Accuracy of Frozen-Section Diagnosis of Ovarian Mucinous Tumors

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Objective: The objective of the study was to evaluate the diagnostic accuracy of intraoperative frozen sections of ovarian mucinous tumors and to identify the features associated with an inaccurate diagnosis.

Methods: Cases of ovarian mucinous tumors (benign, low malignant potential [LMP] or borderline, primary malignant, and metastatic) diagnosed by frozen section or final histology were recruited. Frozen-section diagnoses were compared with the final histologic diagnoses. Possible variables associated with diagnostic discrepancy were analyzed.

Results: A comparison of the diagnoses was done in 195 cases (102 benign, 61 LMP, 18 primary malignant, and 14 metastatic). Diagnostic agreement was observed in 164 cases (84.1%) and discrepancy in 31 cases (15.9%). The sensitivity of frozen-section diagnosis was low in LMP (67.2%) and malignant tumors (55.6%). The specificity was the lowest in the benign category (78.5%). The positive predictive values of all categories were less than 90% (range, 83.3%–85.7%). Diagnostic discrepancy was associated with tumor size of greater than 13 cm ($P = 0.019$) and the number of frozen sections of 4 or more ($P = 0.035$). However, in a multivariate analysis, there was no independent predictor of diagnostic discrepancy. The number of frozen sections 4 or more was strongly associated with tumor size of greater than 13 cm ($P = 0.004$).

Conclusions: The sensitivity of frozen-section diagnosis of LMP and malignant mucinous tumors was low. The inaccuracy of a frozen-section diagnosis of ovarian mucinous tumors may be related to a tumor size of greater than 13 cm. Increasing the number of intraoperative samples over 3 sections per case may not effectively increase the accuracy of frozen-section diagnosis in mucinous tumors.

Key Words: Mucinous tumor, Ovary, Frozen section, Diagnostic accuracy

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Mucinous tumors comprise a histologic subtype of surface epithelial neoplasms of the ovary. Similar to the other subtypes of ovarian epithelial tumors, mucinous tumors are classified into benign, low malignant potential ([LMP] or "borderline" or "atypical proliferative"), and malignant categories.[1,2] The guidelines for management in each of these categories of ovarian epithelial neoplasm are now well established. Primary ovarian mucinous tumors may be mimicked by metastatic tumors from the other primary sites, mostly adenocarcinomas of the digestive tract.[3] An accurate diagnosis is important because metastatic tumors are managed differently from primary ovarian cancer.

Intraoperative frozen sections provide important information that helps gynecologic surgeons make decisions on the surgical management of ovarian masses. Studies on the accuracy of intraoperative frozen-section diagnosis of ovarian neoplasms have been extensively reported.[4] Decreased diagnostic accuracy of frozen sections of ovarian tumors was associated with large tumor size, mucinous histology, and LMP tumor category.[4–6] However, the analysis of frozen-section diagnosis of ovarian mucinous tumors is rather limited. To our knowledge, the features that affect the accuracy of frozen-section diagnosis in ovarian mucinous tumors have not been specifically evaluated.

The aims of this study were to evaluate the diagnostic accuracy of intraoperative frozen section of ovarian mucinous tumors and to identify the features associated with inaccurate frozen-section diagnoses.

MATERIALS AND METHODS

The study was approved by the research ethics committee of the institution. The surgical pathology files of the Department of Pathology, Faculty of Medicine, Chiang Mai University, between January 2002 and December 2010 were searched for cases of ovarian lesions that were submitted for intraoperative frozen sections. The frozen-section diagnosis and the final histologic diagnosis of each case were identified. The histologic diagnoses of ovarian neoplasm were based on the current World Health Organization classification.[1,7] Cases with the diagnoses either by frozen section or with a final histology as mucinous tumors (benign, LMP, malignant, or metastatic) were recruited into this study. Cases examined between 2002 and 2005 had been included in a previous study on frozen-section diagnosis of ovarian neoplasms,[8] which did not separately analyze the mucinous tumor group. For intraoperative frozen sections, the gross examination and tissue sampling of each ovarian mass were performed by 1 of 4 pathologists (S.S., S.K., J.S., and K.S.). The number of frozen section(s) in each case depended on the decision of the attending pathologist. The final diagnosis was based on the histologic materials sampled for at least 1 section for each centimeter of maximal tumor diameter.

