



Are Preoperative Features Effective in The Incompatibility of Intraoperative Frozen Section and Final Pathology in Operated Patients Diagnosed with Atypia Endometrial Hyperplasia?

Atipili Endometrial Hiperplazi Tanısı ile Opere Edilen Hastalarda İntraoperatif Frozen Patoloji ile Nihai Patoloji Uyumsuzluğunda Preoperatif Özellikler Etkili Midir?

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Abstract

Aim: We aim to investigate the relationship between demographic characteristics and preoperative laboratory findings with the discordance between intraoperative frozen section diagnoses and final diagnoses in patients undergoing surgery with endometrial hyperplasia with atypia.

Material and Method: The study included 154 patients who underwent surgery for endometrial hyperplasia with atypia and who received intraoperative frozen section (IFS) diagnosis between January 2015 and January 2021. Frozen section diagnoses and the final diagnoses of the patients were compared. Patient groups were split into two: patients with an IFS diagnosis concordant and patients with an IFS diagnosis discordant with the final diagnosis. These two groups were compared regarding body mass index (BMI), age, systemic diseases, laboratory parameters, and ultrasonography findings.

Results: When final diagnoses and IFS diagnoses were contrasted, the results were concordant in 126 patients and discordant in 28 patients. The agreement rate was 81.8% (Kappa=0.635; $p < 0.001$; significant agreement). When the concordant and discordant groups were compared regarding demographic characteristics and preoperative laboratory findings, it was found that the BMI was higher, and the rate of complex atypia in the preoperative pathological examination was higher in the discordant group ($p < 0.05$). Other inflammatory markers and demographic variables were not significantly different between groups ($p > 0.05$).

Conclusion: Among patients operated for endometrial hyperplasia with atypia, IFS diagnoses were mostly concordant with the final diagnoses. It should be kept in mind that the discordance rate may be higher in atypical hyperplasias with complex structures and in patients with high BMI.

Keywords: Endometrial hyperplasia, atypia, complex, malignancy, frozen section

Öz

Amaç: Atipili endometrial hiperplazi tanısı ile opere edilen hastalarda intraoperatif frozen section patoloji ile postoperatif final patoloji sonuçları arasındaki farklılıkların demografik özellikler ve preoperatif laboratuvar bulguları ile ilişkisinin araştırılmasıdır.

Gereç ve Yöntem: Kliniğimizde Ocak 2015-Ocak 2021 tarihleri arasında atipili endometrial hiperplazi nedeniyle opere olan ve intraoperatif frozen section patoloji (FSP) çalışılan 154 hasta çalışmaya alındı. Hastaların FSP ve postoperatif final patoloji sonuçları karşılaştırıldı. Hastalar FSP ve final patoloji uyumlu olanlar ve uyumlu olmayanlar olmak üzere iki gruba ayrıldı. Bu iki grup; yaş, vücut kitle indeksi (VKİ), sistemik hastalıklar, laboratuvar parametreleri ve ultrasonografi bulguları açısından karşılaştırıldı.

Bulgular: FSB ve final patoloji sonuçları karşılaştırıldığında 126 hastada sonuçlar uyumluyken 28 hastada sonuçlar uyumsuz olarak değerlendirildi. Uyumluluk oranı %81.8 olarak saptandı (Kappa=0.635; $p < 0.001$; önemli derecede uyumlu). Uyumlu olan ve uyumlu olmayan gruplar demografik ve preoperatif laboratuvar bulguları açısından karşılaştırıldığında uyumsuz grupta VKİ'nin daha yüksek ve preoperatif patolojide kompleks atipi oranının daha fazla olduğu saptandı ($p < 0.05$). Diğer demografik özellikler ve inflamatuvar göstergeler açısından iki grup arasında fark saptanmadı ($p > 0.05$).

Sonuç: Atipili endometrial hiperplazi nedeniyle opere olan hastalarda FSP sonuçları büyük oranda final patoloji sonuçları ile uyum içerisindedir. Uyumsuzluk oranının kompleks yapıli atipili hiperplazilerde ve yüksek VKİ sahip hastalarda daha fazla olabileceği akıld tutulmalıdır.

