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ORIGINAL ARTICLE

Diagnostic Accuracy of Frozen Section and Its Influence on Intraoperative Management of Indeterminate Epithelial Ovarian Tumors

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Abstract

The objective of this study is to determine the diagnostic accuracy of frozen section in detecting epithelial ovarian tumor histological types and its effect on management. A retrospective review was done of all patients who had an intraoperative frozen section for an indeterminate ovarian tumor over a six-year period. The reference standard was final histology. The validity indices for frozen section in diagnosing benign, borderline, and malignant lesions were determined. One hundred thirty-five intraoperative frozen section–diagnosed epithelial ovarian tumors were reviewed. The mean age was 44.9 ± 14.2 years, the median parity was 2, and 57% (77/135) of patients were post-menopausal. The commonest histological subtype was mucinous 48.1% (65/135) on frozen section and 46.7% (63/135) on final histology. The overall concordance rate of frozen section to final histology was 81.5% (= 0.719, $p = 0.0001$). The accuracy, sensitivity, specificity, and positive predictive value of frozen section to diagnose benign lesions were 86.7%, 85.7%, 97.2%, and 79.2% respectively. In borderline tumors, the diagnostic test characteristics were 88.1%, 81.2%, 90.3%, and 72.2%. For malignant lesions, these values were 88.1%, 77.8%, 95.1%, and 91.3% respectively. The odds ratios for frozen section being correct were 40.9 (95% CI 14.8–113.5) for benign lesions, 40.3 (95% CI 13.4–121.3) for borderline tumors, and 67.4 (95% CI 20.5–222.0) for malignancy. Over-treatment or under-treatment occurred in 19.3% of patients. Intraoperative frozen section is useful in situations where the nature of the ovarian tumor is uncertain. However, borderline ovarian tumors are more likely to be over-diagnosed. About a fifth of patients received inappropriate treatments based on the frozen section report.

Keywords Diagnostic test · Ovarian neoplasm · Frozen section · India

Introduction

Epithelial tumors make up more than half of all cases of ovarian tumors with three broad categorizations of benign, borderline, and malignant [1, 2]. Several modalities have been utilized in making a preoperative diagnosis of ovarian lesions such as imaging and tumor markers, but their respective diagnostic accuracy leaves much to be desired in differentiating the various histological categories [3–6]. The exact diagnosis determines the surgical interventions necessary; in malignant lesions, laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymphadenectomy are required. In benign lesions, a cystectomy or unilateral salpingo-oophorectomy might suffice. The situation is made more complex if a woman wants to preserve her fertility, where the surgeon needs to know if the ovarian tumor is benign, borderline, or malignant, not only to tailor the extent of surgery but also to consider fertility-sparing surgery [7]. When imaging, tumor markers, and intraoperative findings are inconclusive, then it would be ideal if frozen section can give a definitive diagnosis. This would prevent either under-treatment or over-treatment, both of which carry their own costs and risks.

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Intraoperative frozen section has been used by surgical oncologists in the area of head and neck tumor management with good outcome, but its role in ovarian lesions has been debated [8, 9]. Pathologists often find it difficult to give a definitive diagnosis on frozen sections of ovarian tumors. The lack of easy preoperative access, fear of disseminating cancer, and the totipotent nature of the ovaries in women make it difficult for clinicians to obtain a definitive diagnosis prior to surgery. Fine needle aspiration cytology or biopsy is done only if it has been decided not to operate on the patient to avoid needless upstaging of an early cancer. Thus, frozen section for an ovarian tumor is commonly requested to decide on optimal surgery [10]. There is a risk of over- or under-diagnosis and subsequently over- or under-treatment increasing avoidable morbidity for the patient or necessitating a second operation [11].

Diagnostic accuracy indices of intraoperative frozen section vary with factors such as the expertise of the pathologist and tumor subtype [12–15]. The accuracy of frozen section to distinguish between malignant and benign in most health institutions is about 90%, but its ability in borderline tumor is much less [13, 14]. The aim of this study was to determine the diagnostic accuracy of frozen section as an add-on test when clinical findings, tumor markers, and imaging were not conclusive in determining whether an adnexal mass was malignant or not. This study was conducted at a teaching institution in India.