Benign mucinous tumors (cystadenoma or cystadenofibroma) were characterized by a single layer of mucinous epithelial lining without nuclear atypia. Mucinous LMP tumors were diagnosed when atypical epithelial proliferation accounted for 10% or more of the histologic materials.[2,9] Benign mucinous tumor with minor atypical epithelial proliferation was diagnosed if there was focal epithelial atypia and stratification in less than 10% of the histologic materials. The malignant category included invasive carcinoma with a stromal invasion of expansile or infiltrative pattern exceeding 10 mm^2 in area.[1,7] A stromal invasion of 10 mm^2 or less was considered as microinvasion in the LMP category. Mucinous tumors associated with minor foci of mature cystic teratomas were included in this study and were classified into the benign, LMP, or malignant category based on the histomorphology of a mucinous component, although these tumors may now be proposed to be of germ cell origin rather than surface epithelial tumors.[10] In the metastatic group, only tumors with mucinous histology, characterized by the predominance of mucin-producing neoplastic cells, were included. Metastatic tumors with typical signet-ring cells or endometrioid-like histomorphology were excluded. Ovarian mucinous tumors associated with pseudomyxoma peritonei and appendiceal mucinous neoplasms were classified into the metastatic category.[1,2]

The frozen-section diagnoses with the qualifying term "to be ruled out" for malignant tumors or metastatic tumors were classified into such malignant diagnoses as they were likely to result in a similar surgical management such as complete staging for primary malignant tumors or abandonment of radical surgical resection for metastatic tumors. Mucinous tumors with minor atypical epithelial proliferation were classified into a subgroup of the benign category.

Diagnostic agreement was considered when both the frozen-section and final diagnoses were identical or when there was only a minor difference that did not cause a major change in the management; for example, difference in the histologic subtypes of the same category, minor atypical epithelial proliferation in benign mucinous tumors, or microinvasion in mucinous LMP tumors.

Diagnostic discrepancy was considered when the frozen-section diagnosis and final diagnosis in each case were classified into different categories as this could lead to a major change of the surgical management. The discrepancy included underdiagnosis, overdiagnosis, or disagreement regarding the primary site of tumor (primary ovarian versus metastatic).

The sensitivity, specificity, and positive predictive and negative predictive values of the frozen-section diagnoses were calculated in each category of mucinous tumors (Table 1). The comparison between the discrepancy group and the agreement group was made regarding the following variables: patients' age, tumor size, number of frozen sections, ratio of tumor size per frozen-section number, and number of years of work experience in general pathology of the attending

TABLE 1. Calculation methods for the sensitivity, specificity, positive predictive value, and negative predictive value of the frozen-section diagnoses in each of the 4 categories of ovarian mucinous tumors (benign, LMP, primary malignant, and metastatic)

	Final Diagnoses	
Frozen-Section Diagnoses	**No. Cases in the Selected Category**	**No. Cases in the Other 3 Categories**
No. cases in the selected category	A	B
No. cases in the other 3 categories	C	D

Total number of cases from all categories = A + B + C + D. Number of cases with correct frozen-section diagnosis of the selected category = A. Sensitivity = (A/A + C) × 100%. Specificity = (D/B + D) × 100%. Positive predictive value = (A/A + B) × 100%. Negative predictive value = (D/C + D) × 100%.

TABLE 2. Correlation between frozen-section and final diagnoses in 196 cases

	Final Diagnosis				
Frozen-Section Diagnosis	**Benign**	**Benign With Minor Atypia***	**LMP**	**Malignant**	**Metastatic**
Deferred, unspecified	1	—	—	—	—
Benign (n = 102)	90	4	6	2	—
Benign with minor atypia* (n = 19)	4	3	12	—	—
LMP (n = 48)	1	—	41	5	1
Malignant (n = 12)	—	—	1	10	1
Metastatic (n = 14)	—	—	1	1	12
Total (n = 196)	96	7	61	18	14

*Benign mucinous tumor with minor atypical epithelial proliferation.

pathologists. The association between diagnostic discrepancy and these variables was analyzed by χ^2 test, Fisher exact test, or *t* test as appropriate. Multivariate analysis was performed by logistic regression. Statistical significance was considered when $P < 0.05$.

