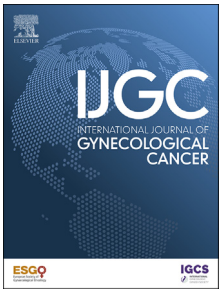
ORIGINAL RESEARCH

Value of frozen section to tailor surgical staging in apparent early-stage epithelial ovarian cancer



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Received 10 December 2024, Accepted 17 February 2025; Available online xxx

ABSTRACT

Objective: Frozen section (FS) has been shown to have high accuracy in determining ovarian malignancy. However, its utility in guiding surgical approaches, particularly, lymph node staging, for early-stage epithelial ovarian cancer remains unclear. This study aimed to evaluate the post-test positive probability of FSs in identifying cases requiring lymph node or peritoneal staging. The secondary aims were sensitivity, specificity, and accuracy assessments.

Methods: This retrospective study analyzed patients undergoing surgery for early-stage epithelial ovarian cancer with FS performed on ovarian masses between July 2007 and March 2023 at a tertiary center. The FS results were compared with the final histology (gold standard paraffin sections). The FS cases were categorized based on further actions as follows: lymph node staging (type A), peritoneal staging only (type B), or no additional procedures (type C). The patients were divided into group 1 (requiring lymph node and peritoneal staging) and group 2 (requiring only peritoneal staging). A comparison between specialized and general pathology diagnoses was also performed. Incorrect FS assessments were classified as under-diagnosed or over-diagnosed.

Results: Of the 715 patients, group 1 had appropriate staging in 425 of 447 cases, with 4.9% over-treatment. In group 2, staging was correct in 109 of 195 cases, with 44.1% under-treatment. For type A FSs, the post-test positive probability was 95% (95% CI 93% to 97%), with sensitivity, specificity, and accuracy rates of 76.4%, 86.1%, and 78.6%, respectively. For type B FSs, the post-test positive probability was 56% (95% CI 50% to 61%), with sensitivity, specificity, and accuracy rates of 68.6%, 84.5%, and 81%, respectively. There was no significant difference in the agreement between the specialized and general pathology groups ($p = 0.92$).

Conclusions: Frozen sections suggestive of a cancer diagnosis requiring peritoneal and lymph node staging in a population with apparent early-stage epithelial ovarian cancer are highly reliable. In the case of FSs suggesting only peritoneal staging, malignancy is frequently underestimated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Intra-operative frozen section (FS) analysis demonstrates excellent overall diagnostic accuracy for assessing malignancy potential. However, not all early-stage ovarian cancers require retroperitoneal staging, which is associated with relevant morbidity.

WHAT THIS STUDY ADDS

This study evaluated the role of FSs of early-stage epithelial ovarian carcinomas to assist gynecologic oncologists in determining the optimal surgical strategy. Frozen sections demonstrated excellent diagnostic accuracy for identifying ovarian carcinomas that require peritoneal and retroperitoneal staging. In contrast, when FS reports a result requiring peritoneal staging only, the risk of under-diagnosis was reported in 56% cases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

Although underestimation of the need for retroperitoneal staging remains a challenge, over-estimation occurs less frequently. Future efforts should focus on refining the diagnostic approaches to more accurately identify early-stage epithelial ovarian cancer cases requiring peritoneal staging alone, aiming to reduce the rate of under-diagnosis while maintaining a low over-diagnosis rate.

Keywords:
Frozen Section; Early-Stage Epithelial Ovarian Cancer; Lymph Node Staging; Peritoneal Staging

INTRODUCTION

The traditional surgical staging of early-stage epithelial ovarian cancer is based on peritoneal and lymph nodal staging.[1] The incidence of lymph node metastases in apparent early-stage epithelial ovarian cancer is estimated to be up to 25% according to the histologic subtype.[2,3] Therefore, systematic pelvic and paraaortic lymphadenectomy is recommended as part of surgical staging because information on nodal status is relevant to guide

