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RESEARCH ARTICLE

INSTITUTIONAL ACCURACY MATTERS: DOES DECISION OF LYMPH NODE DISSECTION IN ENDOMETRIAL ADENOCARCINOMA DEPEND ON HOW THE INSTITUTION CORRELATES FROZEN SECTION AND FINAL PATHOLOGY?

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ABSTRACT

Purpose: The frozen section analysis results help determine the appropriate surgery and treatment for patients with endometrial adenocarcinoma. This study investigates the degree of compliance between the results of frozen section analysis and final pathology reports in patients with endometrial cancer.
Material and Methods: This study included 357 patients with endometrial adenocarcinoma who underwent operation, follow-up, and treatment at our hospital. The patients' demographic, clinical, surgical, and pathological data were retrospectively analyzed. We compared the results of the frozen section and pathological specimens in terms of final pathology, tumor grade, myometrial invasion, tumor size, and lymphovascular system involvement (LVSI).
Results: The frozen section analysis and final pathology results for tumor size and LVSI were significantly correlated when patients were divided by tumor type (tumor size: P=0.006, LVSI: P=0.024) or by risk for lymph node involvement (P=0.000).
Overall, the frozen section analysis had an accuracy of 70% for tumor grades.
The histological results of the frozen section analysis had an accuracy of 77.1% for type 1 tumors and 72.7% for type 2 tumors. Overall, the frozen section analysis had an accuracy of 95% for myometrial invasion.
Conclusion: Intraoperative frozen section analysis can prevent unnecessary lymph node dissection when performed at qualified institutions.

Keywords: Endometrial cancer, neoplasm, tumor staging, frozen section, lymph node dissection

INTRODUCTION

Endometrial cancer is the most common female genital system malignancy in the world (1). Surgical staging is the standard method used to determine a patient's prognosis and need for postoperative adjuvant therapy as well as to identify the extent of

Table 1. The surgical stage distribution by final pathology grade and histological type

Variable		1A	1B	2	3-4	p
Grade1	*n* (211)	161	37	8	5	0.000*
	%	76%	18%	4%	3%	
Grade2	*n* (120)	58	29	4	29	
	%	48%	24%	3%	24%	
Grade3	*n* (26)	8	8	2	8	
	%	31%	31%	8%	32%	
Type 1	*n* (258)	180	47	9	22	0.011*
	%	70%	18%	4%	9%	
Type 2	*n* (99)	47	27	5	20	
	%	48%	27%	5%	20%	

* $p < 0.05$

the disease. Lymph node metastasis is predicted using the tumor's histologic type and grade, depth of myometrial invasion, and size (2). Therefore, intraoperative frozen sectioning is very useful. When frozen section results indicate invasion into more than 1/2 the depth of the myometrium, grade 2–3 histology, or a tumor >2 cm, a high probability of pelvic lymph node metastasis is assumed and surgical staging is indicated (3).

As the frozen section analysis results help determine the appropriate surgery and treatment for patients with endometrial adenocarcinoma, the reliability of the frozen section analysis is important. Lymph node metastasis is the most crucial factor that affects the survival of patients and the decision for postoperative radio-chemotherapy. Therefore, accurate frozen section analysis results are essential to identify patients at risk for lymph node metastasis.

Retroperitoneal lymph node dissection is a necessary part of surgical staging. An intraoperative frozen section analysis can help prevent unnecessary lymph node dissections in patients with a low risk of extra-uterine metastasis. Therefore, the correlation between the results of the frozen section analysis and the final pathological report must be investigated to avoid unnecessary lymph node dissections and apply appropriate surgical procedures. We retrospectively analyzed frozen section analyses and permanent pathological specimen data in patients with endometrial adenocarcinoma to determine the degree of compliance between these two diagnostic reports.

MATERIAL AND METHODS

The data of 386 patients diagnosed with endometrial adenocarcinoma between January 2008 and May 2018 at our institution were retrospectively analyzed. Patients with uterine malignancies other than adenocarcinoma and those who were diagnosed, treated, or followed at an outside hospital were excluded. Therefore, 357 patients were included in this study.

The patients' demographic, clinical, surgical, and pathological data were collected. Pathological results have been analyzed by two pathologists specialized in gynecologic oncology with more than twenty years of experience. We recorded the results of the frozen section analyses and the final pathology reports, including tumor grade, myometrial invasion (≤1/2 or >1/2 the depth of the myometrium), tumor size (≤2 or and >2 cm), and lympho-vascular space involvement (LVSI) (yes or no).