RESULTS

From a total of 490 cases of ovarian masses submitted for intraoperative frozen sections during the study period, 196 cases (40.0%) had the diagnosis of mucinous tumors by frozen section or final histology. The final histologic diagnoses included benign mucinous tumors in 103 cases (52.6%), LMP tumors in 61 cases (31.1%), primary malignant tumors in 18 cases (9.2%), and metastatic tumors in 14 cases (7.1%). Microinvasion was also present in 11 (18.0%) of 61 cases of mucinous LMP tumors. Of 14 cases of metastatic tumors, the primary sites included intrahepatic cholangiocarcinoma (5 cases), large intestine (3 cases), appendix (3 cases), and unknown origin (3 cases).

The overall mean tumor size was 18.9 (SD, 7.0) cm (range, 4.5–41.5 cm); benign, 18.5 (SD, 7.4) cm; LMP, 21.1 (SD, 5.4) cm; primary malignant, 19.2 (SD, 7.6) cm; and

TABLE 3. Discrepancies between frozen-section and final histologic diagnoses

Frozen-Section Diagnosis	**Final Histologic Diagnoses**	**No. Cases (%)**
Underdiagnosis		25 (100)
Benign (n = 8)	Mucinous LMP	6 (24)
	Large cell neuroendocrine CA and mucinous LMP*	1 (4)
	Squamous cell CA in mature teratoma and benign mucinous tumor*	1 (4)
Benign with minor atypia† (n = 12)	Mucinous LMP	12 (48)
Mucinous LMP (n = 3)	Mucinous CA	2 (8)
	Mixed epithelial CA	1 (4)
Mucinous LMP with microinvasion (n = 2)	Mucinous CA	1 (4)
	Large cell neuroendocrine CA and mucinous LMP with microinvasion*	1 (4)
Overdiagnosis		2 (100)
Mucinous LMP (n = 1)	Benign mucinous	1 (50)
Mucinous CA (n = 1)	Mucinous LMP with microinvasion	1 (50)
Disagreement of primary site		4 (100)
Mucinous LMP	Metastatic tumor	1 (25)
Endometrioid CA, with secretory features	Metastatic tumor	1 (25)
Metastatic tumor	Mucinous LMP	1 (25)
	Mucinous CA	1 (25)

*Mucinous tumor is the predominant component of tumor.
†Benign mucinous tumor with minor atypical epithelial proliferation.
CA, carcinoma.

TABLE 4. Accuracy of frozen-section diagnosis of ovarian mucinous tumors

Frozen-Section Diagnosis	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Benign	99.2	78.5	83.5	98.6
LMP	67.2	94.8	85.4	86.5
Primary malignant	55.6	98.9	83.3	95.7
Metastatic	85.7	98.9	85.7	98.9

metastatic, 11.9 (SD, 5.2) cm. The overall mean number of frozen sections was 2.6 (SD, 1.0) (range, 1–8), and the mean ratio of tumor size per the number of frozen sections was 8.2 (SD, 4.4) (range, 2.3–26.0). The correlation between the frozen-section diagnoses and the final histologic diagnoses is shown in Table 2. There was 1 case (0.5%) with deferred intraoperative diagnosis because of the absence of epithelial lining in the frozen sections of an infarcted mucinous cystadenoma. This case was excluded from further analysis.

Of 195 cases, diagnostic agreement was observed in 164 cases (84.1%) and diagnostic discrepancy in 31 cases (15.9%). Diagnostic discrepancy included underdiagnosis in 25 cases (12.8%), overdiagnosis in 2 (1.0%), and disagreement of the primary site in 4 (2.0%). The details of diagnostic discrepancies are shown in Table 3. Of 4 pathologists responsible for frozen-section diagnosis, the number of years of work experience at the time of diagnosis ranged from 5 to 20 years. The rate of diagnostic discrepancy for each pathologist ranged from 13.6% to 17.3% of cases under one's responsibility, the difference of which was not statistically significant ($P = 0.956$).