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https://doi.org/10.1016/j.ijgc.2025.101746

decisions on adjuvant therapy and eventual maintenance. However, pelvic and para-aortic lymphadenectomy is associated with major complications, including vascular and nerve injuries, increased blood loss, lymphoceles, lymphorrhea, and lymphedema.[4,5] The operating time and hospital stay are significantly longer for patients who undergo systematic lymphadenectomy than for those who do not.[6]

In some histologic subtypes, the indication for lymph node staging surgery may be questioned because of the low prevalence of nodal metastases.[7] According to the European Society For Medical Oncology - European Society of Gynaecological Oncology - European Society of Pathology guidelines, lymph node staging may be omitted in mucinous expansile pattern and low-grade serous ovarian cancer.[1] In other histotypes, such as endometrioid grade 1 (G1), lymph node staging is still a matter of debate.[8,9] Previous studies on frozen section (FS) analysis have reported high overall accuracy in distinguishing benign, borderline, and malignant ovarian masses.[10] Nevertheless, knowing whether a pelvic mass is malignant is not enough to perform an appropriate surgical treatment. By considering only malignant cases at FS analysis, there is still a risk of either underestimating women subsequently found to have a malignancy and requiring lymph node staging or over-estimating women for whom only peritoneal staging is needed. The primary aim of this study was to assess the post-test positive probability of FSs to identify cases requiring lymph node and/or peritoneal staging. The secondary aims were sensitivity, specificity, and accuracy.

METHODS

Patient Selection

This retrospective study was conducted in a tertiary care center in Italy. Data from patients with primary early-stage (International Federation of Gynecology and Obstetrics [Fédération Internationale de Gynécologie et d'Obstétrique] stage I-II) epithelial ovarian cancer at the final histologic examination treated with radical or fertility-sparing surgery between July 2007 and March 2023 were reviewed. The exclusion criteria were restaging surgery, *FS* not performed or not performed on ovarian mass(es), cases diagnosed with intra-abdominal malignancy within 5 years before surgery, intraepithelial ovarian carcinomas, or other synchronous carcinomas at the final diagnosis. Given that the study period covered 16 years, some included entities had received different names over time; to standardize nomenclature, final diagnoses were made according to the 2014 World Health Organization classification of the ovarian tumor: grade 2 (G2) serous adenocarcinoma was converted to "high-grade serous carcinoma" and cases diagnosed as mucinous carcinoma with microinvasion (invasion <5 mm) were reclassified based on the 2014 World Health Organization criteria as "mucinous borderline tumors" and excluded.[11]

Comparison Between Frozen Section and Final Histology

Regarding FS, the pathologist, after examining and slicing the whole tumor, selects the most representative samples, normally 1 or 2, which are then frozen and cut at 5-micron thickness at the cryostat and ultimately stained with hematoxylin and eosin in an automated slide stainer. The results of the FS analysis were compared with the final pathological diagnosis, which is considered the gold standard. A comparison between specialized and general pathology diagnoses was also performed. Owing to changes in the archiving systems, the name of the physician who reported the FS could only be retrieved from June 2018 onward. Therefore, this comparison can only be performed for cases between June 2018 and March 2023.

The FS analysis had 3 possible outcomes: the first is carcinoma with features for high risk of lymph node dissemination (high-grade serous, endometrioid G2 and grade 3 [G3], clear cell or "undifferentiated, high and moderate grade carcinoma") and "carcinoma/adenocarcinoma" not otherwise specified. In the latter case, considering the significantly lower incidence of histotypes with a low risk of lymph node dissemination, we performed peritoneal and lymph node staging to avoid under-treatment.[7] The second is carcinoma with features for low risk of lymph node dissemination (low-grade carcinoma, borderline tumors, non-epithelial malignant tumor, and mucinous carcinoma). In the latter case, considering the rarity of the infiltrative pattern, we performed peritoneal staging only at the primary approach to avoid over-treatment in a large number of patients[12] and we offer a second-step lymphadenectomy if needed. The third includes benign tumor, metastasis, or inconclusive assessment of malignant potential.