Anahtar Kelimeler: Endometrial hiperplazi, atipi, kompleks, malignite, frozen section

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INTRODUCTION

Endometrial hyperplasia (EH) is a precancerous lesion associated with developing endometrial cancer (EC) risk that occurs as a result of prolonged endometrium to estrogen exposure and progesterone deficiency. In developed countries, EC is the most frequent and common gynecological malignancy, and endometrioid adenocarcinoma is the most common histological type.^[1] EH is divided into four groups: complex hyperplasia with cytological atypia, complex hyperplasia without cytological atypia, simple hyperplasia with cytological atypia, and simple hyperplasia without cytological atypia. The association between stromal and glandular tissue determines the simple and complex type of hyperplasia, and atypia reflects nuclear abnormalities. The EH progressing to carcinoma risk requires cytological atypia.^[2]

If a hysterectomy is performed in patients in whom EH with atypia is detected in endometrial tissue sampling, it is observed that approximately 25%–43% are accompanied by well-differentiated endometrial carcinoma.^[3] For this reason, an intraoperative frozen section (IFS) examination may be required in cases with a preoperative diagnosis of EH because surgical staging is required in EC treatment. The surgical staging procedure requires bilateral salpingo-oophorectomy with dissection of the paraaortic lymph node and bilateral pelvic lymph node and total abdominal hysterectomy.^[4] Since surgical staging has an association with increased perioperative mortality and morbidity, the IFS examination in this patient group prevents unnecessary staging surgery on the one hand and avoids second surgery in case postoperative pathological examination reveals cancer on the other hand.

Many studies have examined the necessity of performing an IFS examination and its comparison with final diagnoses in EH with atypia patients.^[5-10] There are some reports of a high concordance rate between IFS diagnoses and final diagnoses in patients with EH with atypia, whereas some reported a low concordance rate and inadequacy in detecting EC. Although there are studies evaluating the usefulness of demographic and ultrasound findings in predicting EC detection in patients with EH with atypia, there is a paucity of studies evaluating the factors that may have an impact on the discordance between IFS diagnoses and final diagnoses.^[11,12] This study investigates the relationship between demographic characteristics and preoperative laboratory findings and the discordance between IFS diagnoses and final diagnoses in patients undergoing surgery with an EH with atypia diagnosis.

MATERIAL AND METHOD

The study was carried out with the permission of İzmir Tepecik Training and Research Hospital Non-interventional Researches Ethics Committee (Date: 17.01.2022, Decision No: 2022/01-02). All procedures were carried out in

accordance with the ethical rules and the principles of the Declaration of Helsinki. This study included 154 patients diagnosed with EH with atypia and operated on in our clinic between January 2015 and January 2021.

The patients were examined in terms of body mass index (BMI), age, menopausal status, parity, comorbidity (diabetes, hypertension), smoking, preoperative laboratory findings (neutrophil-to-lymphocyte ratio [NLR], inflammatory markers, fibrinogen-to-albumin ratio [FAR]), endometrial thickness (ET) on preoperative ultrasonography, IFS diagnosis and final diagnosis. We considered two groups for participants: patients with an IFS diagnosis concordant and patients with an IFS diagnosis discordant with the final diagnosis. These two groups were compared regarding the demographic and medical data mentioned above. The study was performed retrospectively and medical data was retrieved from patient charts.

The patient's diagnosis was according to an endometrial biopsy. The endometrial biopsy method used in patients undergoing biopsy for gynecological reasons was fractional dilation and probe curettage (D&C). Every diagnosed patient received treatment surgically by total hysterectomy without or with bilateral salpingo-oophorectomy.

Every patient who underwent surgery received an IFS examination. In the IFS examination, the hysterectomy material was opened, and then the cavity was examined for its color and irregularity. After that, 2 to 5 thick slices were taken from the uterine wall, and the myometrial invasion's deepest area was selected for IFS. In case no obvious tumor was observed in the cavity, five or more sections were taken randomly. The freezing temperatures for all samples was -25°C , and 8 μ -thick sections were cut and stained with haematoxylin-eosin. If no tumor was observed in these sections; No additional sections were taken.

