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Intraoperative frozen section analysis of ovarian tumors: a 11-year review of accuracy with clinicopathological correlation in a Hong Kong Regional hospital

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ABSTRACT

Objective Intra-operative frozen section (IFS) can provide an instinct guide for treatment of ovarian tumors intra-operatively, though limitations exist. This study intended to evaluate the diagnostic performance of IFS and possible clinicopathological factors influencing the diagnostic accuracy of IFS.

Methods A retrospective review of IFS of ovarian lesions from 2006 to 2016 was done. The diagnostic performance of benign, borderline, and malignant IFS diagnosis was evaluated. Logistic regression analysis was used to assess the influence of clinicopathological parameters on the likelihood of underdiagnosis.

Results There were 1143 consecutive cases during the study period. The overall accuracy was 93.7%. For benign diagnoses, the IFS diagnostic accuracy, sensitivity, and specificity were 97.20%, 100%, and 92.51%, respectively. If borderline and malignant diagnoses were considered as a single group, the IFS diagnostic accuracy was 97.20%, with 92.51% sensitivity and 100% specificity. At univariate regression analysis, intact capsules at time of delivery (OR_{unadj} = 1.9), stage I lesions (OR_{unadj} = 3.76) and ultrasound (USG) score 0 (OR_{unadj} = 2.52) were positively associated with underdiagnosis. Further multivariate analysis showed that only stage I lesions (OR = 3.62) and USG score 0 (OR = 2.32) were positively associated with underdiagnosis. For the cases with underdiagnosed IFS, 54% (34/63) received incomplete primary staging surgery.

Conclusions The study demonstrated that IFS provided excellent specificity to differentiate borderline or malignant tumors from benign lesions. IFS in early-stage ovarian cancers needs to be interpreted with caution, though IFS is most important for this group of lesions. A reliable IFS diagnosis often requires efficient communication between surgeons and pathologists.

INTRODUCTION

Intra-operative frozen section (IFS) as an intra-operative diagnostic tool to guide procedural decision has been used for more than 100 years, since Louis B. Wilson published his technique in a JAMA article dated December 1905.[1] In gynecological oncology, the most common scenario requiring IFS is probably in the evaluation of ovarian masses. Risk of Malignancy Index (RMI) has been used in many national guidelines to predict malignant risk of ovarian masses. Newer models, such as the Assessment of Different NEoplasias in the adnexa (ADNEX) model, perform better than RMI.[2] However, gynecologists may still encounter unexpected ovarian masses intra-operatively that are of unknown nature or suspicious of malignancy. An accurate IFS can provide a reliable guide, thus minimizing the chance of overtreatment with unnecessary procedures or undertreatment requiring a second operation or adjuvant chemotherapy. A recent systematic review has concluded that IFS has an average sensitivity of 90% and specificity of 99.5% in diagnosing ovarian malignancy.[3] It is well known that IFS has its limitations, such as in the diagnosis of borderline and mucinous ovarian tumors.[4] Although a survey in the United Kingdom found that IFS is less commonly performed, in many countries this practice is still considered routine in most cases.[5]

In this study, we assessed the accuracy of IFS as a diagnostic test for benign, borderline, and malignant ovarian tumors in a regional hospital in Hong Kong. Possible clinicopathological factors affecting the diagnostic accuracy of IFS were investigated.

METHODS

A retrospective review of IFS of ovarian lesions from January 2006 to December 2016 was done at a regional hospital in Hong Kong. All consecutive cases of ovarian lesions with IFS done in the studied period were retrieved from the electronic histopathology database, using systematized nomenclature of medicine codes (SNOMED). The histopathology reports, medical records, and operation notes were reviewed in the Clinical Management System (CMS). Medical records were further retrieved from the Medical Records Office for review of ultrasound (USG) images of tumors (if not well documented in the electronic records). Retrieved data included age of the patients, menopausal status, tumor histology, FIGO (International Federation of Gynecology and Obstetrics) staging,[6] tumor capsule integrity at time of tumor excision, number of IFS tissue blocks required, whether imprints were performed or not, tumor size

Table 1 Comparison of frozen section and final diagnosis (N=1143)