According to the inclusion criteria that selected patients with cancer at final histology, the women were divided into 2 groups according to surgical staging: group 1, peritoneal staging and lymph node staging (corresponding to high-grade serous, endometrioid G2-G3, clear cell, mixed high-grade, and mucinous infiltrative pattern), and group 2, peritoneal staging only (corresponding to mucinous expansile pattern, low-grade serous, and endometrioid G1).

Incorrect assessments of the FSs were defined as under-diagnosis or over-diagnosis: under-diagnosis in all cases in which FSs led to under-treatment with respect to final histology for which patients were referred to an additional surgery and may include cases with FS types B and C and over-diagnosis in all cases in which FSs led to over-treatment with respect to final histology for which patients were referred to unnecessary surgical procedures and may include cases with FS type A.

Failure to specify the precise histologic subtype of the carcinoma was not considered an error if correct staging was possible.

Statistical Analysis

The outcome measures used were positive likelihood ratio and post-test positive probability, ie, the probability to perform a correct staging for an early-stage epithelial ovarian cancer with FS result.[13] Sensitivity, specificity, and accuracy were also calculated. The c^2 test was used to analyze the distribution of correct and incorrect diagnoses in the FS analysis according to the different pathologists who performed the intra-operative examinations. Statistical analyses were performed using SPSS statistical software (version 20.0; IBM Corp). In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purpose of additional data analysis or for the reproducibility of this study in other centers if requested.

RESULTS

A total of 1336 cases were reviewed, of which 621 were excluded (Fig. 1). The clinicopathologic features of the 715 patients with early-stage cancer are shown in Table 1. The distribution of