Methods

This was a retrospective cross-sectional design with frozen section as the index test and final histology as the reference standard. Permission for the study was obtained from the Institutional Review board (IRB). It was estimated that to demonstrate an accuracy of 85% with a precision of 10%, 98 patients would need to be studied assuming a prevalence of malignancy of 50%.

The electronic medical records of all 135 consecutive patients with epithelial ovarian tumors and who had an intraoperative frozen section from 1 January 2011 to 31 December 2016 were included. Frozen sections were done in our department for tumors that were not definitely benign or malignant on clinical evaluation and imaging. Patients with non-epithelial tumors were excluded. The analysis of epithelial ovarian tissue subtypes could be done on 112 as either the subtype information was not provided in the frozen section or the final histological diagnosis in 23 records. The pathologists who arrived at the final histopathological diagnosis on paraffin sections were not blinded to the frozen section report. The frozen section report preceded the final paraffin section report by 10 days on average.

Information on demographic characteristics (age, parity, menopausal status), tumor type (borderline, benign, or malignant), and histological subtypes (mucinous, serous, endometrioid, clear cell, other types) made by frozen section and final histology was collected. Data were entered into Microsoft Excel and exported to the Statistical Package for the Social Sciences (SPSS) version 20 (IBM, Armonk, NY, USA) for statistical analysis. McNemar's chi-square was used to test for differences in paired observations. Normally distributed variables were then summarized using means and standard deviations. Numerical variables that were not normally distributed were summarized as medians and ranges. The validity of frozen section diagnosis was determined in relation to final histology diagnosis using sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Agreement of the diagnosis between frozen section and final histology was assessed using percentage agreement and kappa statistics.

Results

Among the patients studied, 75.6% (102/135) were ≥ 35 years of age with a mean age of 44.9 years (SD 14.2, range 16–72 years). Parity ranged from of 0 to 7 with a median of 2 and 28.9% (39/135) were nulliparous. The majority (57%) of women were post-menopausal as shown in Table 1.

Table 1 Characteristics of patients ($n = 135$)

Variables	Frequency	Percentage
Age category		
15–24 years	17	12.6
25–34 years	16	11.9
35–44 years	30	22.2
45–54 years	38	28.1
≥ 55 years	34	25.2
Parity		
Para 0	39	28.9
Para 1	16	11.9
Para ≥ 2	80	59.2
Menopausal status		
Pre-menopausal	58	43.0
Post-menopausal	77	57.0
Final histology		
Borderline	32	23.7
Malignant	54	40.0

In the determination of the histological subtypes of epithelial tissues, a total of 112 patients were evaluated. The accuracy of frozen section to diagnose histological subtypes of epithelial tumors was 97% with a very strong degree of agreement (= 0.789; 95% CI 0.05–11.38). The mucinous epithelial tumors were the commonest histological subtype both on frozen section and histology with distribution of 57.1% (64/112) and 53.6% (60/112) respectively. The other subtypes on final histology were serous in 33.6% (37/112), endometrioid in 8.9% (10/112), and mixed epithelial in 2.7% (3/112) as shown in Table 2.

In the final histological assessment of the 135 frozen section–diagnosed epithelial tumors, 54 were malignant, 49 were benign, and 32 were borderline, while on frozen section, 46 were malignant, 53 were benign, and 36 were borderline. Frozen section tended to under call malignancy. The Cohen's kappa value was 0.719 with a P value = 0.0001, and the McNemar's chi-square value was 4.693 with a P value = 0.197. This is illustrated in Table 3.

The validity statistics of frozen section, using final histology as the gold standard, in the identification of borderline, benign, and malignant ovarian lesions are shown in Table 4. The accuracy values of frozen section were 86.7%, 88.1%, and 88.1% for benign, malignant, and borderline lesions respectively. The sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, odds ratio, and kappa value of frozen section to diagnose benign lesions were 85.7%, 97.2%, 79.2%, 91.5%, 6.70, 0.16, 40.91, and 0.72 respectively. For malignant lesions, they were 77.8%, 95.1%, 91.3%, 86.5%, 15.75, 0.23, 67.38, and 0.75, while for borderline lesions, they were 81.2%, 90.3%, 72.2%, 93.9%, 0.72, 8.37, 40.3, and 0.67 respectively.