Frozen section diagnosis	Final diagnosis			
	Benign	Borderline	Malignant	Total
Benign	716	15	17	748
Borderline	0	116	38	154
Malignant	0	2	239	241
Total	716	133	294	1143

(cm), tumor laterality, presence of ascites, USG score, preoperative CA125 level (IU/ml), RMI, route of surgery (open surgery vs laparoscopic surgery), and whether the surgery was scheduled surgery or emergency operation. RMI and USG score were calculated using RMI I as described by Jacobs in 1990.[7] USG score was based on presence of five items in the sonographic images, namely bilateral lesion, multilocular cyst or septation, evidence of solid areas, evidence of metastasis, and presence of ascites. USG score was 0 if none were present, 1 if one item was present, and 3 if two or more items were present. RMI was calculated for each subject by multiplying USG score (U), menopausal score (M) and serum CA125 level (RMI=U x M x serum CA125 level). Cases with IFS deferred until paraffin section were excluded. Discordant cases were defined as cases with the IFS diagnosis and final histology falling into different categories (benign, borderline, or malignant). Discordant cases were further classified as underdiagnosis and overdiagnosis. The tumor was underdiagnosed if the final diagnosis was malignant but the IFS diagnosis was benign or borderline, or if the final diagnosis was borderline but the IFS diagnosis was benign. The tumor was overdiagnosed if the final diagnosis was benign but the IFS diagnosis was borderline or malignant, or if the final diagnosis was borderline but the IFS diagnosis was malignant. Specimen slides of discordant cases were reviewed by a specialist pathologist. Both archived IFS slides and final paraffin slides were reviewed. Overall accuracy, proportion of underdiagnosis, and overdiagnosis for all IFS were calculated. The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95% CI were also calculated for benign, borderline, and malignant lesions. Further clinicopathological correlation analysis was performed. Pearson's χ^2 test or Fisher's exact test were used to examine differences between concordant group and discordant group. The association of subjects' clinicopathological characteristics with discordant cases was subsequently assessed by logistic regression, with multivariate logistic regression using backward selection method for variables with p value <0.1 in the univariate analysis. Statistical analyzes were performed using SPSS 22.0 for Windows (IBM Corp., Armonk, New York) and OpenEpi: Open Source Epidemiologic Statistics for Public Health, version 3.01 (http://www.openepi.com). Statistical significance was set at p value <0.05. Finally, the effect of discrepancy on the completeness of the primary surgery was evaluated. Concerning the staging procedure, principles of surgery suggested in the National Comprehensive Cancer Network Guidelines on Ovarian Cancer were used as standard.[8] For newly diagnosed apparently early-stage ovarian malignancy, staging laparotomy including bilateral salpingo-oophorectomy, hysterectomy, omentectomy, pelvic, and para-aortic lymphadenectomy should be performed. For borderline tumors, staging laparotomy may omit lymphadenectomy but should include omentectomy and multiple peritoneal biopsies. Any case not fulfilling the required extent of procedure will be regarded as incomplete staging.

RESULTS

The cohort included 1149 ovarian lesions sent for IFS reporting from January 2006 to December 2016. Six cases were excluded as the diagnosis was deferred from the time of the IFS (0.5%). The final study cohort comprised 1143 cases, with 716 benign, 133 borderline, and 294 malignant. Table 1 shows the comparison of IFS and paraffin section diagnoses. There were 1071 concordant and 72 discordant cases. The overall accuracy was 93.7%. All IFS and paraffin slides of discordant cases were retrieved and reviewed, and discrepancy confirmed. Seventy cases (97%) of the discordant cases were underdiagnosed at IFS, with only two cases (3%) of overdiagnosis, resulting in an overall underdiagnosis rate of 6.1% and an overall overdiagnosis rate of 0.2%. No benign lesion was overdiagnosed as borderline or malignant in IFS. Table 2 shows the diagnostic values of benign, borderline, and malignant IFS diagnoses, respectively. For benign diagnoses, the IFS diagnostic accuracy, sensitivity, and specificity were 97.20%, 100%, and 92.51%, respectively. For borderline diagnoses, the IFS diagnostic accuracy,

Table 2 Diagnostic value of frozen section for benign, borderline, and malignant lesions (N=1143)

