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CLINICAL ARTICLE

Gynecology

Is routine frozen section analysis necessary in patients with non-endometrioid cancer or grade 3 endometrioid cancer?

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Abstract

Objective: To explore the accuracy related to type and subtype between frozen section (FS) results and final pathology results in patients with endometrial cancer and to suggest whether it should be routinely performed.

Methods: Retrospective data were collected from 184 patients with endometrial cancer who underwent surgery at a single center (January 2014–December 2018). FS results were compared with the final pathology results with respect to histotype, tumor grade, and depth of invasion to define the accuracy of FS analysis.

Results: Frozen section analysis was performed in 141 (76.6%) patients. The accuracy rates and κ values between the FS and final pathology results with respect to histotype, tumor grade, and depth of invasion were 87.23%, 81.15%, and 98.2% and 0.41, 0.7, and 0.9, respectively ($P < 0.001$). Among the 18 patients with preoperative non-endometrioid cancer (non-EC), six underwent FS analysis, and final pathology confirmed EC in three, of whom 75% were detected by FS analysis. Eight of 19 patients with preoperative grade 3 EC underwent FS analysis and the accuracy rate was 87.5%.

Conclusion: Intraoperative FS analysis is a reliable method that can help intraoperative decision making. It should be performed routinely in patients with non-EC and grade 3 EC.

KEYWORDS
accuracy, endometrial cancer, frozen section, grade 3 endometrioid cancer, non-endometrioid cancer

1 | INTRODUCTION

Frozen section (FS) analysis is widely used for ovarian and endometrial cancers and plays a key role in intraoperative decisions. However, what is its diagnostic value, and is it necessary for all endometrial cancer patients? The present study aimed to explore these questions.

Endometrial cancer is one of the most common gynecologic cancers. The most common histotype is endometrioid cancer (EC).[1] A preoperative diagnosis of endometrial cancer is made by dilatation and curettage, endometrial biopsy, or hysteroscopic biopsy. The accuracy of preoperative and final pathology results varies from 60% to 80%,[2,3] and according to a study of 1804 patients, the κ value is only 0.52,[4] indicating moderate agreement.

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Therefore, preoperative diagnosis has a limited ability to predict pathology, and it is becoming increasingly difficult to ignore the role of FS analysis.

The conventional consensus for endometrial cancer treatment includes total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymphadenectomy.[5] However, management should be individualized according to the risk assessment. Systematic pelvic and para-aortic lymphadenectomy is performed when patients have myometrial invasion (MI) greater than 50%, a non-endometrioid histology, or both. Bogani et al.[6] found a less than 1% risk of lymphatic spread in low-risk patients with a preoperative diagnosis of grade 1 or grade 2 EC and a tumor diameter of 2.0 cm or less; however, the risk was more than 10% in patients with a tumor diameter >2.0 cm or with a preoperative diagnosis of grade 3 EC or non-EC.

The Mayo Clinic criteria define grade 1 or 2 ECs with less than 50% MI as "low-risk" cancers.[7] Patients with these cancers can omit lymphadenectomy. Therefore, the FS pathology affects the intraoperative management. Several studies have supported FS analysis in determining the scope of surgery.[8–10] Some studies have found that it does not correlate well.[11,12] Therefore, our retrospective analysis was first performed to assess the accuracy rate of FS results compared with final pathology results. Second, we attempted to assess the role of FS analysis in patients with non-EC or grade 3 EC.

2 | MATERIALS AND METHODS

This study was conducted to collect demographic and clinical data retrospectively on endometrial cancer patients at Fujian Maternity and Child Health Hospital (Gynecologic Department Two) from January 1, 2014 to December 31, 2018. All procedures performed in studies involving human participants were approved by the Institutional Review Board. All patients were diagnosed with endometrial cancer by dilatation and curettage or hysteroscopic biopsy before hysterectomy. Patients underwent surgery within 6 weeks of diagnosis. The study's inclusion criteria were as follows: (1) the preoperative pathology was endometrial cancer; (2) the patient was not treated with hormone therapy before hysterectomy; (3) the medical records were complete; and (4) the patients orally consented to the use of their medical records by telephone.