Table 5 shows that the diagnostic discordance resulted in over-diagnosis rate of 27.8% (10/36) for borderline lesions, 20.8% (11/53) for benign, and 8.7% (4/46) for malignant. Over-treatment or under-treatment occurred in 19.3% (26/135) of patients.

Discussion

The interest of the gynecological oncologist in the review of any ovarian pathology is to identify the presence of malignancy or its absence, no matter how occult it may be and offer the patient the best possible treatment to cure, halt disease progression, or improve the quality of life. Ovarian malignancy is the most lethal of gynecological cancers globally. Women who are affected by epithelial ovarian malignancies are usually post-menopausal and over the age of 50 years [16, 17]. The demographic distribution of patients for which frozen sections were done in this study fits into those at risk with the mean age of 44.9 ± 14.2 years and more than half of them being menopausal.

Frozen section, being an intraoperative tool to assist the surgeon make crucial decisions, should be reliable enough to avoid under- or over-diagnosis and subsequently inappropriate intervention. The overall diagnostic concordance of frozen section to final histology in this study was 81.4% which is lower than that observed by Ilker et al. where a diagnostic concordance of 96.5% was obtained [3]. However, in their study population, all ovarian tumors were included with a high proportion of benign lesions. In a study on primary ovarian epithelial tumors by Fatemali et al. [18], the diagnostic accuracy rates of frozen section for borderline, malignant, and benign tumors were 80.3%, 67.2%, and 98% respectively as against 88.1%, 88.1%, and 86.7% observed in this study. The reasons for the wide variations are probably due to sampling error, technical error, and histological variants considered [19, 20]. In a systematic Cochrane review of 38 studies by Ratnevelu et al. [14], an average sensitivity of 90% (a range of 71–100%) and a specificity of 89.5% (typical range 58–99%) were identified for frozen section in the identification of malignant and borderline ovarian tumors considered as one pool. For benign tumors, the sensitivity was 96.5% (range 83–100%) and specificity

Table 2 Validity of frozen section in identifying subtypes in relation to histology (n = 112)

	Mixed epithelial	Mucinous	Serous	Endometrioid	Clear cell
Sensitivity	33.3%	95.0%	83.8%	90.0%	0.0%
Specificity	100%	86.5%	97.3%	96.1%	100%
PPV	100%	89.1%	93.9%	69.2%	*
NPV	98.2%	93.8%	92.4%	99.0%	98.2%
Accuracy	98.2%	91.1%	92.9%	95.5%	98.2%
LR+	*	7.058	31.419	22.95%	*
LR−	0.72	0.058	0.167	0.104	*
OR	*	122.143	188.587	220.5	*

PPV Positive predictive value, ***NPV*** Negative predictive value, *LR* Likelihood ratio; ***OR*** Odds ratio

*These validity tests are statistically not possible with available data

Table 3 Comparison of tumor type (benign, borderline, and malignant) at intraoperative frozen section and final histology

		Final histology			Total
		Benign	Malignant	Borderline	
Frozen section diagnosis	Benign	42	6	5	53
	Malignant	3	42	1	46
	Borderline	4	6	26	36
	Total	49	54	32	135

McNemar chi-square = 4.683, p value = 0.197

Percentage agreement = 81.5, kappa = 0.72, p value = 0.0001

was 89.5% (range of 58–99%). A study with only epithelial ovarian tumors indicated validity values largely similar to our study with sensitivity and specificity for benign epithelial lesions of 97.9% and 95%, malignant 67.2% and 100% and 91% and 88.4% for borderline tumors [15]. In another study, the positive predictive values (PPV) were 99.7%, 93.8, and 62.5% for malignancy, benign, and borderline lesions, and the negative predictive values (NPV) were 95.1%, 100%, and 97% for the same categories [11]. A higher PPV of frozen section for malignant lesions is an indication of the ability to predict more accurately the presence of malignant lesions in relation to borderline and benign ovarian lesions in the study population. Predictive values are dependent on prevalence and case mix.

Under-diagnosis is a recipe for under-treatment and findings from this study indicate a higher degree of under-diagnosis in patients with malignancy. This implies a greater recourse to a second operation with an increase in cost and morbidity.

The mucinous epithelial histological subtype which is predominant in this study, has been linked to a higher degree of under-diagnosis because of its size, complex morphology and having both borderline, benign, and malignant components in the same lesion [15, 19, 20].

