

ORIGINAL RESEARCH

What is the correlation between the results of the intraoperative histopathological consultation and the final pathological examinations in uterine cancer patients? Results and retrospective analysis of 218 cases

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Abstract

Background: Endometrial carcinoma (EC) is the most common gynecological malignancy in developed countries. For optimal treatment, the clinicopathological characteristics of EC need to be revealed. This study aimed to evaluate the compatibility of intraoperative frozen section (IFS) and final diagnostic results. **Methods:** In this study, two hundred and eighteen EC patients, who were operated on for EC between 2008 and 2018, were evaluated retrospectively. The IFS and final diagnosis results of the patients were compared in terms of myometrial invasion (MI), cervical invasion, tumor size, histological subtype and grade, and the concordance rate between IFS and final diagnosis was calculated. **Results:** One hundred thirty-nine patients were included in the study. The average age of the patients was 57.60 ± 10.41 years, the average body mass index (BMI) was 37.82 ± 8.75 kg/m², and the average surgery duration was 258.24 ± 151.30 minutes. The concordance between IFS and final diagnosis was 81.3%, 88.5%, 89.2%, 71.9% and 95.9% for tumor histology, tumor grade, MI, tumor diameter and cervical involvement, respectively. None of the 139 patients received unnecessary treatment, three patients received inadequate treatment due to MI, and seven patients received inadequate treatment due to grade incompatibility. **Conclusions:** The compliance results of our study suggest that IFS is a good indicator for decisions about the appropriate surgical procedure.

Keywords

Cervical invasion; Endometrial carcinoma; Histological subtype; Myometrial invasion; Tumor size

1. Introduction

Endometrial carcinoma (EC) represents the most prevalent gynecological neoplasm in nations classified as middle- and high-income, with a continual upward trend in its incidence. In the United States, EC ranks as the fourth most frequently diagnosed malignancy, accounting for an estimated 65,690 new diagnoses and 12,550 fatalities in the year 2022 [1]. Between the years 2010 and 2019, the mortality rate attributable to EC has exhibited an average annual increase of 1.7% [2]. The recent escalation in the incidence of EC can be attributed to factors such as rising obesity rates, hormonal influences, and enhancements in cancer detection methodologies. Nevertheless, the incidence of EC demonstrates variability across different nations, attributable to disparities in associated risk factors [3, 4]. In Turkey, the incidence of EC has seen a rise, representing 6% of the total cancer burden, with a lifetime risk of 2.5% among the female population [5].

Approximately 85% of EC cases are diagnosed in the early stage and 15% in the advanced stage. The standard

treatment, especially for early-stage EC, is total hysterectomy and systematic lymphadenectomy with bilateral salpingo-oophorectomy [6]. Surgical stage is an important prognostic factor to accurately determine the stage and decide on postoperative treatment. Non-endometrioid histology, myometrial invasion (MI) >50%, cervical stromal invasion, lymphovascular space invasion and FIGO (International Federation of Gynecology and Obstetrics) grade 3 tumor are indicators of poor prognosis [7]. According to European Society for Medical Oncology (ESMO) guidelines [8], lymph node dissection (LND) is contraindicated for “low-risk” endometrial cancers (ECs) (G1/G2 type 1—stage Ia, *i.e.*, myometrial invasion <50%) due to the minimal likelihood of lymph node involvement in this patient cohort and the absence of any survival advantage conferred by LND. In contrast, LND may be indicated for staging purposes in cases classified as “intermediate-risk” ECs (stage Ia G3 type 1 or stage Ib; myometrial invasion $\geq 50\%$), while it is imperative that LND be performed for patients diagnosed with “high-

risk” ECs (stage Ib G3 type 1; stage Ia/b type 2) and stage II ECs. Consequently, an accurate preoperative diagnosis holds significant importance in the identification of high-risk women suitable for LND, thereby preventing unnecessary overtreatment in other patients.