Tumor differentiation was graded as well (G1), moderate (G2), or poor (G3), according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines. Surgical staging was performed according to the final pathology results, according to the FIGO guidelines (4). The levels of tumor markers, including Ca 125 and Ca 19-9, were recorded.

Risk Group Distribution Criteria According to Final Pathology Result

Patients with grade 1–2 myometrial invasion <1/2 the depth of the myometrium and tumor size ≤2 cm were categorized as low-risk, while patients with grade 1–2 myometrial invasion ≥1/2 the depth of the myometrium, grade 3 invasion <1/2 the depth of the myometrium, grade 3 invasion ≥1/2 the depth of the myometrium, and non-endometrioid cancer types were categorized as intermediate/high-risk (5,6).

Table 2. The correlation of age, tumor size, LVSI, and tumor markers by histological tumor type

		Type 1	Type 2	
		Mean ± sd	Mean ± sd	p
Final Type	Age	59.71 ± 9.765	60.62 ± 9.807	0.435
	Tumor size (cm)	2.74 ± 1.785	3.38 ± 2.259	0.006*
	Ca 125 (IU / ml)	28.88 ± 71.291	31 ± 44.527	0.833
	LVSI (%)	0.15 ± 0.356	0.27 ± 0.448	0.024*
	CA19-9 (IU / ml)	41.04 ± 129.776	37.86 ± 110.168	0.878

* p < 0.05, LVSI: lymphovascular system involvement

Endometrial adenocarcinomas were classified into two groups, Type 1 (endometrioid, mucinous) and Type 2 (serous, clear cell) carcinomas, based on the histo-morphologic characteristics, pathogenesis, and prognosis (7).

The study was approved by the appropriate institutional review board (decision date and number: 06.20.2018 - 2222) and conducted according to the principles of the Declaration of Helsinki. The requirement of informed consent was waived due to the retrospective nature of the study.

Table 3. Comparison of risk groups in final pathology and frozen section

		low	high / intermediate	p
		mean ± sd	mean ± sd	
Final Risk Group	Tumor size (cm)	2.3702 ± 1.588	3.5047 ± 2.118	0.000*
	LVSI (%)	0,04 ± 0.198	0.33 ± 0.470	0.000*
Frozen Risk Group	Tumor size (cm)	2.368 ± 1.456	3.4874 ± 2.209	0.000*
	LVSI (%)	0.07 ± 0.262	0.29 ± 0.456	0.000*

* p < 0.05, LVSI: lymphovascular system involvement

Statistical Analysis

Categorical data are expressed as number and percentage, while continuous data are shown as mean ± standard deviation. A chi-square test was used to analyze categorical data, and an independent group *t*-test was used to compare continuous data. The distribution of the data was evaluated using the Kolmogorov-Smirnov test. Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using SPSS version 20 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Surgical Stage Distribution by Final Pathology Grade and Histological Type

Statistically significant relationships between the final grade and the surgical stage, and histologic type and the surgical stage were obtained ($P = 0.000$, $P < 0.001$). Among the tumors categorized based on the surgical stage, most tumors in group 1A were grade 1, and the percentage of tumors decreased from grade 1 to grade 3. Additionally, most tumors in group 1B were grade 3, and the percentage of tumors increased from grade 1 to grade 3. The rates of tumors in grades 1, 2, and 3 were not significantly different for other surgical stages. Further, statistically significant relationships were seen between histologic types and final surgical stage ($P = 0.011$, $P < 0.05$). Most patients with type 1 endometrial adenocarcinoma had surgical stage 1A disease (70%) and 18% had surgical stage 1B disease. Nearly half of the patients with type 2 endometrial adenocarcinoma had surgical stage 1A disease (48%), while 27% had surgical stage 1B disease (Table 1).

Comparison of Age, Tumor Size, LVSI, and Tumor Markers by Histological Tumor Type

When examining the distribution of age, tumor size, LVSI, and tumor markers according to final tumor type, only the correlations between final tumor type and tumor sizes ($P = 0.006$) and LVSI rates ($P = 0.024$) were statistically significant. Patients with type 2 disease had significantly larger tumors and higher rates of LVSI than those with type 1 disease, though