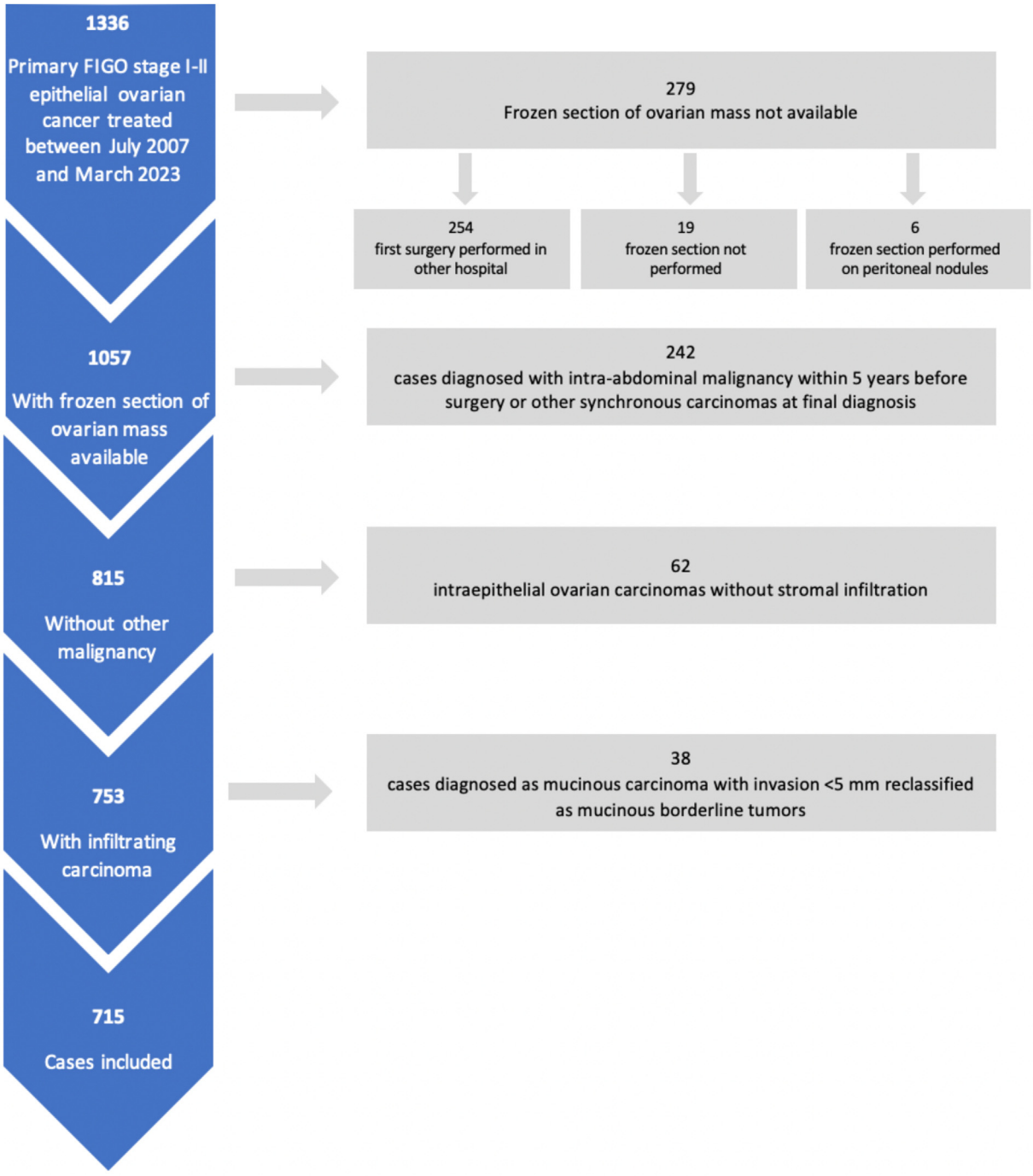

Figure 1 Selection criteria for included cases. FIGO, International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique).

diagnoses in the FSs is detailed in Table 2. In 534 patients (74.7%), FSs led to correct surgical management, whereas in 181 patients (25.3%), it led to an inappropriate intra-operative strategy. Staging, as defined for group 1, was appropriate in 425 of the 447 (95.1%) cases with FS type A. In the remaining 22 women, there was an over-treatment (4.9%). Staging, as defined for group 2, was appropriate in 109 of 195 (55.9%) cases with FS type B and under-treatment in 86 patients (44.1%). All 73 patients (10.2%) with FS type C underwent an inappropriate intra-operative strategy according to the inclusion criteria.

Cases with discordant results between FSs and the final histology are shown in Table 3. Overall, 159 ovarian cancer cases (22.2%) were under-diagnosed using FSs. In group 1, the most frequently reported misdiagnosis in FSs was borderline tumors in 50 cases (38.2%), which included 6 high-grade serous (4.6%), 25 endometrioid G2 to G3 (19.1%), 14 clear cell (10.7%), 2 mixed

Table 1 Clinical-Pathologic Features

Characteristics	*n*	(%)
All cases	715	
Median age (y) IQR, range	55	(48-64)
Histology		
High-grade serous carcinoma	242	(33.9)
Low-grade serous carcinoma	45	(6.3)
Endometrioid carcinoma	197	(27.5)
G1	41	(5.7)
G2-G3	156	(21.8)
Clear cell carcinoma	137	(19.2)
Mixed high-grade carcinoma	11	(1.5)
Mucinous carcinoma	83	(11.6)
Expansile pattern	73	(10.2)
Infiltrative pattern	10	(1.4)
Final FIGO stage		
IA	251	(35.1)
IB	44	(6.1)
IC1	112	(15.7)
IC2	87	(12.2)
IC3	20	(2.8)
IIA	73	(10.2)
IIB	128	(17.9)
Type of surgery		
Peritoneal staging only	260	(36.4)
Peritoneal and lymph node staging	455	(63.6)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique); G1, grade 1; G2, grade 2; G3, grade 3; IQR, interquartile range.

high-grade tumors (1.5%), and 3 mucinous infiltrative ovarian cancers (2.3%). In group 2 and overall, there were 22 over-diagnoses (3.1%) in the FSs, and all reported high-grade ovarian cancer with no mention of the histotype.