Preoperative and/or intraoperative methodologies for the assessment of high-risk factors in female patients diagnosed with endometrial carcinoma (EC) are crucial for informed surgical decision-making. Preoperative magnetic resonance imaging (MRI), transvaginal sonography, preoperative endometrial biopsy, intraoperative gross examination, or intraoperative frozen section (IFS) are employed to ascertain the prognostic implications of EC [9]. The 2005 Practice Bulletin issued by the American College of Obstetricians and Gynecologists advocated for the utilization of IFS analysis in cases of EC to reduce the incidence of undertreatment [10]. However, not all medical institutions possess the capability to conduct IFS, and ongoing discourse persists regarding the precision of IFS in forecasting myometrial invasion (MI) in EC [11, 12]. A substantial discrepancy in rates (23–56%) has been documented between preoperative and postoperative European Society for Medical Oncology (ESMO) risk classifications. Furthermore, the accuracy of IFS exhibits a variability range of 54–95% concerning MI and 58–98% pertaining to tumor grading [13]. The 2021 guidelines put forth by the European Society of Gynecological Oncology (ESGO) exhibit hesitance in endorsing IFS due to the challenges associated with its reproducibility and the potential interference with optimal pathological processing [14]. The concordance between IFS and definitive diagnosis has been scrutinized; however, given the divergent outcomes regarding the adequacy and dependability of IFS-driven conclusions, further investigations are warranted in this domain [15]. Consequently, the objective of this study is to evaluate the consistency of the ultimate results of IFS concerning tumor grading, histological subtype, MI, tumor dimension, and cervical invasion in patients diagnosed with EC who underwent surgical intervention at our institution.

2. Materials and methods

This retrospective study was conducted at the Gynecology and Obstetrics Clinic of Health Sciences University (SBU) Ümraniye Training and Research Hospital. Ethical approval was received from the Clinical Research Ethics Committee of SBU Ümraniye Training and Research Hospital, (decision number 521735/01.2018). The inclusion criteria for the study were patients who underwent surgery for EC, patients who underwent IFS, and patients with final pathology results. Exclusion criteria from the study were patients who did not undergo IFS and patients whose final pathology result was hyperplasia with atypia. Two hundred eighteen patients who underwent surgery with a preliminary diagnosis of EC, between 2008 and 2018, were evaluated retrospectively. Seventy-one patients without IFS and eight patients with atypical hyperplasia were excluded, and 139 patients were included in the study.

Following the exploration of the abdominal cavity via robotic, laparoscopic or laparotomy techniques, the uterus, bilateral ovaries, and fallopian tubes were excised and subsequently submitted for frozen section analysis. In certain

young patients presenting with low-grade and early-stage conditions, ovary-preserving surgical interventions were conducted. A comprehensive final pathological assessment of the obtained samples was executed according to standard protocols, focusing on metrics such as mitotic index, tumor grade, tumor diameter, histological classification, and cervical involvement. All pathological assessments were conducted by a pathologist possessing specialized expertise in the field of gynecopathology.

IBM SPSS Statistics v22 (IBM SPSS, Armonk, NY, USA) program was used for statistical analysis. The Kolmogorov-Smirnov test was used to evaluate the suitability of the measured data for normal distribution. Mean, standard error, minimum and maximum values of continuous variables, and *n* and percentage values of categorical variables were given. Intraclass correlation coefficient (ICC) was calculated to determine the agreement between quantitative parameters, and Kappa coefficient of agreement was calculated to determine the agreement between qualitative parameters. For statistical analysis, a *p*-value of less than 0.05 was considered statistically significant.

3. Results

The demographic data distribution of the participants is given in Table 1. The mean age of the patients was 57.60 ± 10.41 (29–85) years, the mean BMI was 37.82 ± 8.75 (15.8–58.6) kg/m², and the mean surgery duration was 258.24 ± 151.30 (60–705) minutes. Ninety-eight (70.5%) patients complained of postmenopausal bleeding and 33 (23.7%) patients complained of postmenopausal endometrial line thickening. Robotic surgery was performed in 50.4% of the patients, laparoscopic surgery in 22.3%, and laparotomic surgery in 27.3%.

The results of lymph node involvement as a result of LND are presented in Table 2. Lymph node metastases were detected in 13 of 83 patients (15.7%) who underwent pelvic LND, seven of 67 patients (10.4%) who underwent para-aortic pelvic lymph node dissection (PLND), and five of 67 patients (7.5%) who underwent pelvic and para-aortic LND. Table 3 shows the final diagnosis FIGO grade and IFS FIGO grade results. Kappa agreement level was 82.1% and concordance rate was 88.5% (123/139).

Table 4 shows the results of evaluation of MI of the uterus by IFS and final diagnosis. Kappa agreement level was 82.4% and concordance rate was 89.2% (124/139). The Kappa level of agreement between the final diagnosis and IFS cervical involvement results was 83.4% and the concordance rate was 95.9% (118/123) (Table 5).