Diagnostic value (% (95% CI))	Benign	Borderline	Malignant	Borderline/malignant
Accuracy	97.20 (96.07 to 98.01)	95.19 (93.79 to 96.28)	95.01 (93.59 to 96.13)	97.20 (96.07 to 98.01)
Sensitivity	100 (99.47 to 100)	87.22 (80.48 to 91.86)	81.29 (76.44 to 85.34)	92.51 (89.61 to 94.64)
Specificity	92.51 (89.61 to 94.64)	96.24 (94.88 to 97.25)	99.76 (99.15 to 99.94)	100 (99.47 to 100)
Positive predictive value	95.72 (94.02 to 96.95)	75.32 (67.95 to 81.46)	99.17 (97.03 to 99.77)	100 (99.04 to 100)
Negative predictive value	100 (99.04 to 100)	98.28 (97.26 to 98.92)	93.90 (92.15 to 95.29)	95.72 (94.02 to 96.95)

sensitivity, and specificity were 95.19%, 87.22%, and 96.24%, respectively. For malignant diagnoses, the IFS diagnostic accuracy, sensitivity, and specificity were 97.20%, 81.29%, and 99.76%, respectively. If borderline and malignant diagnoses were considered as a single group, the IFS diagnostic accuracy increased to 97.20%, with 92.51% sensitivity and 100% specificity.

There were 427 cases with final pathology of either borderline or malignant for logistic regression in the current study. As there were only two cases with overdiagnosis, this group was not further analyzed for lack of statistical power. Finally 425 cases remained for subsequent logistic regression. Pearson's χ^2 test or Fisher's exact test were performed to compare the correct diagnosis and underdiagnosis groups. Table 3 shows the clinicopathological characteristics of the cases of borderline and malignant lesions, and whether the cases had correct diagnosis, underdiagnosis, or overdiagnosis. The mean age of the study population was 49.83 (13–91) years, with 79.4% (338/427) aged 40+ years, and 46.4% (198/427) were post-menopausal. Epithelial tumors accounted for 79.6% of cases, including 15.7% (67/427) serous tumors, 29.0% (124/427) mucinous tumors, 17.1% (73/427) endometrioid tumors, and 17.8% (76/427) clear cell tumors. Almost 70% (299/427) of cases were stage I. The mean ovarian tumor diameter was 14.5 cm (2–40 cm), and 43.6% (186/425) of cases with diameter 15 cm or above. The mean pre-operative CA125 value was 320.89 IU/mL (3.7–8831 IU/mL), with 72.1% (307/427) of cases higher than 35 IU/mL. Ascites was present in 23.4% (100/427) of cases. USG scores were 0, 1, and 3 in 7.5% (32/427), 41.9% (179/427), and 50.6% (216/427) of cases, respectively. For RMI score, 52% (221/425) of the tumors scored greater than 250, while only 15.5% (66/427) scored less than 25. Almost 94.8% (405/427) of cases had laparotomies, and 97.7% (417/427) of cases were elective operations. Concerning tumor integrity, 61.8% (264/427) of the tumors were ruptured during manipulation. The majority of cases had either one or two blocks prepared during frozen section, with only 7.0% (30/427) of cases having three or more blocks. Imprints were not a common practice, and were done in only 15.9% (68/427) of cases.

Table 4 shows the association of clinicopathological parameters with underdiagnoses using logistic regression analysis. Of the total 425 cases, 355 were in the correct diagnosis group and 70 were in the underdiagnosis group. At univariate regression analysis, presence of intact capsule was positively associated with underdiagnosis (unadjusted OR (OR_{unadj})=1.9, 95% CI 1.13 to 3.19). Compared to other histologic types, the odds of underdiagnosis in serous and clear cell lesions were lower (OR_{unadj}=0.33, 95% CI 0.12 to 0.88 and OR_{unadj}=0.41, 95% CI 0.17 to 0.97, respectively), while mucinous lesions did not show significant difference. Stage I lesions were positively associated with underdiagnosis when compared with higher-stage lesions (OR_{unadj}=3.76, 95% CI 1.57 to 9.01). A USG score of 0 was also positively associated with underdiagnosis (OR_{unadj}=2.52, 95% CI 1.14 to 5.59). At multivariate analysis, only staging and USG score were positively associated with underdiagnosis, where the adjusted OR for stage I lesions was 3.62 (95% CI 1.50 to 8.69), and that for a USG score of 0 was 2.32 (95% CI 1.03 to 5.21).