Of 19 cases with frozen-section diagnoses of benign tumors with minor atypical epithelial proliferation, 12 cases (63.2%) had final diagnoses of mucinous LMP tumors without microinvasion, and none had a malignant component (Table 2). Among the group with frozen-section diagnoses of mucinous LMP tumors, 3 also had stromal microinvasions identified in the frozen sections. The final diagnoses in these 3 cases were mucinous LMP tumor and with microinvasion in 1 case and malignant lesions in the other 2 cases.

The sensitivity, specificity, and positive and negative predictive values of frozen-section diagnosis in each category of mucinous tumors are shown in Table 4. The sensitivity of frozen-section diagnosis was low in LMP tumors (67.2%) and primary malignant tumors (55.6%). The frozen-section diagnosis of the benign category had the lowest specificity (78.5%). Positive predictive values of all categories were less than 90% (range, 83.3%–85.7%). The comparison of variables between the diagnostic agreement group and the discrepancy group is shown in Table 5. The mean values of the patients' age, tumor size, number of frozen sections, ratio of tumor size per number of sections, and number of years of work experience of pathologists were not significantly different between both groups. When subgroup analysis was made in each variable, the tumor size of greater than 13 cm and the number of frozen sections 4 or more were significantly associated with diagnostic discrepancy ($P = 0.019$ and 0.035, respectively). However, in a multivariate analysis, there was no independent predictor of diagnostic discrepancy. A correlation was made between the number of frozen sections (≤3 vs ≥4) and other variables including the final diagnosis category (benign, LMP, or malignant/metastatic), tumor size, and number of years of work experience of pathologists (data not shown). The number of frozen sections 4 or more was associated only with the tumor size of greater than 13 cm ($P = 0.004$).

DISCUSSION

Intraoperative frozen section of ovarian tumors has a high diagnostic accuracy, ranging from 90% to 98%,[5] with a rate of 93.8% in our previous study.[8] Large tumor size,

TABLE 5. Comparison between the diagnostic agreement group and the discrepancy group

Variable	Agreement Group (n = 164 Cases)	Discrepancy Group (n = 31 Cases)	*P*
Age, mean (SD),* y	48.5 (16.3)	47.4 (16.7)	0.725 (T)
≤45	65 (40%)	11 (35%)	0.646 (C)
>45	98 (60%)	20 (65%)	
Tumor size, mean (SD), cm	18.6 (7.1)	20.5 (6.2)	0.160 (T)
≤13	41 (25%)	2 (6%)	0.019 (F)
>13	123 (75%)	29 (94%)	
No. frozen sections, mean (SD)	2.6 (1.0)	2.8 (1.1)	0.286 (T)
≤3	147 (90%)	23 (74%)	0.035 (C)
≥4	17 (10%)	8 (26%)	
Ratio of tumor size per no. frozen sections	8.2 (4.4)	8.5 (4.2)	0.726 (T)
≤8.0	101 (62%)	18 (58%)	0.712 (C)
>8.0	63 (38%)	13 (42%)	
No. years of work experience of pathologists, mean (SD)	12.0 (3.7)	11.8 (3.6)	0.707 (T)
≤10	64 (39%)	10 (32%)	0.476 (C)
>10	100 (61%)	21 (68%)	

*Age unknown in 1 patient.
C, χ^2 test; F, Fisher exact test; T, *t* test.

TABLE 6. Cumulative data on the comparison between frozen-section diagnoses and final histologic diagnoses of ovarian mucinous LMP tumor

		Final Diagnosis (No. Cases)		
Authors (Reference)	**Frozen-Section Diagnosis**	**Benign**	**LMP**	**Malignant**
Puls et al[19]	Benign	—	5	—
	LMP	0	14	7
	Malignant	—	1	—
Geomini et al[6]	Benign	—	4	—
	LMP	2	10	4
	Malignant	—	0	—
Stewart et al[11]	Benign	—	14	—
	LMP	1	28	4
	Malignant	—	1	—
Present study	Benign	—	18	—
	LMP	1	41	6
	Malignant	—	2	—
Cumulative cases	Benign	—	41	—
	LMP	4	93	21
	Malignant	—	4	—