The operation was terminated in patients in whom malignancy was not detected in IFS. In patients with EC detected in IFS examination, hysterectomy materials were also evaluated regarding myometrial invasion, grade, lymph-vascular space invasion, and tumor size. As a result of these evaluations, patients having non-endometrioid histological type and high-grade tumor with deep myometrial invasion ($\geq 1/2$) and a tumor diameter >2 cm with cervical involvement underwent surgical staging.

The pathological material remaining after the IFS examination was embedded in paraffin blocks with formalin for further histopathological examination. Patients with a final diagnosis of malignancy in the postoperative pathological examination were staged based on the FIGO 2009. All materials, including preoperative endometrial biopsy pathologies, IFS pathologies and final pathologies, were examined by 5 gynecopathologists who are experts in their fields.

SPSS (SPSS Statistics version 22.0, SPSS Inc.) statistical software was used for statistical analysis. The positive

predictive value (PPV), negative predictive value (NPV), specificity, sensitivity, and accuracy were calculated with a 95% confidence interval for each parameter. Using Cohen's κ coefficient, the correlation between the IFS diagnosis and the final diagnosis was determined. A t-test was used in order to compare parametric variables, and Fisher's Exact and Pearson's chi-square tests were used to compare categorical variables. Categorical variables were expressed as numbers and percentages (n; %), and numerical variables were expressed as mean \pm standard deviation (mean \pm SD) and median [quartile]. A p-value less than 0.05 was considered statistically significant.

RESULTS

The study included 154 patients with EH combined atypia in total. The patients' mean age was between 32 to 80 years, with a mean of 54.2 years. Ninety patients were postmenopausal. Although all of the D/C applications were performed in our hospital, the diagnoses of all patients were made by our pathologists. The average amount of time between D&C and surgery was 18 days (10–45 days). Table 1 shows the demographic and pathological characteristics of all participants. The IFS section revealed malignancy in 48 (31.8%) patients, whereas the final pathological examination revealed malignancy in 76 (49.4%) patients. In postoperative histopathological examination, all patients found to have malignancy had endometrioid type EC. The rates of Grade-1, 2, and 3 tumors were 29.2%, 18.8%, and 0.6%, respectively, while the rates of Stage 1a, 1b, and 2 of the disease were 39.0%, 6.5%, and 3.9%, respectively (Table 1).

Table 1: Demographic characteristics and pathological results of the patients

Characteristics	All patients
Age	54.2 (9.6)
BMI	32.6 (5.7)
Nulliparity	3 (1.9)
Postmenopausal	90 (58.4)
Hypertension	69 (44.8)
Diabetes	49 (31.8)
Smoking	79 (51.3)
Malignant (IFS)	48 (31.8)
Malignant (Permanent)	76 (49.4)
Grade-1	46 (29.2)
Grade-2	29 (18.8)
Grade-3	1 (0.6)
Stage 1a	60 (39.0)
Stage 1b	10 (6.5)
Stage 2	6 (3.9)

BMI; body mass index, IFS; intraoperative frozen section, Parametric variables are given as mean (standard deviation) (SD) and non-parametric variables are given as n (%)

All 48 patients reported to have malignancy in IFS examination were also found to have malignancy in postoperative histopathological examination, while 78

out of 106 patients reported to have benign lesions were also found to have benign lesions and 28 were found to have malignant lesions in postoperative histopathological examination (Table 2). The IFS diagnoses were concordant with the final diagnoses in 126 out of 154 patients, whereas the diagnoses were discordant in 28 patients. The agreement between the IFS diagnoses and the final diagnoses was statistically significant (Kappa=0.635; $p < 0.001$). Cancer detection's sensitivity and specificity by IFS examination were 63.1% and 100%, and the NPV and PPV were 100% and 73.5%, respectively.