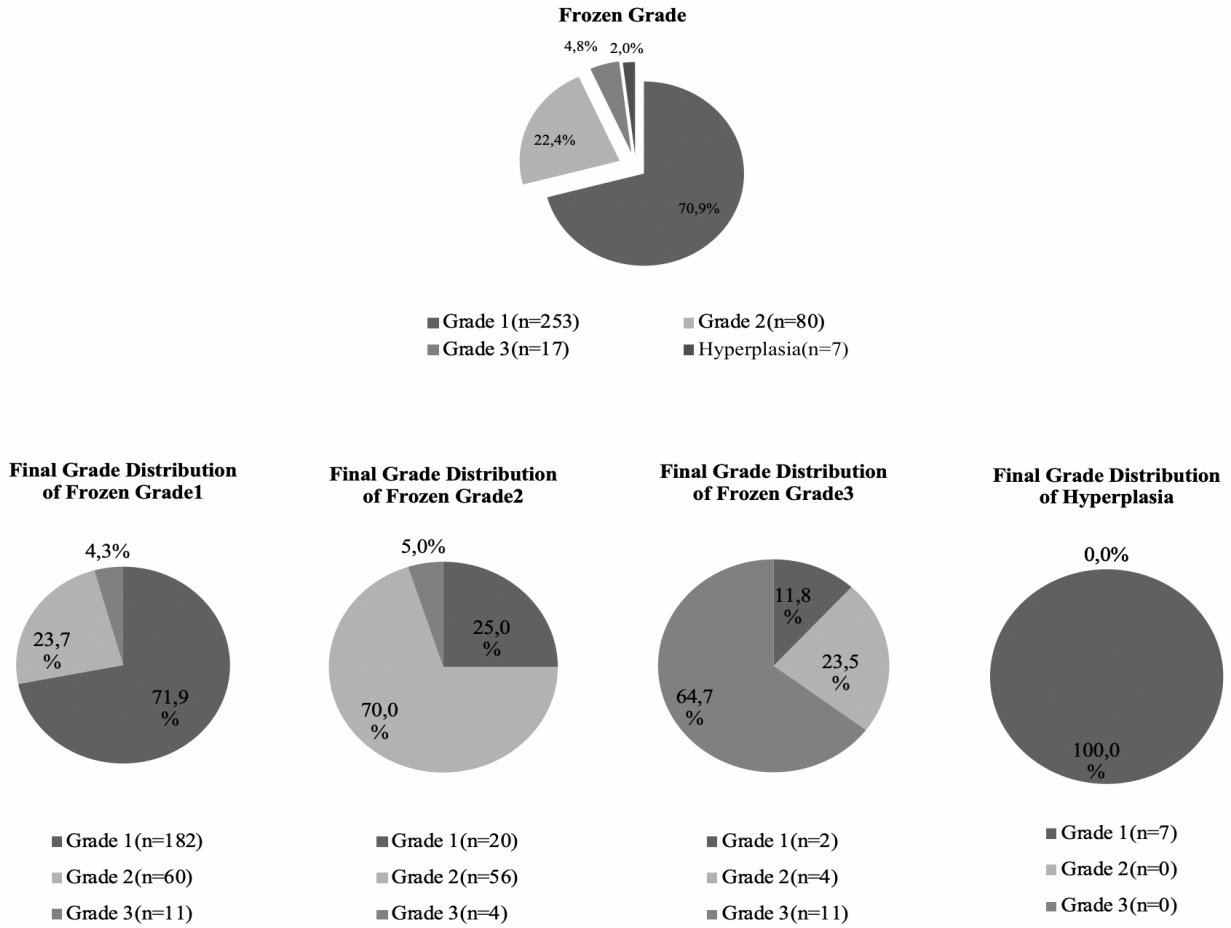

Figure 1. Comparison of frozen section and final grade compliance
*p=0.000, p<0.05

there were no significant differences in age or tumor markers between the groups (Table 2).

Comparison of Age, Tumor Size, LVSI, and Tumor Markers in Low- and Intermediate/High-Risk Groups

Patients in the intermediate/high-risk group were significantly older (P = 0.000) with significantly larger tumors (P = 0.001) and higher rates of LVSI (P = 0.000) than patients in the low-risk group. Similar results were found when using data from the frozen section analysis (Table 3). According to the final risk group, patients with a low risk of metastasis had a mean serum Ca 125 of 24.14 ± 49.016, which was not significantly different from the mean serum Ca 125 of patients in the intermediate/high-risk group (mean Ca 125=35.25 ± 78.572) (P = 0.215). Similarly, there was no significant difference in the mean Ca 19-9 levels between the two groups (low-risk: 24.53 ± 41.796; high-risk: 58.18 ± 175.644; P = 0.071). There was no significant difference in mean age (57.9 ± 9.337; 62.19 ± 9.767; P > 0.05) between the two groups.