mucinous histology, and LMP tumor category were reported to be limiting factors in frozen-section diagnosis of ovarian masses.[4–6] As mucinous tumors are typically large, these tumors are an important source of difficulties in frozen-section diagnosis. Mucinous LMP tumors seem to be a particularly difficult subset because they combine the important features associated with decreased diagnostic accuracy.[4,6,11] The information related to the accuracy of frozen-section diagnosis of mucinous tumors, particularly of LMP category, is rather limited because most studies included mucinous tumors as a part of analysis of the entire group of ovarian neoplasms or LMP tumors.[5,11–15] Two recent reports with a large number of cases only briefly described the results of frozen-section diagnosis in 145 to 172 cases of mucinous LMP tumors and 70 mucinous adenocarcinomas as a part of their clinicopathologic studies.[16,17]

The diagnostic accuracy values of frozen sections of mucinous tumors were lower than those of all ovarian neoplasms, even in the benign category.[5] In a large analysis of ovarian frozen-section diagnosis by Stewart et al,[11] only 1 mucinous LMP tumor was identified among cases with a "benign" frozen-section diagnosis. However, the total number of benign mucinous tumors was not given. Few metastatic tumors were also misinterpreted as benign neoplasms.[11] Thus, the diagnostic accuracy of the benign category is also of interest. Although the sensitivity of frozen-section diagnosis in the benign mucinous category was high, the specificity (78.5%) was lower than that of the other categories of mucinous tumors (94.8%–98.9%).

Benign mucinous tumors with minor atypical epithelial proliferation may be variably reported as "benign" or a deferred diagnosis "benign versus LMP" pending adequate sampling. In this study, we classified these diagnoses into the benign category as they were likely to result in a conservative management similar to a benign diagnosis. Excluding these cases from analysis may result in a bias toward increased diagnostic accuracy.[4] Of 19 cases with frozen-section diagnosis in this group, 12 (63.1%) had the final diagnosis of mucinous LMP tumors. The review of the final histologic slides of these cases showed low-grade epithelial proliferation in 10 cases. In another 2 cases, only a tiny focus of marked epithelial atypia ("intraepithelial carcinoma") was seen in each tumor, constituting less than 5% of tumor tissue. These were favorable features in mucinous LMP tumors and were related to a very low risk (1.0%) of disease recurrence.[18] A conservative surgical management for this type of frozen-section diagnosis may be acceptable, and a reoperation for complete staging may not be necessary.[16]

Mucinous LMP tumors cause difficulties in frozen-section diagnosis of ovarian neoplasms.[11] They accounted for a significant proportion (46.2%–72.7%) of deferred cases in frozen-section diagnosis.[5,8,14] Tempfer et al[13] commented that frozen-section analysis may not be suitable for large ovarian tumors, with the cutoff size of greater than 3 cm as a predictor of underdiagnosis of LMP tumors. This would raise a suspicion against the use of frozen section in most mucinous tumors as these tumors are usually large. Houck et al[12] reported the agreement rate between the frozen-section and final diagnoses of mucinous LMP tumors of 48.9% in their 47 cases, with underdiagnosis and overdiagnosis in 42.6% and 8.5% of cases, respectively. In our review for cumulative cases from previous studies with available detailed data that allow a comparison between frozen-section and final diagnoses of mucinous LMP tumors in 3 × 3 tables,[6,11,19] the

diagnostic agreement rate was 57.1% (93 of 163 cases), with an underdiagnosis rate of 38.0% and an overdiagnosis rate of 4.9% (Table 6). The sensitivity and the positive predictive value were 67.4% and 78.8%, respectively. The diagnostic agreement rate of mucinous LMP tumors was lower than that of the entire group of LMP tumors (62.6%–67.1%).[13,15]

In our study using the current World Health Organization classification approach,[1,7] the sensitivity for mucinous LMP group (67.2%) and malignant group (55.6%) was within the range of other recent reports within the last 5 years, which was 65.1% to 71.4% for LMP and 52.6% to 64.3% for malignant tumors.[6,11,16,17] The rather low sensitivity of frozen sections in both groups of mucinous tumors was mainly related to underdiagnosis and sampling error.