The surgeon opened longitudinally for gross examination in the operating room. Tumor size was measured with a ruler if there was a suspected lesion. Tumor size was documented as zero if there was no abnormality in the uterine cavity on gross examination. The surgeon also observed tumor location, range, MI, and cervical invasion macroscopically. Then, the tissue samples were sent for FS analysis. The decision was sometimes personalized for each patient, so not every patient underwent FS analysis. The uterine corpus was opened longitudinally for visual examination at approximately 5-mm intervals from the endometrial side towards the serosa to evaluate the depth of invasion. random sections were removed if there were no gross lesions. FS analysis was performed by several experienced gynecologic pathologists. The final pathologic diagnoses were assumed as the reference standard.

In our department, we follow the Mayo Clinic criteria. If patients are at high risk, for example, grade 2 tumors larger than 2 cm, more than 50% MI, grade 3 tumors, cervical involvement, serous or clear cell histology, they receive lymphadenectomy. Conversely, those with tumors of the EC histotype and of low grade (grade 1) with less than 50% MI do not receive lymphadenectomy.

All statistical analyses were conducted using SPSS software 18.0 (SPSS Inc., Chicago, IL, USA). Data are presented as the mean ± standard deviation. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated with their associated 95% confidence intervals (CIs). Fisher's test was used for cross tabulations. Cohen's κ was used to assess agreement between the FS and final pathology results according to the endometrial histotype, EC grade, and infiltration depth in the myometrium. P values <0.05 were considered statistically significant.

3 | RESULTS

Of the 193 patients with a preoperative diagnosis of endometrial cancer, 184 fulfilled the inclusion criteria, nine patients were excluded because they received hormone therapy or had incomplete data. The baseline characteristics of the study women are summarized in Table 1. In all, 141 (76.6%) patients received FS analysis. Pelvic lymphadenectomy was performed in 81 (44.0%) patients, whereas 45 (24.5%) patients underwent para-aortic lymphadenectomy.

Table 2 summarizes the histotype correlation between the FS and final pathology results. An intraoperative diagnosis of EC was upgraded to a postoperative diagnosis of non-EC in five patients. One patient with non-EC was downgraded to EC. The correlations with the endometrial cancer histotype were 92.1%, 16.6%, 60%, and 66.7% in EC, non-EC, hyperplasia, and no tumor, respectively. The total accuracy rate was 87.23%, with a κ statistic of 0.41 (95% CI 0.21–0.61; $P < 0.001$), showing an almost moderate agreement rate.

Table 3 shows the tumor grade correlations between the FS and final pathology results. A total of 122 patients were diagnosed with EC intraoperatively. Among them, 13 patients (10.7%) were upgraded from preoperative grade 1 to grade 2. One (0.82%) patient was upgraded from grade 2 to grade 3. Four patients experienced downgrading: three from preoperative grade 2 to grade 1, and one from preoperative grade 3 to grade 2. Five patients were diagnosed with non-EC in the final pathology. The accuracy rates for grade 1, grade 2, and grade 3 prediction were 85.25%, 83.61%, and 97.54%, respectively. The total accuracy of tumor grade was 81.15% (99/122). The κ value for tumor grade was 0.7 ($P < 0.001$; 95% CI 0.62–0.83), which indicates substantial agreement.

Table 4 shows the accuracy of MI on FS according to tumor subtype. With final MI and tumor grade as reference standard, the accuracy rates for grade 1 and 2 were 95% and 98%. The interpretations of MI on FS in patients with grade 3 and non-EC were all

correct. There was no significant correlation in determing MI on FS between four groups ($P = 0.760$). Only one patient had less than 50% MI among the 24 patients with more than 50% MI detected on FS analysis. One hundred patients had less than 50% MI, but three patients had more than 50% MI. In addition, in these three patients, two had EC grade 1, and one had a mixed tumor on FS, so the two patients did not undergo lymphadenectomy, ultimately resulting in undertreatment in our department. The accuracy rate for the depth of MI was 98.2% (120/124), with a κ value of 0.9 ($P < 0.001$; 95% CI 0.80–0.99), which indicates excellent agreement.