Table 2: Comparison of the IFS and the final diagnoses

IFS Diagnosis	Final Diagnosis		
	Malignant	Benign	Total
Malignant	48	0	48
Benign	28	78	106
Total	76	78	154

IFS; frozen section pathology. Sensitivity: 48/76=63.1%, Specificity: 78/78=100%, Positive predictive value (PPV): 48/48=100%, Negative predictive value (NPV): 78/106=73.5%, Concordance: 126/154=81.8% (Kappa=0.635; $P < .001$) with significant agreement.

When the concordant and discordant groups were compared regarding age, BMI, parity, menopausal status, systemic diseases (hypertension and diabetes mellitus), and smoking, it was found that BMI was higher in the discordant group (32.0 \pm 5.4 vs. 35.5 \pm 5.9 kg/m²; $p=0.006$). Regarding further demographic factors, there was no statistically significant difference between the two groups (Table 3). No difference was found between the two groups in the evaluation of preoperative laboratory parameters such as NLR, PLR, FAR, Ca125 and preoperative ultrasonography in terms of ET ($p > 0.05$). The rate of EH with complex atypia was 29.4% in the concordant group in the preoperative diagnosis, whereas this rate was 50.0% in the discordant group ($p=0.036$).

Table 3: Comparison of demographic and laboratory variables between groups

Characteristics	Concordant (n=126)	Discordant (n=28)	P value
Age	53.9 (9.9)	55.3 (8.0)	0.437
BMI (kg/m ²)	32.0 (5.4)	35.5 (5.9)	0.006
Nulliparity	2 (1.6)	1 (3.6)	0.499
Postmenopausal	71 (56.3)	19 (67.9)	0.264
Hypertension	56 (44.4)	13 (46.4)	0.849
Diabetes	40 (31.7)	9 (32.1)	0.967
Smoking	63 (50.0)	16 (57.1)	0.494
ET (before PC)	13.2 (5.3)	12.2 (4.9)	0.386
PC (complex HP)	37 (29.4)	14 (50.0)	0.036
NLR	2.4 (0.9)	2.5 (0.9)	0.467
PLR	139.5 (51.1)	130.7 (33.8)	0.270
FAR	75.0 (22.9)	83.6 (28.1)	0.296
Ca125	12 [9-17]	12 [9-17.5]	0.964

BMI; body mass index, ET; endometrial thickness, PC; probe curettage, HP; hyperplasia, NLR; neutrophil lymphocyte ratio, PLR; platelet lymphocyte ratio, FAR; fibrinogen albumin ratio, Parametric variables are given as mean (standard deviation) (SD) and median [quartiles] and non-parametric variables are given as n (%).

DISCUSSION

In our study, a comparison was made between the two groups to investigate the effect of demographic and laboratory characteristics that may have affected the discordance between the IFS and the final diagnoses in patients operated for EH with atypia. It was found that, BMI among demographic characteristics and EH with 'complex' atypia among laboratory characteristics might have affected concordance.

The use of IFS examination in gynecological practice greatly influences the care of oncology patients. IFS examination is used for differentiation between benign and malignant tumors to determine the extent of the operation. IFS examination in gynecological oncology is sufficient in sensitivity and specificity for clinical use. In general, the rate of false positives is negligible, and the rate of false negatives is low. Deferred or discordant diagnoses are usually due to technical limitations in cases such as those with mucinous ovarian tumors.^[13] In a study evaluating 203 gynecological (35.6% ovarian, 22.7% cervical, 18.2% endometrial and 11.4% vulvar) operations in which IFS examination was performed, false negative, false positive, and deferred rates were 0.5%, 2.0%, and 1.0% respectively.^[14] In this study, the cause of false positivity was misinterpretation, while the cause of false negativity was reported as an error in block selection. The reasons for false positivity and false negativity in the IFS examination in gynecological oncology are attributed to interpretation errors and technical reasons during the frozen section procedure.^[14,15] However, since the concordance between IFS diagnoses and the final diagnoses has not been evaluated in previous studies, evaluating preoperative patients and demographic and laboratory data that increase the potential for malignancy in cases with EH with atypia were evaluated in the present study.