When FS reported carcinoma with features for high risk of lymph node dissemination (type A), the positive likelihood ratio was 5.52 (95% CI 3.74-8.16) and the post-test positive probability was 95% (95% CI 93%-97%) (Fig. 2). In case of FS type B, the positive likelihood ratio was 4.43 (95% CI 3.55-5.53) and the post-test positive probability was 56% (95% CI 50%-61%) (Fig. 2). Table 4 shows the sensitivity, specificity, and accuracy of FSs for identifying patients with appropriate staging.

Regarding the data available for comparison between specialized and general pathologists, although all definitive diagnoses were primarily made or secondarily revised by a specialized pathologist, FS examinations were performed in 148 (35.3%) cases by a specialized pathologist, and 271 (64.7%) cases by a general pathologist. In the specialized pathologist group, the intra-operative diagnosis was correct in 108 of 148 cases (73%). In the general pathologist group, the FS examination results were correct in 199 of the 271 cases (73.4%). There was

Table 2 Frozen Section Report by Histotype ($N = 715$)

FS assessment	Total	Final histology								
		Group 1						Group 2		
		High-grade serous	Endometrioid G2-G3	Clear cell	Mixed high grade	Mucinous infiltrative	Total	Mucinous expansile	Endometrioid G1	Low-grade serous	Total
FS a[a]	447 (100)	225 (50.3)	101 (22.6)	88 (19.7)	8 (1.8)	3 (0.7)	**425 (95.1)**	5 (1.1)	11 (2.5)	6 (1.3)	**22 (4.9)**
FS b[b]	195 (100)	11 (5.6)	41 (21)	27 (13.8)	2 (1)	5 (2.6)	**86 (44)**	46 (23.6)	24 (12.4)	39 (20)	**109 (56)**
FS c[c]	73 (100)	6 (8.2)	14 (19.2)	22 (30.1)	1 (1.4)	2 (2.7)	**45 (61.6)**	22 (30.1)	6 (8.3)	0 (0)	**28 (38.4)**

Abbreviations: FS, frozen section; G1, grade 1; G2, grade 2; G3, grade 3.
All values are given in *n* (%).
[a] High-grade serous, endometrioid G2 to G3, clear cell and "undifferentiated, high- and moderate-grade carcinoma."
[b] Low-grade carcinoma, borderline tumors, non-epithelial malignant tumor, and mucinous carcinoma.
[c] Benign tumor, metastasis, or not diriment for assessment of the malignant potential.

Table 3 Cases With Discordant Results Between Final Histology and Frozen Section About Surgical Strategy to be Adopted ($N = 181$)

Final histology	*n* (%)	Frozen section	
Need for LNS and peritoneal staging	**131/556 (23.5)**		
High-grade serous	17/242 [7]	Under-diagnosis:	
		LGOC	4
		Borderline tumor	6
		Benign tumor/lesion	4
		Metastasis	2
		Mucinous carcinoma[a]	1
Endometrioid G2-G3	55/156 (35.2)	Under-diagnosis:	
		LGOC	5
		Borderline tumor	25
		Benign tumor/lesion	8
		Non-epithelial malignant tumor	4
		Metastasis	2
		Mucinous carcinoma[a]	8
		Not diriment malignant potential	3
Clear cell	49/137 (35.8)	Under-diagnosis:	
		LGOC	3
		Borderline tumor	14
		Benign tumor/lesion	6
		Non-epithelial malignant tumor	4
		Metastasis	1
		Mucinous carcinoma[a]	6
		Not diriment malignant potential	15
Mixed high-grade	3/11 (27.3)	Under-diagnosis:	
		Borderline tumor	2
		Not diriment malignant potential	1
Mucinous infiltrative	7/10 (70)	Under-diagnosis:	
		Borderline tumor	3
		Benign tumor/lesion	1
		Mucinous carcinoma[a]	2
		Not diriment malignant potential	1
Need for peritoneal staging only	**44/159 (31.4)**		
Mucinous expansile	27/73 (37)	Over-diagnosis:	
		HGOC	5
		Under-diagnosis:	
		Benign tumor/lesion	10
		Metastasis	1
		Not diriment malignant potential	11
Endometrioid G1	17/41 (41.5)	Over-diagnosis:	
		HGOC	11
		Under-diagnosis:	
		Benign tumor/lesion	6
Low-grade serous	6/45 (13.3)	Over-diagnosis:	
		HGOC	6

Abbreviations: G1, grade 1; G2, grade 2; G3, grade 3; HGOC, high-grade ovarian cancer; LGOC, low-grade ovarian cancer; LNS, lymph node staging.