A total of 18 patients were diagnosed with non-EC preoperatively. When the preoperative and final pathology results were compared, only five (27.8%) patients had a consistent histotype. Among these 18 patients, six underwent FS analysis. The results are summarized in Table 5. Four patients converted to EC during the operation, one patient changed from mixed carcinoma to serous carcinoma and the other one was consistent with preoperative pathology. Among the four patients in whom EC was detected during the operation, the FS results were consistent with the final pathology results in three of them, demonstrating an accuracy rate of 50% (3/6) in the histotype upon comparing the FS and final pathology results. Only one patient did not receive lymphadenectomy because of tumor size. Nineteen patients had preoperative grade 3 EC, and eight patients underwent FS analysis. The concordance rate between the preoperative and final pathology results was 42.1% (8/19). In patients receiving FS analysis, four were down graded to grade 1 or grade 2 comparing preoperative pathology results. Only one patient received undertreatment and other patients received complete staging surgery because of tumor size. The FS results were consistent with the final pathology results in seven patients, with an accuracy rate of approximately 87.5% (7/8). Only one patient had serous carcinoma indicated by the final pathology.

As shown in Table 6, 10 (71%) of 14 patients with preoperative grade 3 and non-EC who had FS had a concordance rate. In contrast, eight (34%) of 23 patients who did not undergo FS had a concordance rate in determining subtype ($P = 0.045$).

TABLE 1 Characteristics of the population[a]

Characteristic	
Age at diagnosis, year	53.88 ± 9.00
Menstrual status	
Premenopause	78 (42.4%)
Postmenopause	106 (57.6%)
BMI	25.13 ± 3.72
Gravidity	0–8 (2, 4)
Parity	0–6 (1, 3)
Hypertension	80 (43.5%)
Diabetes	48 (26.1%)
Maximum tumor diameter, cm	2.1 ± 1.8
Diagnostic method	
D&C	154 (83.7%)
Hysteroscopy	30 (16.3%)
Surgical approach	
Laparoscopy	144 (78.3%)
Laparotomy	40 (21.7%)
Frozen section analysis	
Yes	141 (76.6%)
No	43 (23.4%)
Lymph node dissection	
Para-aortic lymph node	45 (24.5%)
Pelvic lymph node	81 (44.0%)
No	103 (56.0%)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); D&C, dilatation and curettage.

[a]Values are given as mean ± standard deviation, range (P25, P75), or as number (percentage).

4 | DISCUSSION

The present findings show that FS analysis can be a reliable method for the intraoperative management of individuals with endometrial cancer. About 50% of ECs were correctly detected by FS analysis in patients with preoperative non-EC. The accuracy rate between the FS and final pathology results was 87.5% in patients with preoperative

TABLE 2 Tumor subtype correlations between the intraoperativefrozen section and final pathology results[a]

	Final pathology				
Frozen pathology	Endometrioid cancer	Non-endometrioid cancer	Hyperplasia	No tumor	Total
Endometrioid cancer	117	5	0	0	122
Non-endometrioid cancer	1	1	0	0	2
Hyperplasia	7	0	3	1	11
No tumor	2	0	2	2	6
Total	127	6	5	3	141
Correlation (%)	92.1%	16.6%	60%	66.7%	/

Note: $\kappa = 0.41$ ($P < 0.001$) (95% confidence interval 0.21–0.61).

[a]Values are given as number or percentage.

TABLE 3 Tumor grade correlations between intraoperative frozen section and final pathology results[a]

	Final pathology				
Frozen pathology	**Grade 1**	**Grade 2**	**Grade 3**	**Non-endometrioid cancer**	**Total**
Grade 1	62	13	0	2[b]	77
Grade 2	3	32	1	2[c]	38
Grade 3	0	1	5	1[d]	7
Total	65	46	6	5	122

[a]Values are given as number.
[b]Two mixed tumors.
[c]Two serous tumors.
[d]One serous tumor.