Table 6 shows histological subtype results by IFS and final diagnosis. Kappa Agreement Level was 49.5% and Concordance rate was 81.3% (113/139). The Kappa level of agreement between the final diagnosis and IFS for tumor size was 95.8% and the concordance rate was 71.9% (100/139) (Table 7).

TABLE 1. Demographic data of the patients.

Variables	Mean \pm S.D (Min–Max)
Age, yr	57.60 \pm 10.41 (29–85)
BMI, kg/m ²	37.82 \pm 8.75 (15.8–58.6)
Surgery Duration, minutes	258.24 \pm 151.30 (60–705)
Admission Complaint	n (%)
Postmenopausal Bleeding	98 (70.5%)
Abnormal Uterine Bleeding	4 (2.9%)
Postmenopausal Endometrial Line Thickening	33 (23.7%)
Other Complaints	4 (2.9%)
Surgery Types	
Robotic Surgery	70 (50.4%)
Laparoscopic	31 (22.3%)
Laparotomy	38 (27.3%)

S.D: Standard Deviation; Min: Minimum; Max: Maximum; BMI: Body Mass Index.

TABLE 2. The results of lymph node involvement.

	n (%)
Lymph node involvement in PLND (n = 83)	
Yes	13 (15.7%)
No	70 (84.3%)
Lymph node involvement in PALND (n = 67)	
Yes	7 (10.4%)
No	60 (89.6%)
Lymph node involvement in PPALND (n = 67)	
Yes	5 (7.5%)
No	62 (92.5%)

PLND: Pelvic Lymph Node Dissection; PALND: Paraaortic Lymph Node Dissection; PPALND: Pelvic and Paraaortic Lymph Node Dissection.

TABLE 3. Compatibility of final diagnostic FIGO grade and frozen section FIGO grade.

Frozen	Final Diagnosis			
	Grade 1	Grade 2	Grade 3	Total
Grade 1	38 (27.3%)	8 (5.8%)	0 (0.0%)	46 (33.1%)
Grade 2	1 (0.7%)	56 (40.3%)	3 (2.2%)	60 (43.2%)
Grade 3	0 (0.0%)	4 (2.9%)	29 (20.9%)	33 (23.7%)
Total	39 (28.1%)	68 (48.9%)	32 (22.0%)	139 (100.0%)
Kappa Coefficient	0.821; 95% C.I: 0.738–0.903			

C.I: Confidence interval.

TABLE 4. Compatibility of final diagnostic myometrial invasion and frozen section myometrial invasion.

Frozen	Final Diagnosis			
	<1/2	\geq 1/2	No	Total
<1/2	59 (42.4%)	3 (2.2%)	2 (1.4%)	64 (46%)
\geq 1/2	2 (1.4%)	48 (34.5%)	0 (0.0%)	50 (36%)
No	8 (5.8%)	0 (0.0%)	17 (12.2%)	25 (18%)
Total	69 (49.6%)	51 (36.7%)	19 (13.7%)	139 (100%)
Kappa Coefficient	0.824, 95% C.I: 0.741–0.908			

C.I: Confidence interval.

TABLE 5. Compatibility of final diagnostic cervical involvement and frozen section cervical involvement.

Frozen	Final Diagnosis		
	Yes	No	Total
Yes	15 (12.2%)	1 (0.8%)	16 (13%)
No	4 (3.3%)	103 (83.7%)	107 (87%)
Total	19 (15.4%)	104 (84.6%)	123 (100%)
Kappa Coefficient	0.834, 95% C.I: 0.691–0.976		

C.I: Confidence interval.

TABLE 6. Compatibility of final diagnostic histological subtype of tumor and frozen section histological subtype of tumor.

Frozen	Final Diagnosis								Total
	1	2	3	4	5	6	7	8	
1	99 (71.2%)	18 (12.9%)	2 (1.4%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	121 (87.1%)
2	0 (0.0%)	6 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (4.3%)
3	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
4	0 (0.0%)	2 (1.4%)	0 (0.0%)	2 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (2.9%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
6	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
7	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.4%)	0 (0.0%)	2 (1.4%)
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	3 (2.2%)
Total	99 (71.2%)	26 (18.7%)	3 (2.2%)	3 (2.2%)	1 (0.7%)	2 (1.4%)	4 (2.9%)	1 (0.7%)	139 (100.0%)
Kappa Coefficient	0.495, 95% C.I: 0.320–0.670								

1: Endometrioid; 2: Mix; 3: Mucinous; 4: Serous; 5: Clear Cell; 6: Undifferentiated; 7: Endometrial stromal sarcoma; 8: Malignant Mixed Müllerian Tumor.