[a] Considering the rarity of the infiltrative pattern, we performed peritoneal staging only with the primary approach to avoid over-treatment in a large number of patients and offered a second-step lymphadenectomy if needed.

no significant difference in the agreement between the specialized and general pathology groups ($p = .92$).

DISCUSSION

Summary of Main Results

In this study, we showed that invasive cancer diagnosis requiring lymph node staging obtained using FSs was highly reliable. Although the false-positive rate was low (4.9%), additional morbidities related to unnecessary systematic lymphadenectomy should be considered. In contrast, we showed that it is more difficult to offer the appropriate intra-operative staging to patients diagnosed with carcinoma with features for low risk of lymph node dissemination. Indeed, women with FS type B may receive an incorrect diagnosis in approximately half of the cases, and the risk of under-diagnosis with the need for a second surgery is 44%.

Results in the Context of the Literature

It is well-accepted that FSs, when prepared by specialized pathologists,[14] have high sensitivity, specificity, and accuracy rates

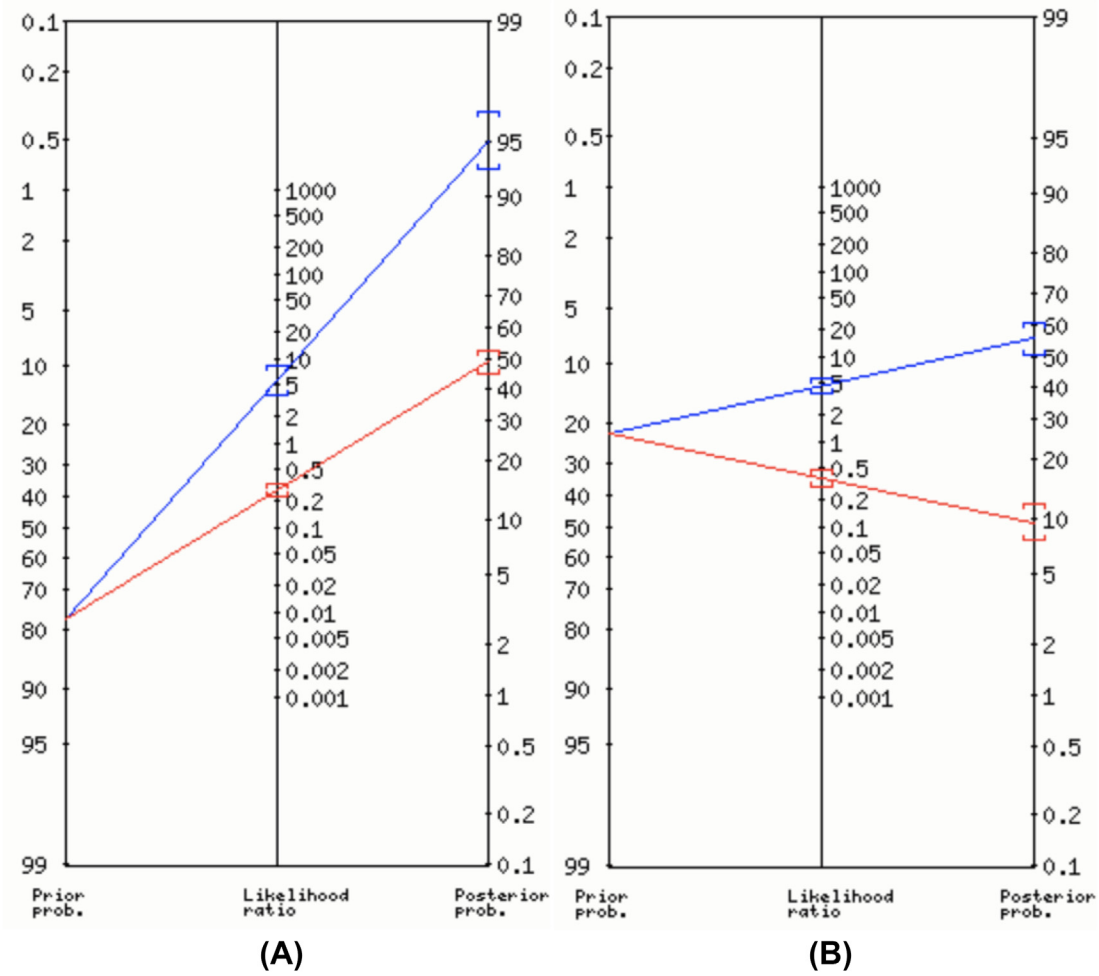

Figure 2 **A**. Nomogram for frozen section likelihood ratios (+ blue; − red) for carcinoma with features for high risk of lymph node dissemination. **B.** Nomogram for frozen section likelihood ratios (+ blue; − red) when reporting diagnosis requiring peritoneal staging only. Prob., probability.

for discriminating the malignant potential of an ovarian mass. In this study, there was no statistically significant difference between specialized and general pathologists. This can be explained by the fact that although previous studies aimed to identify differences in the accurate assessment of malignant potential, the end point in this case was correct intra-operative surgical management. In these terms, no differences appear to exist between the 2 categories of pathologists. Borderline and low-grade tumors are the most difficult to be correctly identified intraoperatively by FS.