We further reviewed how underdiagnoses would affect the completeness of staging operation. Although there were 70 cases of underdiagnoses, as surgical staging is not required if the ovarian tumor is metastatic in nature, we excluded the seven cases with a final diagnosis of metastatic malignant tumors. For the remaining 63 underdiagnosed cases, complete surgical staging was performed in 29/63 (46%) cases, while 54.0% (34/63) of cases were considered as incomplete staging. Among the 29 optimally staged cases, 62% (18/29) were malignant cases and 38% (11/29) were borderline cases. For the 34 incompletely staged cases, 82% (28/34) cases were malignant while borderline tumor only accounted for 18% (6/34) of cases.

DISCUSSION

In the current study, among the 1143 cases with IFS of ovarian lesions, there were 133 borderline tumors and 294 malignant tumors. Apart from a slightly higher prevalence of borderline tumors in our hospital, our series showed a similar distribution to the recent Cochrane systematic review.[3] In that systematic review, borderline and malignant tumors were considered test-positive and benign lesions test-negative, the average IFS sensitivity was 96.5% and specificity was 89.5%. In our study, if combining both borderline and malignant tumors as single positive group similarly, the IFS sensitivity was 92.51% (95% CI 89.61% to 94.64%) and the specificity was 100% (95% CI 99.47% to 100%). A more conservative approach in pathology reporting of IFS could attribute to a slightly lower sensitivity but excellent specificity. A recent retrospective review of 277 cases in a large Australian teaching hospital concluded the overall IFS sensitivity for diagnosing malignant disease was 75.9% and specificity was 100%.[9] Diagnostic values of IFS were also calculated for individual tumor groups. It is interesting to note that the PPV of a borderline IFS diagnosis was only 75.32%. In this study, we adopted a stringent approach; tumors with frozen diagnosis "at least borderline tumor" would be classified as borderline. As expected a significant portion of such cases would be malignant tumors in the final diagnosis. Similarly, the sensitivity of IFS in diagnosing malignant tumors was only 81.29% because of the same reason.

Previous studies found that IFS performed less well in differentiating borderline and malignant tumors.[4] In the current study, 24.7% of borderline tumors at IFS were upgraded to malignant tumors at final diagnosis. The figure was similar to the reported average upgrade rate of 21% .[3] Diagnoses were considered concordant when the IFS diagnosis was borderline or at least borderline with final malignant pathology, as these cases were managed in a similar way intra-operatively.[10]

There are different types of errors affecting the accuracy of IFS diagnosis, including sampling errors, technical errors, and interpretation errors as mentioned by Stewart et al.[11] On reviewing the IFS slides and final paraffin slides of the 70 underdiagnosed cases, sampling errors were noted in 47% (33/70) of cases. As expected, in tumors notoriously known to be heterogeneous in nature, such as mucinous tumors and teratomas, sampling was particularly problematic. Interpretation errors were noted in 6/70 cases (8.6%), the most common scenario was that the atypical cells were not recognized in the first viewing of the IFS slides, but could be appreciated on second review coupled with converted paraffin slides. In general, the preparation of the cryostat slides was considered quite satisfactory. Technical errors were only noted in two cases (2.9%), in which there was under-exposing of tissue in the IFS slides. No obvious errors were found in the remaining 31 underdiagnosed cases. For the two overdiagnosed cases, interpretation errors were regarded as the main contributing factor.

Table 3 Subjects' clinicopathological characteristics and the accuracy of frozen section diagnoses (N=427)*