C.I: Confidence interval.

TABLE 7. Compatibility of final diagnostic tumor size and frozen section tumor size.

	ICC	95% C.I	Concordance
Tumor Size	0.958	0.94–0.97	71.9% (100/139)

ICC: Intraclass correlation coefficient; C.I: Confidence interval.

4. Discussion

This investigation concentrated on the alignment between intraoperative frozen section (IFS) analysis and the definitive diagnosis in individuals diagnosed with endometrial carcinoma (EC). In our research, the Kappa coefficient for IFS concordance with the final diagnosis regarding tumor histological subtype, tumor grade, myometrial invasion (MI), tumor diameter, and cervical involvement was measured at 80.8%, 82.1%, 82.4%, 95.8% and 83.4%, respectively.

Surgery occupies a crucial role in the therapeutic management of endometrial carcinoma, while IFS serves as a pivotal tool in directing the surgical approach. Utilizing IFS minimizes the likelihood of unnecessary surgical interventions in patients classified as low-risk, thereby leading to a significant reduction in both patient morbidity and healthcare costs. Conversely, in individuals identified as high-risk, the implementation of appropriate surgical procedures markedly influences the patient's prognosis and overall life expectancy. The surgical intervention typically comprises total hysterectomy

accompanied by bilateral salpingo-oophorectomy, with additional pelvic-para-aortic lymphadenectomy indicated in certain cases. Nonetheless, lymphadenectomy is regarded as the standard treatment modality for high-risk patients, whereas there exist controversies pertaining to its application in low-risk and early-stage cases. IFS facilitates the determination of the most suitable surgical treatment approach by delivering critical information concerning histological subtype, tumor grade, diameter, MI and even lymphovascular space invasion (LVSI) [16].

Pathological examination of IFS is suitable for detecting MI. In previous studies, the accuracy of IFS for MI ranged from 54% to 95% [15]. Case *et al.* [17] determined the accuracy of IFS to be 67% and suggested that this may lead to inadequate staging and inadequate treatment. On the contrary, in a retrospective analysis including 816 patients with EC, Turan *et al.* [18] observed the accuracy of IFS for MI to be 85.4%, and the sensitivity and specificity to be 88.8% and 98.3%, respectively. In a study conducted with 460 patients, Quinlivan *et al.* [19] reported the correct detection rate of MI

in 88% of cases. In their study, Jonsdottir and colleagues [20] determined the accuracy of IFS for MI to be 92%. Yang *et al.* [16] documented that the sensitivity of IFS for deep MI was 86.21%, the specificity was 97.20% and the concordance rate was 83.4%. Another recent study reported that intraoperative diagnosis for MI (78.0%) showed a significantly higher concordance rate than preoperative diagnosis (53.8%) [21]. We show the concordance rate between IFS and final diagnosis in the evaluation of MI was 89.2% (124/139). Furthermore, our findings confirm the results of previous studies. Only three patients received inadequate treatment due to inadequate definition of MI. Our study results show that IFS has high accuracy in determining MI.

In ECs, information regarding tumor grade can often be obtained through preoperative biopsy. However, there is not always full agreement between the preoperative grade and the final grade [22]. The agreement between IFS and final diagnosis is 65.3–91.1% [23]. Acikalin *et al.* [24] determined that the overall concordance between IFS and final diagnosis in terms of grade was 84.3%, and concordance for grades 1, 2 and 3 was 94.2%, 75% and 66.7%, respectively. Turan *et al.* [18] noted 96.8%, 86% and 91.3% concordance for grade 1, 2 and 3 tumors, respectively. Dogan Durdag and colleagues [23] observed that the overall concordance of the final diagnosis with IFS was 75.4%, and that the concordance decreased as the tumor grade increased. Similarly, Mandato *et al.* [13] also reported that as tumor grade increases, the agreement between IFS and final diagnosis decreases. In contrast, Stephan *et al.* [25] reported that there was no disagreement between IFS and final diagnosis in the evaluation of high-grade tumors. In another study, the overall agreement between IFS and final diagnosis for staging was found to be 93.3%. For stage I, the agreement was 92.7% [15]. Santoro *et al.* [26] identified a concordance rate of 91.09% (184/202) and concluded that, while no diagnoses were downgraded upon final assessment, 18 patients (8.9%) were found to have upgraded diagnoses. In the present investigation, although 46 patients were classified as grade 1 in the IFS, 8 patients were reclassified as grade 2 upon final diagnosis. It was disclosed that three out of 60 patients with grade 2 in IFS were ultimately classified as grade 3 at the final diagnosis, while four out of 33 patients with grade 3 in IFS were identified as grade 2 tumors at the final diagnosis. Consequently, the Kappa statistic reflecting the level of agreement between the final diagnosis grade and IFS grade results was determined to be 82.1%, and the overall concordance rate was established at 88.5% (123/139). Based on the IFS grade outcomes of this study, it was determined that no patients underwent unnecessary treatment; however, seven (5.03%) patients were found to have received inadequate treatment. A prospective study of 784 patients from the Mayo Clinic found the underestimation rate to be 1.3% [27]. In the study of Bandala-Jacques *et al.* [28], the underestimation for grade was 11%, while Gitas *et al.* [15] reported the rate of patients who received suboptimal surgical treatment due to IFS error as 5.3%. Santoro and colleagues [26] stated that the tumor grade is often underestimated in IFS and suggested that pathologists may have avoided overdiagnosing cancer.