[15-18] The size of adnexal masses significantly affects the accuracy of diagnostic procedures, with worse outcomes reported for lesions over 10 cm.[19] This is largely because of sampling challenges and the rapid nature of FS diagnosis, which limits the number of slides compared with paraffin procedures. In cases of low risk of lymph

Table 4 Sensitivity, Specificity, Accuracy, and Post-Test Positive Probability ($N = 715$)

FS	Final histology							
	True positives	True negatives	False positives	False negatives	Sensitivity (%)	Specificity (%)	Accuracy (%)	PTPP[a] (%)
FS a[b]	425	137	22	131	76.4	86.1	78.6	95
FS b[c]	109	470	86	50	68.6	84.5	81	56
FS c[d]	NA	642	73	NA	NA	89.8	NA	NA

Abbreviations: FS, frozen section; G2, grade 2; G3, grade 3; NA, not applicable; PTPP, post-test positive probability.

[a] Post-test positive probability, which is the probability of adequate surgical staging after FS analysis.

[b] High-grade serous, endometrioid G2 to G3, clear cell, and "undifferentiated, high- and moderate-grade carcinoma."

[c] Low-grade carcinoma, borderline tumors, non-epithelial malignant tumor, and mucinous carcinoma).

[d] Benign tumor, metastasis, or not diriment for assessment of the malignant potential.

node dissemination, ovarian tumors, such as mucinous types and low-grade serous, among the largest and most heterogeneous focal solid areas within otherwise benign or borderline cystic tumors, further complicate sampling.[20] These factors, along with variability in pathologists' experience, likely contribute to the reduced reliability of FSs in these cases. However, most studies have reported the correct surgical management of early-stage ovarian cancer using FSs. It must be specified that these studies have only a minor proportion of malignant tumors;[10] second, to date, a malignant tumor correctly classified at FS was automatically included in the adequate case management, but surgical staging of early-stage epithelial ovarian cancer depends on histology and grading to select patients for lymph node staging and peritoneal staging or for peritoneal staging only.