Characteristic	Correct diagnosis (n=355)	Underdiagnosis (n=70)	Overdiagnosis (n=2)	P values†	All (N=427)
Age (years)				0.667	
<40	74 (20.8)	13 (18.6)	1		88 (20.6)
≥40	281 (79.2)	57 (81.4)	1		339 (79.4)
Menopausal status				0.25	
Pre-menopausal	194 (54.6)	33 (47.1)	2		229 (53.6)
Post-menopausal	161 (45.4)	37 (52.9)	0		198 (46.4)
Histology type				0.052	
Germ cell lesions	20 (5.6)	6 (8.6)	0		26 (6.1)
Sex cord-stromal lesions	11 (3.1)	4 (5.7)	0		15 (3.5)
Metastatic lesions	20 (5.6)	7 (10)	0		27 (6.3)
Serous lesions	61 (17.2)	5 (7.1)	1		67 (15.7)
Mucinous lesions	97 (27.3)	26 (37.1)	1		124 (29.0)
Endometrioid lesions	60 (16.9)	13 (18.6)	0		73 (17.1)
Clear cell lesions	69 (19.4)	7 (10)	0		76 (17.8)
Unclassified	17 (4.8)	2 (2.9)	0		19 (4.4)
Staging				0.01	
I	240 (67.6)	57 (81.4)	2		299 (70.0)
II	34 (9.6)	1 (1.4)	0		35 (8.2)
III	59 (16.6)	5 (7.1)	0		64 (15.0)
IV	2 (0.6)	0 (0)	0		2 (0.5)
Unstaged	20 (5.6)	7 (10)	0		27 (6.3)
Capsule intact				0.014	
Intact	127 (35.8)	36 (51.4)	0		163 (38.2)
Ruptured	228 (64.2)	34 (48.6)	2		264 (61.8)
Frozen section blocks (n)				0.504	
1	141 (39.7)	28 (40)	1		170 (39.8)
2	191 (53.8)	35 (50)	1		227 (53.2)
≥3	23 (6.5)	7 (10)	0		30 (7.0)
Imprints				0.669	
Yes	58 (16.3)	10 (14.3)	0		68 (15.9)
No	297 (83.7)	60 (85.7)	2		359 (84.1)
Tumor size (cm)				0.201	
<5	9 (2.5)	3 (4.3)	0		12 (2.8)
5–14.9	197 (55.5)	31 (44.3)	1		229 (53.6)
≥15	149 (42.0)	36 (51.4)	1		186 (43.6)
Tumor location				0.773	
Bilateral	45 (12.7)	8 (11.4)	0		53 (12.4)
Unilateral	310	62 (88.6)	2		374 (87.6)
Ascites				0.446	
Yes	86(24.2)	14(20.0)	0		100 (23.4)
No	269(75.8)	56(80.0)	2		327 (76.6)
Ultrasound score				0.062	
0	22 (6.2)	10 (14.3)	0		32 (7.5)
1	151 (42.5)	26 (37.1)	2		179 (41.9)

Continued

Table 3 Continued

Characteristic	Correct diagnosis (n=355)	Underdiagnosis (n=70)	Overdiagnosis (n=2)	P values†	All (N=427)
3	182 (51.3)	34 (48.6)	0		216 (50.6)
Pre-operative CA125 (IU/ml)†				0.163	
≤35	94 (26.6)	24 (34.8)	0		118 (27.8)
>35	260 (73.4)	45 (65.2)	2		307 (72.2)
Risk of Malignancy Index‡				0.162	
<25	50 (14.1)	16 (23.2)	0		66 (15.5)
25–250	116 (32.8)	21 (30.4)	1		138 (32.5)
>250	188 (53.1)	32 (46.4)	1		221 (52.0)
Route of surgery				0.148	
Laparoscopy	21 (5.9)	1 (1.4)	0		22 (5.2)
Open surgery	334 (94.1)	69 (98.6)	2		405 (94.8)
Type of surgery				1	
Emergency	9 (2.5)	1 (1.4)	0		10 (2.3)
Scheduled elective	346 (97.5)	69 (98.6)	2		417 (97.7)

*Data presented as count (%).
†Pearson's χ^2 test or Fisher's exact test for comparing correct diagnosis and underdiagnosis.
‡n(correct diagnosis)=355 and n(underdiagnosis)=70.