In a study on mucinous ovarian tumors [21], the sensitivity of frozen section for borderline tumors was only 67% and for malignant tumors it was 56%. A size larger than 13 cm and number of frozen sections less than 4 were found to be associated with discrepancy.

In our study, borderline ovarian tumors were over-diagnosed, possibly resulting in some unnecessary omentectomies and lymphadenectomies. Over-diagnosis of borderline ovarian tumors was also highlighted by Jim et al. [22] and Song et al. [23]. Benign tumors were over-diagnosed while malignancies were under-diagnosed, leading to the need for a second surgery. Probably, these were in younger women where fertility or ovarian function was of important considerations.

The result of misdiagnosis is inappropriate surgical care for those concerned. Two patients had under-treatment of their condition according to FIGO guidelines because of fertility concerns even though there was concordance between the histology and frozen section and, thus, should technically not be considered as under-treatment but a considered decision to preserve fertility. The obvious danger of under-treatment is the high rate of treatment failure or the need for subsequent corrective action. Conversely, for over-treatment which was observed in 5.9% of patients studied,

Table 4 Diagnostic test characteristics of frozen section in epithelial ovarian tumors

Tumor type	Accuracy %	Sensitivity %	Specificity %	PPV	NPV	LR +	LR −	OR	Kappa	Under-diagnosis %	Over-diagnosis %
Benign	86.7	85.6	87.2	79.2	91.5	6.701	0.164	40.909	0.717	14.3	20.8
Malignant	88.1	77.8	95.1	91.3	86.5	15.75	0.234	67.375	0.747	22.2	8.7
Borderline	88.1	81.3	90.3	72.2	93.9	8.369	0.208	40.3	0.686	18.8	27.8

*PPV Positive predictive value, NPV Negative predictive value, $LR+$ Positive likelihood ratio, $LR-$ Negative likelihood ratio, OR Odd ratio

**P values < 0.0001 for all variables at 95% confident interval

Table 5 Relationship of frozen section diagnosis and extent of surgery offered compared with final histology

		Surgery extent in relation to final histology			Total
		Adequate	Under-treatment	Over-treatment	
Frozen section diagnosis	Benign*	43	10	0	53
	Malignant**	40	2	4	46
	Borderline	26	6	4	36
Total		109	18	8	135
		(80.7%)	(13.3%)	(5.9%)	(100%)

*One patient had adequate surgery despite discordance between frozen (benign) and final history (borderline). Patient age 57 years + surgeon's clinical decision of malignancy while awaiting FS report

**Two patients had fertility-sparing surgeries despite the fact that there was concordance of malignancy between histology and frozen section and as such classified as under-treatment tumor

undue exposure to surgical risk and also medicolegal issues may arise.

In order to avoid misdiagnosis by frozen section, an improvement in tissue sampling skills on the part of the surgeon and that of the pathologist, location of frozen section facility within the theater complex, and increase in the number of representative slides to enable tissue diagnosis is advised [23, 24]. In addition, training and retraining of pathologists in frozen section techniques may be useful. It is also imperative that patients are duly counseled prior to surgery on the probable institutional diagnostic accuracy of the frozen section on epithelial ovarian tumors to avoid medicolegal issues.

This study is limited by the absence of an established protocol for frozen section requests. Thus, there may be some selection bias. The final histology was not independent of the frozen section diagnosis as the pathologists were not blinded. However, the strengths are that consecutive cases of frozen section were used, and a representative number of histological categories were available to make adequate statistical analysis.

Conclusion

Intraoperative frozen section is useful in detection of the various categories of epithelial ovarian lesions with highest specificity but lowest sensitivity in detection of malignant tumors. It should be used in younger patients before sacrificing fertility and in older patients before morbid surgery. The proactive steps suggested may be of value to improving the overall diagnostic accuracy of frozen section. Surgeons need to work closely with pathologists to maximize the usefulness of frozen section for complex ovarian masses at each center.

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Contributions Nyengidiki T Kennedy: Conceptualization, methodology, analysis, data curation, original draft

Ajit Sebastian: Conceptualization, validation, data curation, writing and review, visualization

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Compliance with Ethical Standards Permission for the study was obtained from the Institutional Review board (IRB).

Conflict of Interest The authors declare that they have no conflict of interest.

Disclaimers None

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