Correlation of Tumor Grade and Histological Type Results of the Frozen Section Analysis with the Final Pathological Results

The correlation between tumor grade results of the frozen section analysis and the final pathology report is shown in Figure 1. The results of the frozen section analysis aligned with those of the final pathology report in 71.9% of grade 1 tumors and 64.7% of grade 3 tumors. Twenty-eight percent of grade 1 tumors were categorized as grade 2 or above, while 5% of grade 2 tumors were categorized as grade 3 or above. As the grade increased, the accuracy rate decreased. All patients with hyperplasia on frozen section were categorized as grade 1 on the final pathology report.

Overall, the accuracy of the frozen specimen analysis was approximately 70% (249/357).

Table 4. Surgical stage distribution by frozen section grade / histologic type

Frozen section	Stage	1A	1B	2	3.A	p
Grade1	*n* (253)	174	48	9	22	0.001*
	%	69%	19%	3%	9%	
Grade2	*n* (80)	42	19	5	14	
	%	52%	24%	6%	18%	
Grade3	*n* (17)	4	7	0	6	
	%	24%	41%	0%	35%	
Type 1	*n* (271)	164	60	13	34	0.101
	%	61%	22%	5%	12%	
Type 2	*n* (79)	56	14	1	8	
	%	71%	18%	1%	10%	

* $p < 0.05$

In the final pathology reports, 27.7% of the patients were diagnosed with type 1 and 72.3% with type 2. %77.1 of the patients with type 1 frozen section analysis and 72.7% of patients with type 2 frozen section analysis were aligned with their final pathology reports.

Accuracy of Frozen Section Analysis Results for Predicting Metastasis

When the surgical stage distribution was examined according to the frozen grade, in patients', whose surgical stages were 3 and 4, frozen grades 1, 2 and 3, the tumor rates were 9%, 18%, and 35%, respectively. The rate of extra-uterine spread increased as the frozen section grade increased. A significantly higher rate of deep myometrial invasion was detected in frozen grade 3(41%) than in grade 1(19%) and 2(24%) in stage 1B tumors.

We summarized the surgical stage and histologic type results of the frozen section analysis of 350 patients (seven patients were excluded due to a finding of hyperplasia) (Table 4). There was no significant difference in surgical stage distribution between type 1 and type 2 tumors ($P = 0.101$, $P > 0.05$).

Accuracy of Frozen Section Analysis for Detecting Myometrial Invasion

Invasion in ≤ 1/2 the depth of the myometrium was detected in 66% of patients, while 34% of patients had invasion in >1/2 the depth of the myometrium. The accuracy of the frozen section analysis in determining the depth of myometrial invasion was 99.1% in tumors with invasion in ≤1/2 the depth of the myometrium. The accuracy of the frozen section analysis in determining the depth of myometrial invasion was 89% in tumors with invasion in >1/2 the depth of the myometrium. Therefore, 10% of tumors with deep invasion were not detected on frozen section analysis. Overall, the results of the frozen section analysis aligned with the final pathology report in 95% of patients.

Accuracy of Frozen Section Analysis for Detecting Low- and Intermediate/High-Risk Patients

According to the final pathology report, 51.8% of patients (185/357) were categorized as low-risk and 48.2% of patients (172/357) were categorized as intermediate/high-risk. Of the 185 low-risk patients, 138 were accurately identified by frozen section analysis (74.6%). Of the 172 intermediate/high-risk patients, 129 were accurately identified by frozen section analysis (75%).

DISCUSSION

In this study we investigated the results of the frozen section analysis to help determine the appropriate surgery and treatment for patients with endometrial adenocarcinoma. We investigated the degree of compliance between the results of frozen section analysis and final pathology reports in patients with endometrial cancer.

The standard surgical treatments of endometrial cancer include total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and periaortic lymph-node dissection. The presence of metastatic lymph-nodes determines the need for adjuvant therapy and the patient's prognosis (8). Comprehensive surgical staging is required for high-

risk patients; however, the role of systematic lymphadenectomy is not clear for low-risk patients (9,13).

While the Gynecologic Oncology Group Study is the leading study focused on the intraoperative detection of the risk of lymph node involvement in early-stage endometrial cancers (14), the most useful method of identifying patients at risk for lymph node involvement was reported by Mariani et al (15). and verified by other studies (16,17). In patients with grade 1- 2 tumors <2 cm with invasion in ≤1/2 the depth of the myometrium, which account for 33% of all patients with endometrial cancer, the risk of lymph node involvement has been reported to be <1% (15).

