in assessing nodal involvement.

Table 2
Concordance between frozen section analysis and final histopathology for diagnosis of malignancy.

Frozen section	Final histopathology		Total
	Carcinoma present n=98	Carcinoma absent n=2	
Carcinoma present	95	0	95
Carcinoma absent	3	2	5
Total	98	2	100

Concordance: 97.0%, (κ = 0.56, 95% CI, 0.12-1.00)

Table 3
Correlation of Tumor Grade, Depth of Myometrial Invasion, Nodal Metastasis Between Intraoperative Frozen Section and Final Histopathology.

Frozen section	Final histopathology			Total
Grade				
	Grade 1 n=43	Grade 2 n=31	Grade 3 n=24	
Grade 1	26	6	0	32
Grade 2	7	18	1	26
Grade 3	2	1	17	20
Total	35	25	18	78
Concordance: 78.2%, (Weighted κ = 0.72; κ = 0.67, 95% CI, 0.52-0.81)				
Invasion				
	No Invasion/<50% n=65	**≥50% n=30**		
No invasion/<50%	63	4		67
≥50%	2	26		28
Total	65	30		95
Concordance: 93.7%, (κ = 0.85, 95% CI, 0.74-0.97)				
Lymph nodal status				
	No Nodal metastasis n=80	**Nodal metastasis n=15**		
No Nodal metastasis	49	1		50
Nodal metastasis	0	10		10
Total	49	11		60
Concordance: 98.3%, (κ = 0.94, 95% CI, 0.83-1.00)				

Cervical and adnexal involvement

FH revealed cervical involvement in six cases, of which five were accurately identified through IFS. Likewise, ovarian metastases were present in three cases, all of which were successfully detected intraoperatively using frozen section evaluation.

Discussion

The Gynecologic Oncology Group (GOG) study GOG 33, published in 1987, highlighted key histopathological factors associated with lymph node metastasis, with tumor grade and depth of invasion being the most significant. Tumors that are poorly differentiated and deeply invasive have a higher propensity to spread to pelvic and para-aortic lymph nodes.[5] Although these risk factors are well recognized, the decision regarding the necessity and extent of lymph node dissection in the surgical treatment of endometrial cancer remains a topic of ongoing debate.[6] Certain institutions utilize preoperative endometrial sampling to guide treatment decisions. However, ensuring accurate correlation between preoperative and final pathological grading is essential to prevent both overtreatment and undertreatment.[7] A systematic review and meta-analysis by Kopatsaris et al. reported a pooled sensitivity of 0.886 and specificity of 0.862 for frozen section in detecting endometrial cancer, confirming its validity and reliability as a diagnostic tool.[4] Consistent with the present study, majority of the published studies reported a high sensitivity and specificity of frozen section for diagnosis of endometrial cancer[8-11] (Table 4).

This study analyzed 100 cases of uterine neoplasms where IFS was performed, demonstrating high concordance with FH. The sensitivity and specificity of IFS for detecting malignancy were 96.9% and 100%, respectively. Tumor grading showed moderate agreement (κ = 0.67), with the highest accuracy for Grade 3 tumors. IFS exhibited strong agreement for assessing MI (κ = 0.851) and nodal metastasis (κ = 0.942), with overall accuracies of 93.7% and 98.3%, respectively. These findings align with those reported by Santoro et al., who observed a high grading concordance rate of 91.09% and a global kappa index of 0.775.[12] Similar results were noted by Acikalin et al.[13]

As the tumor grade identified in final histopathology increases, the likelihood of its accurate detection in frozen section decreases. This discrepancy may arise due to the presence of high-grade tumor foci in areas not sampled during the frozen section analysis, leading to an underestimation of the true tumor grade.[14] Unlike our study, several reports have highlighted a weaker correlation between frozen section and FH, particularly in low-grade lesions.[15] The primary factors contributing to these discrepancies include

Table 4
Studies comparing the diagnostic accuracy of IFS with final histopathology.