At univariate logistic regression analysis, stage I lesion, intact capsule, and a USG score of 0 were positively associated with underdiagnosis. At multivariate logistic regression analysis, stage I tumor and a USG score of 0 remained as significant factors positively associated with IFS underdiagnosis. Owing to time constraints, when performing IFS, the attending pathologist can only select the most suspicious areas for cryostat slides, most commonly looking for solid areas. For those ovarian tumors with USG score zero, probably no obvious solid area could be found during gross examination. The attending pathologist could only take random sectioning from the cyst wall, thus increasing the chance of sampling errors. Conversely, for stage 2 lesions or above, it is common to have outer surface irregular growth, or presence of raw areas owing to excision of tumor with invasion to adjacent areas. All these can provide clues to the pathologist for selecting representative tissue during IFS. This may explain why accuracy was jeopardized in stage I lesions. This suggests a paradoxical dilemma. IFS is most useful in grossly stage I early ovarian cancer.[12] An accurate diagnosis can allow the surgeon to proceed to staging procedure appropriately, including lymphadenectomy, which may upstage the disease if occult spreads were present. With accurate surgical and pathological staging, 18% of grossly stage I ovarian cancer will be upgraded to FIGO stage 2 or higher.[13] Thus extra care needs to be exercised in IFS interpretation in early-stage disease.

Some previous studies investigated factors affecting the accuracy of borderline tumors. Gultekin et al found that ovarian mass dimension, presence of solid component, preoperative CA125 value, and capsule integrity were factors affecting the accuracy of IFS.[14] One study reported mucinous histology to be the only significant factor in IFS underdiagnosis.[15] Ureyen et al also addressed the diagnostic difficulty for frozen analysis for borderline ovarian tumors, especially in mucinous and large tumors.[10] In our multivariate logistic regression analysis we could not demonstrate any significant histology type accounting for underdiagnosis. However, in the univariate analysis we noted that tumors of serous and clear cell histology were negatively associated with underdiagnosis, implying that the performance of IFS in these two histological subtypes were probably superior. Indeed, if using mucinous lesion as a separate variable, statistically significant association with underdiagnosis was found in univariate regression (unadjusted OR=1.94 (95% CI 1.14 to 3.29); p=0.014). This is in accordance with previous studies that showed mucinous tumors impose greater challenges to pathologists when performing IFS. Tangjitgamol et al commented that most cases of incorrect diagnoses were the low malignant potential mucinous tumors, which were usually large and had heterogenic histology.[16] During IFS, when the diagnosis is solely by recognition of architectural pattern and cellular morphology under the microscope, it is not easy to differentiate whether an mucinous tumor is of primary ovarian origin or metastasis. We know that even with the help of further immunohistochemical profiling, sometimes it can still be challenging.

With a large and heterogeneous tumor, the attending pathologist may have difficulty in selecting adequate and representative areas for examination, especially when there are time constraints. Thus, in our hospital, sometimes we may encounter IFS diagnosis being “at least borderline tumor”, of even “focal atypia noted, cannot exclude borderline tumor or malignancy”. At this juncture, the surgeons need to communicate clearly with the pathologist and consider other information before proceeding to further appropriate procedures, including the pre-operative imaging finding and the intra-operative plan verified by the previously signed informed consent.

We further reviewed how underdiagnoses would affect the completeness of a staging operation. For the 63 underdiagnosed

Table 4 Association of clinicopathological characteristics with underdiagnosis: logistic regression analyzes

	Univariate		Multivariate*	
Characteristic	**OR_{unadj} (95% CI)**	**P value**	**OR_{adj} (95% CI)**	**P value**
Age≥40 years	1.15 (0.60 to 2.22)	0.667		
Post-menopausal	1.35 (0.81 to 2.26)	0.251		
Histology type (ref: others)				
Serous lesions	0.33 (0.12 to 0.88)	0.027		
Mucinous lesions	1.07 (0.60 to 1.92)	0.814		
Clear cell lesions	0.41 (0.17 to 0.97)	0.042		
Staging (ref: II–IV)				
I	3.76 (1.57 to 9.01)	0.003	3.62 (1.50 to 8.69)	0.004
Intact capsule	1.90 (1.13 to 3.19)	0.015		
Frozen section blocks (n) (ref: 1)				
2	0.92 (0.54 to 1.59)	0.772		
≥3	1.53 (0.60 to 3.92)	0.372		
Imprints	0.85 (0.41 to 1.76)	0.669		
Tumor size (cm; ref: <5)				
5–14.9	0.47 (0.12 to 1.84)	0.280		
≥15	0.72 (0.19 to 2.81)	0.642		
Bilateral tumor	0.89 (0.40 to 1.98)	0.773		
Ascites	0.78 (0.41 to 1.47)	0.447		
Ultrasound score 0 (ref: ≥1)	2.52 (1.14 to 5.59)	0.023	2.32 (1.03 to 5.21)	0.041
Pre-operative CA125 >35 IU/mL	0.68 (0.39 to 1.17)	0.165		
Risk of Malignancy Index (RMI) (ref: <25)				
25–250	0.57 (0.27 to 1.17)	0.126		
>250	0.53 (0.27 to 1.05)	0.067		
Open surgery	4.34 (0.57 to 32.79)	0.155		
Scheduled elective surgery	1.79 (0.22 to 14.40)	0.582		