Strengths and Weaknesses

To the best of our knowledge, there have been no studies on the efficacy of FSs in classifying ovarian malignancies as high or low risk for lymph node dissemination. The retrospective design of the study, which was conducted at a single center, represents an important limitation. We also recognize the limitations of FSs in being able to specify the histotype, which is why we focused on its role in identifying more generic features divided into 2 macro groups according to the need to perform lymph node staging. However, this method of classification has limitations: regarding mucinous carcinomas, we are conscious that including all FS findings deponent for "mucinous carcinoma" in the group of patients who need only peritoneal staging is not completely correct because the subgroup of infiltrative-type growth pattern needs lymph node staging according to the guidelines.[1] Nevertheless, infiltrative mucinous ovarian cancers are very rare.[12,21] Another limitation of this method of classification of FS concerns those that generically deposes for "carcinoma" without specifying further features. Including this class of FSs among those requiring complete staging could lead to the over-treatment of all cases in which, at the final histology, they would receive a diagnosis that does not require lymph node staging. Nevertheless, in view of the higher incidence of histotypes needing lymph node staging,[7] the policy at our institution was to offer complete staging at the expense of hypothetical over-treatment because under-treatment—related risks and costs would certainly be higher. Although beyond the aims of this study, our approach to FSs of ovarian masses can be useful to drive fertility-sparing in young patients. Indeed, we reported a 4.9% risk of over-diagnosis, which may be correlated with the morbidity related to inappropriate lymphadenectomy and the inappropriate removal of the uterus and contralateral adnexa, causing sterility and iatrogenic early menopause.

Implications for Practice and Future Research

In the last few years, there has been increasing interest in the application of artificial intelligence and radiomics to imaging in gynecologic oncology. Some studies have evaluated the ability of radiomics analysis to classify ovarian masses as benign or malignant with great accuracy,[22-24] but no study has applied radiomics analysis to imaging to discriminate between different types of tumors (or macro groups) in early-stage ovarian cancers. For example, ongoing projects at our center are focused on developing ultrasound radiomics models capable of pre-operatively distinguishing between high- and low-risk masses for lymph node dissemination.

There are few studies related to the application of pathology artificial intelligence in ovarian cancer and none specifically on its role in FS.[25-28] In other cancers, such as breast and thyroid cancer, the application of deep learning on digital pathology of FS slides of from primary tumors to identify cases requiring lymphadenectomy versus those where it can be omitted is showing promising results. In the future, the same approach could be considered for ovarian carcinomas.[29]

A promising advancement for improving intra-operative staging accuracy in ovarian cancer is sentinel lymph node biopsy. Increasingly used in other gynecologic cancers, this technique targets only sentinel nodes, the first nodes to which cancer cells are likely to spread, thereby reducing the morbidity associated with complete lymphadenectomy.[30] Alongside this, optical coherence tomography has emerged as a novel tool for real-time microscopic assessment of lymph nodes during surgery.[31] This minimally invasive approach has the potential to assess lymph node involvement directly in the operating room, complementing FS by allowing immediate and more precise decisions on the extent of surgery required.

We are conscious that applying these new technologies to daily clinical practice is still premature; however, the intent of this study was to inspire new research in this direction.

CONCLUSIONS

Frozen sections suggest that a cancer diagnosis that requires peritoneal and lymph node staging in a population of apparent early-stage epithelial ovarian carcinoma is highly reliable for assisting gynecologic oncologists in selecting the correct surgical strategy. In cases of FSs suggesting peritoneal staging only, malignancy is frequently underestimated; therefore, the need for a potential second surgery needs to be discussed peri-operatively with the patient. In the future, research efforts should aim to more accurately identify the population of patients with early-stage epithelial ovarian cancer requiring only peritoneal staging to decrease the rate of under-diagnosis.

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Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions DBS and CM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: FA, DBS, BN. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: BN, DBS. Critical revision of the manuscript for important intellectual content: FA, BN, MF, PUB, MC, ZGF and SG. Statistical analysis: DBS. Administrative, technical, or material support: PUB, CM. Supervision: FA.

Declaration of Competing Interests Given their role as Editorial Board Members, NB and GS had no involvement in the peer review of this article and have no access to information regarding its peer review. Other 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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