Study	Tissue	Sensitivity (%)	Specificity (%)	NPV (%)	Concordance (κ)
Desouki M.M. et al	Surgical specimen	95	100	67	-
Doğan Durdağ G. et al	Surgical specimen	87.8	76.4	53.1	-
Kashyap A. et al	Endometrial biopsy	90.9	93.19	96.19	0.778
Kucera E. et al	Surgical specimen of early-stage endometrial cancer	77.8	98.1	96.4	-
Present study	Surgical specimen	96	100	40	0.56

technical artifacts inherent to the frozen section process and limitations in tissue sampling.[16] Accurately assessing MI macroscopically can be challenging, especially in low-grade tumors, where invasion patterns may be heterogeneous, and skip metastases can occur.[12] Similarly, in our study, three cases of endometrioid adenocarcinoma were misclassified as endometrial hyperplasia on frozen section analysis.

Assessing the depth of MI using frozen section is a rapid and reliable method, making it valuable for identifying cancers with a high risk of extrauterine spread.[17,18] In our study, frozen section analysis demonstrated a strong correlation with FH in evaluating MI ($\kappa = 0.851$), with an impressive overall accuracy of 93.7%. These findings highlight the effectiveness of intraoperative frozen section in guiding surgical decision-making for endometrial cancer staging.

While intraoperative frozen section analysis is a valuable tool, it has certain limitations, including prolonged surgical time leading to increased risk of infection, extended anesthesia exposure, and resource constraints. As an alternative, preoperative imaging modalities such as magnetic resonance imaging (MRI) have been utilized to assess the depth of MI.[19] Further research is needed to directly compare the effectiveness of frozen section, gross examination, and MRI in predicting MI to optimize patient management strategies.

A key strength of this study is the inclusion of 100 cases, providing a comprehensive evaluation across all risk groups rather than focusing on a specific subset. Multiple histopathological parameters were assessed collectively, offering a broader perspective on frozen section accuracy. Additionally, both intraoperative frozen section and FH evaluations were conducted by a single experienced gynecologic pathologist, minimizing interobserver variability. The study design helps reduce potential biases, such as selective sampling or extended evaluation in certain cases.

However, certain limitations must be acknowledged. The retrospective nature of the study inherently poses constraints. Additionally, as the study was conducted in a high-volume tertiary endoscopic cancer center with access to specialized pathology expertise, the findings may not be directly generalizable to lower-volume centers with less experienced personnel. The correlation between preoperative imaging and endometrial biopsy with intraoperative frozen section analysis and FH was not evaluated. Additionally, the influence of molecular markers on risk stratification and management was not analyzed in this study. Another limitation is that survival and recurrence outcomes were not analyzed in correlation with frozen section and FH, preventing an assessment of the long-term prognostic impact of intraoperative evaluation.

Conclusion

This study demonstrates that intraoperative frozen section evaluation is a reliable tool for assessing tumor grade, myometrial invasion, and nodal metastasis in endometrial cancer, showing strong concordance with final histopathology. The high accuracy of frozen section analysis makes it a valuable adjunct in surgical decision-making, particularly in high-volume centers with experienced pathologists. However, certain discrepancies, particularly in tumor grading, highlight the need for cautious interpretation. Further exploration into protocol optimization for frozen sections, including standardized criteria and improved pathological techniques, may enhance accuracy and address existing limitations. Larger prospective studies are warranted to validate these findings and assess the long-term prognostic impact of intraoperative evaluation.

Statements and Declarations

Ethical approval: The ethical approval was obtained from ACEAS Ethics Committee (ACEAS/EVA/1/3/25)

Availability of data and materials: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions: All the authors have made substantial contribution towards manuscript including conceptualization, methodology and supervision by DL, validation and formal analysis by AH, data curation and writing-original draft by MG, writing-review & editing by DL and AH, and formal analysis by AH.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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