TABLE 4 Myometrial invasion on frozen-section and final pathology according to final tumor grade/subtype on permanent section examination[a]

	Myometrial invasion on FS				
Final tumor subtype	**Concordant with final**	**Not concordant with final**	***P* value[b]**	**Under-estimation by FS**	**Over-estimation by FS**
Grade 1 EC	62 (95.4)	3 (4.6)	0.760	2 (66.7)	1 (33.3)
Grade 2 EC	46 (97.9)	1 (2.1)		1 (1)	0 (0)
Grade 3 EC	6 (1)	0 (0)		—	—
Non-EC	6 (1)	0 (0)		—	—

Abbreviations: EC, endometrioid carcinoma; FS, frozen section.
[a]Values are given as number (percentage).
[b]Fisher's exact test.

grade 3 EC. Only two patients with non-EC or grade 3 EC were undertreated. The correlation was 92.1% in the EC histotype. The accuracy rates for predicting grade 1, grade 2, and grade 3 tumors and depth of MI were 85.25%, 83.61%, 97.54%, and 98.2%, respectively. The κ values for tumor grade and MI were 0.7 and 0.9, respectively. Meanwhile, we must note that we cannot rely simply on the preoperative pathology to determine the surgical scope for patients with non-EC or grade 3 EC. At this point, FS analysis plays a unique role.

The standard surgical treatment for endometrial cancer is total hysterectomy and bilateral adnexectomy, with or without lymphadenectomy. If patients have MI greater than 50%, a non-endometrioid histology or both, systematic pelvic and para-aortic lymphadenectomy are recommended. There are some controversies regarding whether to perform lymphadenectomy in low-risk patients; however, it is generally accepted in high-risk patients.[13] The rate of lymphatic metastasis in low-risk patients is 1.7%–9.7%.[7,14] Several studies have reported that lymphadenectomy does not benefit low-risk patients.[7,15] Those with nodal metastases can benefit from lymphadenectomy to guide the appropriate adjuvant treatment and improve survival.[16] Therefore, FS analysis can be used to assess the tumor histotype, FIGO grade, and depth of MI to guide surgeons in the appropriate direction.

In our study, the concordance rate was 87.23% for the histological type, which was lower than the in the study by Wang et al. (100%)[9] and in Stephan and Hansen's study (97.5%).[8] This inconsistency is because the subjects of those studies were patients with EC. However, the correlation with the EC histotype was 92.1%, indicating similar results with the above studies.[8,9] In our therapeutic center, we achieved accuracy rates of 81.15% for tumor grade and 98.2% for depth of MI, consistent with a study[9] that reported a concordance rate of 89.3% for tumor grade and 97.3% for depth of MI. Though a prospective blinded study[17] found that the grade and depth of invasion on FS analysis correlated poorly with the final pathology results, Desouki et al.[18] reported a concordance rate of 80% for tumor grade and 95% for depth of MI between the FS and final pathology results. These data were consistent with those from the published literature, with reported concordance rates varying from 84.3% to 89.3% for grade and from 94.3% to 98.2% for depth of MI.[8–10,19,20] A meta-analysis showed sensitivity, specificity, positive predictive value, and negative predictive value of 85%, 97%, 32.3%, and 16%, respectively, for FS analysis to detect the depth of MI.[21]

A survey of the Society of Gynecologic Oncologists found that only 31% of gynecologic surgeons use FS results in their decisions regarding EC management.[22] The decision to perform FS analysis varies between centers. If the preoperative pathology is non-EC, if the tumor has a large diameter on the intraoperative finding or if the depth of MI is deep by gross examination, the surgeon may not choose FS but may perform lymphadenectomy directly. It should be taken seriously that evaluation of the depth of MI by gross examination is less accurate than that by FS analysis.[23] In addition, for the preoperative diagnosis of non-EC or grade 3 EC, there was still a certain percentage of discrepancy between the preoperative

TABLE 5 Clinicopathological features of the 14 patients with preoperative non-endometrioid and grade 3 carcinoma who received frozen section analysis