*Multivariate logistic regression using backward selection method with variables including histology type, staging, capsule intact, ultrasound score, and RMI.
OR_{adj}, adjusted OR; OR_{unadj}, unadjusted OR; ref, reference.

cases evaluated, 54.0% (34/63) of operations were considered as incomplete staging. This figure was similar to that of a recent Australian study.[9] However, only 23.5% (8/34) of these incompletely staged cases underwent a second staging operation. In the majority of these eight cases, the primary procedures were either unilateral ovarian cystectomy or unilateral salpingo-oophorectomy, and second staging laparotomies were more strongly indicated. The remaining cases were mainly upstaged to malignant tumors finally with borderline as IFS diagnosis. They were regarded as incompletely staged as lacking systematic lymphadenectomy. Not uncommonly, patients would be reluctant to undergo a second major operation only for an additional lymphadenectomy, especially if pre-operative imaging or intra-operative gross findings showed no evidence of enlarged lymph nodes. Also, a patient's premorbid status is also important when considering the feasibility of a second operation. Conversely, in some cases adjuvant chemotherapies were indicated anyway such as high-grade tumors or stage IC disease, so patients would proceed directly to chemotherapy.[9] The two overdiagnosed cases were borderline tumors with malignant frozen diagnosis. There was no over treatment in both cases as staging laparotomy including systematic lymphadenectomy was still an appropriate procedure for borderline ovarian tumor.

The main limitation of this study was the heterogeneous nature of the cases. All ovarian masses sent for IFS during the 11-year study period were included, from non-neoplastic benign lesions to frank malignancy. Conversely, this allowed a sufficient pool of cases, taking into account the fact that this cohort was retrieved from a single center. Similarly, it would be difficult to have a designated team of personnel, both in the theater or laboratory, to handle all the cases. Most malignant cases would be treated by the gynecological oncologists. General gynecologists would treat cases with no or low suspicion, with involvement of gynecological oncologists for subsequent staging procedures. IFS was performed by on-duty specialist pathologists. Individual pathologist performance and changes in reporting protocols over time are potential confounding factors. Nevertheless, this series included a large number of cases, and the case distribution in this study was comparable to that of a recent systematic review.[3]

The diagnostic criteria of borderline ovarian tumors have generated many challenges and controversies for pathologists.[17] The latest terminology and diagnostic criteria were implemented following the 2014 *WHO Classification of Tumors of the Female Reproductive Organs.*[18] Morton et al regarded ovarian tumors with micro-invasion or intra-epithelial carcinoma as malignant for analysis, which may result in a lower sensitivity for diagnosing malignancy.[9] In our study, we included borderline tumors associated with micro-invasion or intra-epithelial carcinoma in the borderline group, in line with the latest WHO classification.[18]

Our study has demonstrated a high level of accuracy of IFS, especially in differentiating borderline or malignant tumors from benign lesions. Frozen sections should always be interpreted with caution, especially in early-stage ovarian malignancy. Ultimately, the management plan should be well formulated by pre-operative workup, from basic history-taking and physical examination, to serum tumor markers and detailed imaging. Ultrasonography should ideally be performed by experienced operators, coupled with further imaging such as computed tomography and magnetic resonance imaging if indicated. Thorough pre-operative patient counseling and informed consent are mandatory for every case, so that the attending surgeon can proceed in accordance with the different intra-operative findings and IFS reporting. Finally, intra-operative communication between surgeons and attending pathologists is of utmost importance, so that information is accurately shared by both parties to minimize interpretation errors.

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