As known, advanced age, increased BMI (obesity), nulliparity, postmenopausal status and systemic diseases including hypertension and diabetes mellitus, are crucial demographic EC development risk factors.^[16] In our study, only increased BMI among these demographic factors was associated with the discordance between the IFS and final diagnoses. Given that there is a significant relationship between rising BMI and EC and that EH with atypia may have associations with a higher cancer risk, obtaining more sections in IFS examinations may prove effective to catch cancer. A similar number of sections were taken in each case for the IFS examination in our study. In patients with increased risk factors for EC, taking more sections in the IFS examination may reduce false negativity and thus the rate of discordance.

Increased inflammation is one of the factors that are influential in cancer development and progression.^[17] Inflammatory biomarkers, including NLR and PLR, are poor prognosis indicators in EC patients.^[18,19] NLR or PLR

has associations with overall survival and disease-free survival (DFS).^[19] In our study, we found that inflammatory markers such as NLR, PLR, and FAR were not related to the discordance between the IFS and the final diagnoses in cases with EH with atypia. Detection of increased ET (≥ 2 cm) on preoperative ultrasonographic examination is a strong predictor for simultaneous EC in patients having a hysterectomy with a diagnosis of EH with complex atypia and endometrial intraepithelial neoplasia.^[20] Our study found no difference in preoperative ET values between concordant and discordant groups. Therefore, it is considered that the ET was not associated with the discordance between the IFS and the final diagnoses.

While EC was not observed in the final pathological examination in patients operated for EH with simple atypia, EC was observed at a rate of 40%–50% in patients with EH with complex atypia.^[21,22] Therefore, a structurally 'complex' feature in patients with atypical EH is a significant risk factor for malignancy. The rate of 'complex' structure in our study was 29.4% in the concordant group and 50.0% in the discordant group. The presence of EH with complex atypia is considered to be a risk factor for the discordance between the IFS and the final diagnoses.

As a secondary result of our study, IFS diagnoses significantly correlated with the final diagnoses in patients with EH with atypia. In a research comparing 66 patients with EH with atypia's ultimate diagnoses to their IFS diagnoses, Morotti et al. reported a good level of concordance ($\kappa=0.75$).^[7] Moreover, the sensitivity, specificity, PPV, NPV, and accuracy rates of IFS examination to predict EC were found to be 73%, 93.1%, 73%, and 93.1%, respectively. In another study, 75% of patients operated on with a diagnosis of EH with atypia and diagnosed with EC were successfully detected with IFS examination.^[8] In another study evaluating 125 patients with EH with complex atypia, 62.4% of final diagnoses were found to be concordant with the IFS diagnoses, and the sensitivity and specificity of IFS examination in detecting EC were 81.1% and 97.9%, and the negative and positive predictive values were 76.7% and 98.4%, respectively; however, the authors reported that IFS examination did not restrain the potentiality of EC in patients with a preoperative diagnosis of EH with complex atypia and adequate endometrial sampling was more important for accurate diagnosis.^[9] As can be seen, the rate of EC detection with IFS examination in our study is consistent with reports in other studies in the literature.

The strengths of this study include the following: (a) it is the first study to compare the reasons for discordance between the IFS and the final diagnoses in patients undergoing hysterectomy for EH with atypia, (b) it is the most extensive series in the literature evaluating the performance of IFS examination in diagnosing EC among patients with EH with atypia, (c) the short period between preoperative diagnosis and hysterectomy (reduced risk of EC progression), (d) all

preoperative diagnoses were made by the pathologists our hospital. The limitations of this study can be listed as the following: (a) Technical problems during IFS examination are not known since the study was not a prospective study by design, (b) Preoperative D&C material, IFS and final pathological examinations were not performed by the same pathologist.

CONCLUSION

High BMI and the presence of EH with complex atypia are important factors in the discordance between the IFS and the final diagnoses. In the IFS examination of patients with EH with complex and high BMI, a higher number of sections should be taken to increase the concordance rate.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İzmir Tepecik Training and Research Hospital Non-interventional Researches Ethics Committee (Date: 17.01.2022, Decision No: 2022/01-02).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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