Patient	Pre-operative diagnosis	Tumor diameter, cm	Frozen section		Final pathology		Surgery	Impact decision
			Type	Grade	Type	Grade		
1	MIX	1.0	MIX	/	EC	2	TAH + BSO + PLND + omentectomy + appendectomy	No
2	DC	5.0	EC	2	EC	2	TAH + BSO + PLND + PaLND	No
3	MC	2.0	EC	2	EC	2	TAH + BSO + PLND	No
4	MIX	0	EC	1	EC	1	LTH + BSO	Yes
5	MIX	0.5	CCC	/	MIX	/	LTH + BSO + PLND + PaLND	No
6	MIX	2.5	EC	1	MIX	/	LTH + BSO + PLND + PaLND	No
7	EC/G3	4.0	EC	2	EC	2	LTH + BSO + PLND + PaLND	No
8	EC/G3	3.0	EC	3	EC	3	LTH + BSO + PLND + PaLND	No
9	EC/G3	0	EC	3	EC	3	LTH + BSO + PLND + PaLND	No
10	EC/G3	1.0	EC	1	EC	1	TAH + BSO	Yes
11	EC/G3	4.0	EC	3	SC	/	LTH + BSO + PLND + PaLND	No
12	EC/G3	5.0	EC	2	EC	2	LTH + BSO + PLND + PaLND	No
13	EC/G3	4.0	EC	2	EC	2	TAH + BSO + PLND	No
14	EC/G3	6.5	EC	3	EC	3	LTH + BSO + PLND + PaLND	No

Abbreviations: BSO, bilateral salpingo-oophorectomy; CCC, clear cell carcinoma; DC, dedifferentiated carcinoma; EC, endometrioid carcinoma; G3, grade 3; LTH, laparoscopic total hysterectomy; MC, mucinous adenocarcinoma; MIX, mixed tumor; PaLND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection; TAH, total abdominal hysterectomy.

TABLE 6 Accuracy comparison between preoperative pathology and frozen section with final pathology in patients with grade 3 endometrial cancer and non-endometrioid cancer[a]

Frozen section	Concordant with final	Not concordant with final	*P* value[b]
Yes	10 (71.4)	4 (28.6)	0.045
No	8 (34.8)	15 (65.2)	

[a]Values are given as number (percentage).

[b]Fisher's exact test.

and postoperative pathology results. Approximately 50% of ECs were correctly detected by FS analysis in patients with preoperative non-EC. In addition, for preoperative grade 3 EC, only 42.1% of patients had the same preoperative pathology and final pathology results. Four patients were downgraded to grade 1 or grade 2 EC on FS results, and the concordance rate between the FS and final pathology results was 87.5%. Furthermore, the misinterpretation of FS results rarely affects the extent of surgery. Only two patients with non-EC or grade 3 EC were undertreated in our center; the other patients received the correct treatment based on tumor size, the depth of invasion, or the non-EC histotype on FS results. In our study, higher (71%) for patients with grade 3 and non-EC who had FS compared with the 34% accuracy rate in patients that did not have FS. We may overtreat patients with preoperative non-EC or grade 3 EC if we simply use the preoperative histotype and do not perform FS analysis. Senol et al.[24] performed a prospective study on 31 patients with mismatched FS results with the final pathology results according to grade, degree of MI, and type of histopathology; the authors found that a misinterpretation of FS results does not affect disease-free or overall survival in patients with endometrial cancer. Hence, we propose that it is necessary to perform FS analysis in patients with endometrial cancer.

Certain factors may account for the discordance between the FS and final pathology results. First, the inadequate sample size of gross suspected lesions on FS results and even random sections if there were no gross lesions may have influenced the results. Desouki et al.[18] found that only 15% of patients had a diagnosable malignancy on a random section in the absence of a gross lesion. Second, dehydration and shrinkage, which occur with loss of cellular characteristics on FS analysis, can cause a misinterpretation of the histotype and tumor grade.[25] The experience of the pathologist may also account for the discrepancies. The limitations of this study are inherent to its retrospective study. A randomized, multicenter, controlled, wider-ranging study is needed in the future. However, our study included patients with various pathological types of endometrial cancer. In addition, we tried exclusively to explore the agreement rate in patients with a preoperative diagnosis of non-EC or grade 3 EC between the FS and final pathology results.

In summary, our data show that intraoperative FS analysis is a reliable method that can be used to assess tumor grade, the depth of MI, and the EC histotype, though there was a low agreement rate in the diagnosis of non-EC. We suggest that FS analysis be performed routinely in patients with non-EC or grade 3 EC, as it can be used to stratify patients into different risk groups to avoid overtreatment, increased costs, and associated complications.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

XZ and QG contributed to the study idea, designed the study and were involved at all stages. HY and XC conducted the analysis and interpretation of results, and wrote the manuscript. JS was involved in study design, provided clinical information, and collected data. LC was involved in data analysis and prepared the tables. All authors discussed the results, commented on the manuscript versions, and approved this final version.

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