In frozen section, the detection of stromal microinvasion in mucinous LMP tumors may be a significant finding as 2 of 3 cases in this study had the final diagnoses of malignant neoplasms. Taken together with the tendency toward underdiagnosis of frozen-section examination, this supports the recommendation that tumors with microinvasion detected in frozen sections should be considered as a malignancy for management decisions.[4]

Tumor heterogeneity and sampling error were the explanations for inaccuracy of frozen-section diagnosis in most cases, especially in the underdiagnosis category.[11] Based on previous suggestions,[5,20] a sampling of at least 1 frozen section for each 8 to 10 cm of maximal tumor dimension may help decrease sampling error. In our study, we had an overall mean ratio of tumor size per frozen-section number of 8.2 cm per section. However, diagnostic discrepancy was more frequent in cases with 4 or more frozen sections than in those with fewer frozen sections. We believe that this finding may be explained by the presence of a more suspicious gross appearance of tumors (large complex masses) in the discrepancy group that led pathologists to increase the number of samples. The finding also suggests that the increase in intraoperative sampling of more than 3 sections per case may not effectively increase the accuracy of frozen-section diagnosis in ovarian mucinous tumors.

Large tumor size has been reported to be a predictor of an inaccurate frozen-section diagnosis of ovarian masses.[6] The cutoff size threshold for an inaccurate diagnosis of ovarian neoplasms or LMP tumors was variably reported as 10,[6,21] 15,[15] or 20 cm.[5] In this study, the subgroup of mucinous tumors with a size of greater than 13 cm was significantly associated with inaccuracy of frozen-section diagnosis, although this association was not independent. The 13-cm cutoff size provided the best performance in the prediction of diagnostic discrepancy as compared with the other cutoff values of 10, 15, and 20 cm (P = 0.209, 0.036, and 0.191, respectively). The tumor size of 13 cm has also been proposed to be useful in the distinction between primary and metastatic mucinous tumors.[22]

Technical factors and interpretation errors may contribute to diagnostic inaccuracy,[11] examples of which were cases with overdiagnosis in our study. The assessment of histologic details is less reliable in frozen sections than in routinely processed sections,[11] and the evaluation of the degree of nuclear atypia could be difficult because of freezing-related nuclear artifacts. The pathologists' experience may also be a factor that affects the accuracy of frozen-section diagnosis of ovarian tumors.[21,23,24] In this study, there was no significant difference in the rate of diagnostic discrepancy between each pathologist or between the levels of pathologists' experience. However, all pathologists involved in this study had experience in gynecologic pathology, and their performance may not be representative of that of pathologists in general practice.

Metastatic mucinous tumor to the ovary can be a diagnostic challenge to pathologists and may sometimes be misclassified as benign tumors in frozen sections.[23] In this study, the accuracy of the diagnosis of metastatic mucinous tumors was rather high. In addition to the recent improvement of the diagnostic criteria,[3,25] we believe this was also partly associated with the availability of supporting clinical data. The preoperative and intraoperative information, particularly a previous history of the other cancer and bilateral ovarian involvement, was very helpful in the intraoperative assessment. On the other hand, a previous cancer history led to a bias of frozen-section diagnosis for metastatic tumors in a case of primary ovarian mucinous adenocarcinoma, which occurred 9 years after the treatment of cervical adenocarcinoma with uneventful follow-up. Stewart et al[23] reported that 14.5% of primary ovarian tumors were suspected or diagnosed as metastatic tumors by the frozen-section examination.

In conclusion, the sensitivity of frozen-section diagnosis of ovarian mucinous tumors was low in the LMP and malignant categories. Inaccurate frozen-section diagnosis of mucinous tumors may be related to the tumor size of greater than 13 cm. Increasing the number of intraoperative samples over 3 sections per case may not effectively increase the accuracy of frozen-section diagnosis in ovarian mucinous tumors. In multicystic mucinous tumors, if the frozen sections (at least 3 frozen sections should be obtained) show only features of cystadenoma, the diagnosis should be mucinous neoplasm; LMP or carcinoma cannot be ruled out. Tumor size and laterality should be used to suggest primary versus metastases.

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