In our study, IFS and final diagnosis results of tumor size, cervical invasion and histological subtype, as well as MI and

grade, were compared. The agreement between IFS and final diagnosis results of cervical invasion, histological subtype, and tumor size was 95.9%, 81.3% and 71.9%, respectively. Dogan Durdag *et al.* [23] determined that the agreement between IFS and final diagnosis in terms of tumor size was 92%, and when tumor size was categorized as <2 cm and ≥ 2 cm, the accuracy was 95%. In their study on 75 patients, Giglio *et al.* [29] observed that the kappa agreement rate between IFS and final diagnosis in terms of tumor size was 69%. Different results have also been reported for the agreement between IFS for cervical invasion and final diagnosis. Karabagli *et al.* [30] reported a 100% correlation of cervical involvement between IFS and final diagnosis. In another study, the concordance of IFS and final diagnosis for cervical invasion was determined as 93% [23]. Santoro *et al.* [26] found that the accuracy rate for IFS and cervical invasion in the final diagnosis was 95%. However, in another study, the accuracy rate for cervical invasion was determined as 77% [28]. In their study, Guo *et al.* [31] reported the concordance rate for histological type as 87%, Wang *et al.* [32] as 100%, and Stephan *et al.* [25] as 97%. Santoro *et al.* [26] determined the overall concordance for each histotype as 93%. However, the researchers observed accuracy of 97% vs. 59% for endometrioid and non-endometrioid ECs, respectively. In a recent study, the overall concordance rate between IFS and final diagnosis was 92% for histological type and 100% for tumor size [33]. The tumor size, cervical invasion and histological subtype results obtained in our study are compatible with the results of previous studies.

Our investigation presents several limitations. Primarily, the research was executed in a retrospective manner, and the patient cohort exhibits considerable heterogeneity. Furthermore, a notable limitation is the comparatively small patient sample size. Additionally, the involvement of five distinct pathologists in conducting the pathology evaluations represents a significant contributing factor to this limitation. This variability may have resulted in discrepancies between intraoperative frozen section (IFS) analysis and the definitive diagnoses.

5. Conclusions

In this study, the concordance between IFS and final diagnosis was evaluated in terms of tumor histology, tumor grade, MI, tumor diameter and cervical involvement. Our study results showed that the concordance in terms of tumor histology, tumor grade, MI, tumor diameter, and cervical involvement was 80.8%, 82.1%, 82.4%, 95.8% and 83.4%, respectively. For the time period in which we conducted the study, we observed that the use of IFS in ECs was beneficial. In particular, IFS is useful when classical histopathological prognostic information is uncertain or inconclusive regarding imaging and endometrial biopsies. However, since the current recommendation is to perform systematic lymph node dissection (SND) instead of LND because SND has significantly fewer contraindications and side effects, the necessity of performing IFS in every EC should be clinically reconsidered.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

AI—Conceptualization. IE, GK, NB—Acquisition of data. AI, NB—Analysis and/or interpretation of data. AI, MM, NB—Drafting the manuscript. IE, MM, GK—Revising the manuscript critically for important intellectual content. All authors Approve the version of the manuscript to be published.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by Clinical Research Ethics Committee of SBU Ümraniye Training and Research Hospital, (decision number 521735/01.2018). Written informed consent was waived because of its retrospective observational nature.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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