The recurrence rate of endometrial cancer is increased in patients with lymph node involvement. The recurrence rate in intermediate/high-risk patients who do not receive adjuvant therapy is reported to be approximately 15% (18). Based on the Surveillance, Epidemiology, and End Result (SEER) database, the presence of lymph node involvement reduces the 5-year survival from 95% to 69% (19). However, postoperative radiotherapy techniques have led to a significant reduction in recurrence, even in the presence of lymph node involvement (18). Lymph node dissection is the only way to detect lymph node involvement; however, various complications can occur after a lymph node dissection, including lymphedema (found in 23-28% of patients who undergo lymph node dissection), decreased lymphocytes (found in 10% of patients who undergo lymph node dissection), and thrombosis (found in 2-5% of patients who undergo lymph node dissection) (20). To prevent these complications, avoiding unnecessary lymph node dissection is necessary by detecting cases with a low risk of lymph node involvement via intraoperative frozen section analysis. The use of intraoperative frozen section analysis can prevent unnecessary lymph node dissection in approximately one-third of patients with endometrial cancer. However, the accuracy of frozen section analysis results depends on the quality of the institution and the qualifications of the institutional staff. A high margin of error may exist at centers that do not control their frozen compliance rates, leading to unnecessary or incomplete staging. Each center should determine the accuracy of its frozen section analyses and attempt to eliminate any causes of inaccurate results. In this study, we determined the accuracy of the frozen section analyses conducted at our institution in terms of tumor type and grade and myometrial invasion in low-risk and intermediate/high-risk patients.

Remarkable differences between frozen section analyses and final pathology reports have been reported. The tumor grade compliance rate varies from 30-89% (21,24). The accuracy of frozen section analyses to determine the myometrial invasion has been reported as 72-95% (25,26). However, one recent study reported that frozen section analyses were in 35% disagreement with final pathology for tumor grading, 28% for myometrial invasion, 13% for cervical involvement, and 32% for LVSI (23). In this study, the accuracy of the frozen section analysis for tumor grades was 70%, though it was only 65% among grade 3 tumors. This low accuracy may lead to incomplete surgical staging. Similarly, we found a 10% reduction in the frozen section accuracy rate when the depth of myometrial invasion increased. Overall, the accuracy of frozen section analysis at our institution is consistent with the previously reported rates.

Yueqian et al (27). reported noncompliance rates of 28.6% and 50% in type 1 and type 2 cancers, respectively, which are consistent with our results.

The ultimate objective of frozen section analysis is to identify characteristics to predict the risk of metastasis and lymph node involvement to prevent unnecessary lymph node dissections. The detection rates of low- and intermediate/high-risk patients using intraoperative frozen section analysis vary considerably, as previously noted. Malviya et al.(25) and Yueqian et al.(27) reported ≥ 90% accuracy, while Papadia et al.(28) reported 16% accuracy and Case et al.(29) reported 18% accuracy. Other studies have also reported low accuracies (30,31). These data indicate significant differences between healthcare centers. In our study, frozen section analysis/final pathology compliance rates were 75% in both groups when we compared low- and intermediate/high-risk patients, which is acceptable considering previous reports. Despite the accuracy of the frozen section analysis, the patient must be informed of the risks of inaccurate results of the frozen specimen analysis and the risks of unnecessary lymph node dissections.

This study is not without limitations. First, it is a single-center, retrospective study that is not generalizable as the accuracy of frozen section analysis is institution-dependent. Multiple prospective studies with more patients are needed to provide a better analysis of the overall accuracy of frozen section

analyses at several institutions. Individual institutions should determine their own frozen section analysis rates. In addition, contradictory reports and limitations of intraoperative frozen section analysis should be discussed in a systematic literature review to determine the proper decision-making protocol regarding lymph node dissection during surgery. Lastly, studies regarding the use of pelvic MRI or preoperative endometrial biopsies are required to investigate the usefulness of these diagnostic tools.

CONCLUSION

In conclusion, using sentinel lymph node sampling in patients with endometrial cancer is rapidly increasing. However, institutions that cannot execute sentinel lymph node sampling method still use frozen section analysis. Therefore, each institution needs to determine the accuracy of its frozen section analysis results and develop surgical protocols accordingly. As each institution gains experience using intraoperative frozen section analysis, the reliability of this method will improve.

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