Relationship of Preoperative Biopsy Results with Postoperative Histopathological Grade in Endometrioid Type Endometrium Cancer

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Abstract

Aim: To assess the concordance between preoperative endometrial biopsy and final postoperative histopathological findings in patients with endometrioid-type endometrial cancer, and to identify factors associated with diagnostic discrepancies.

Methods: This retrospective study included 134 patients who underwent surgery between 2005 and 2018 following a preoperative diagnosis of endometrioid-type endometrial cancer at a tertiary center. Demographic, clinical, and histopathological data were reviewed. Concordance between preoperative biopsy and final pathology was evaluated using Cohen's kappa coefficient. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated.

Results: A statistically significant correlation was observed between preoperative and final tumor grades ($p < 0.001$). In 35.8% of patients (n = 48), the final pathology revealed a higher grade than the initial biopsy. Grade 3 tumors demonstrated the highest diagnostic accuracy (89.5%), while Grades 1 and 2 showed an overall accuracy of 66.0%. Tumor size greater than 2 cm and lymph node metastasis were significantly associated with grade upgrading ($p = 0.014$ and $p = 0.004$, respectively).

Conclusions: Preoperative biopsy alone may not be sufficient for accurate risk stratification in patients with endometrial cancer. Tumor upgrading was significantly associated with adverse prognostic indicators such as larger tumor size and nodal involvement. A multimodal diagnostic approach is recommended, particularly in cases initially classified as low-grade.

Keywords: *Endometrial Cancer; biopsy; histopathology; grade concordance; lymph node involvement*

1. Introduction

Endometrial cancer, the most prevalent gynecological malignancy in developed nations, has been experiencing a steady rise in incidence.[1,2] Several contributing factors have been identified, including obesity, dietary changes, an aging population, delayed menopause, and diabetes.[3] Over 75% of endometrial cancer cases are diagnosed at an early stage, primarily due to symptoms such as abnormal vaginal bleeding.[4,5]

Despite the high rate of early detection, the continued increase in incidence and mortality highlights persistent challenges in achieving accurate diagnosis and providing optimal treatment. Standard diagnostic procedures include pipelle endometrial biopsy, dilatation and curettage (D&C), and hysteroscopic evaluation.[5-7] In general, surgery is the first-line treatment unless there is extrauterine pelvic disease that precludes surgical intervention.

The primary surgical treatment for suspected early-stage endometrial cancer is hysterectomy with bilateral salpingo-oophorectomy, with or without lymph node dissection. In certain cases, adjuvant therapies such as chemotherapy and/or radiotherapy may be considered based on recurrence or mortality risk.[8-10] Patients are stratified into risk categories based on histopathological evaluation. Preoperative biopsy plays a pivotal role in predicting the final pathology result, which significantly

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influences surgical decision-making. The triple rating (grade) system developed by the International Federation of Gynecology and Obstetrics (FIGO) is commonly used to classify endometrioid-type endometrial cancer. Extensive research has demonstrated the prognostic importance of tumor grade, with Grade 1 tumors typically associated with favorable outcomes, and Grade 3 tumors linked to poor prognosis.[9,10] According to recent ESMO-ESGO-ESTRO consensus guidelines, preoperative risk stratification and histological grading are essential for tailoring surgical staging and adjuvant treatment strategies.[11]

This study aimed to evaluate the concordance between preoperative endometrial biopsy and final postoperative histopathological findings in patients with endometrial cancer. It also assessed whether the surgical treatment based on preoperative biopsy was appropriate by examining if it was excessive, sufficient, or insufficient when compared with the final pathology results. In addition, the study investigated potential factors that may contribute to discrepancies, including tumor grade, tumor size, depth of myometrial invasion, cervical stromal invasion, and lymph node involvement.

2. Materials and Methods

A retrospective analysis was conducted on patients with endometrioid-type endometrial cancer who underwent surgery between January 2005 and December 2018. Ethical approval for the study was obtained from the institutional review board of Istanbul Training and Research Hospital. Patients diagnosed with non-endometrioid-type endometrial cancer in the final postoperative pathology or those who did not undergo surgical staging were excluded. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables are presented as mean ± standard deviation, while categorical variables are expressed as frequencies and percentages. Group comparisons were made using the Chi-square test or Fisher's exact test, as appropriate.

The strength of agreement was interpreted based on the value of Cohen's kappa coefficient, where values below 0.20 indicated slight agreement, 0.21 to 0.40 indicated fair agreement, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and values above 0.80 were considered to indicate almost perfect agreement.[12] Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. A p-value of < 0.05 was considered statistically significant.

3. Results

A total of 134 patients diagnosed with endometrioid-type endometrial cancer based on preoperative biopsy underwent hysterectomy and bilateral salpingo-oophorectomy. Patient ages ranged from 32 to 81 years, with a mean age of 59.3 ± 9.1 years. Parity ranged from 0 to 12, with an average of 2.5 ± 2.1 (median: 2).

According to preoperative biopsy, 63.4% (n = 85) of patients were classified as Grade 1, 26.1% (n = 35) as Grade 2, and 10.5% (n = 14) as Grade 3. Lymph node dissection was performed in 86.6% of patients (n = 116). Among them, 59.0% (n = 79) underwent pelvic dissection alone, while 27.6% (n = 37) underwent both pelvic and para-aortic dissection. No lymphadenectomy was performed in 13.4% (n = 18) of cases.

Lymph node involvement was detected in 11 patients (9.5%). Of these, 4 had isolated pelvic node metastasis, and 7 had both pelvic and para-aortic metastases. All patients who underwent para-aortic dissection also had pelvic node dissection.

Table 1

Postoperative Pathology Results

	Number (n)	Percent (%)
Tumor Size		
• 2 Cm ≤	38	28.4
• 2 Cm >	96	71.6
Myometrial Invasion		
• % 50 <	84	62.7
• % 50 ≥	50	37.3
LVS Invasion		
• Invasion (+)	21	15.7
• Invasion (-)	113	84.3
Cervical Invasion		
• Invasion (+)	17	12.7
• Invasion (-)	117	87.3
Total	134	100

LVS: Lymphovascular Space

Table 2

Relation of Preoperative and Postoperative Grade Results

Preoperative Grade	Postoperative Grade							
	Grade 1		Grade 2		Grade 3		NE	
	n	%	n	%	n	%	n	%
Grade 1	42	95,5	36	54.5	3	21.4	4	40.0
Grade 2	2	4.5	28	42.4	4	28.6	1	10.0
Grade 3	0	0.0	2	3.0	7	50.0	5	50.0

Kappa:0.393; p<0.001 NE: Non-Endometrioid Type

Table 3

Preoperative Grade Sensitivity, Specificity PPD and NPD

	Preoperative Grade					
	Grade 1		Grade 2		Grade 3	
	%	CI	%	CI	%	CI
Sensitivity	95.5	89.3-101.6	42.4	30.5-54.3	50.0	30.0-70.0
Specificity	52.2	41.9-62.5	89.7	82.5-96.9	98.2	95.7-100.7
PPV	49.4	38.8-60.0	80.0	66.7-93.3	85.7	67.4-104.0
NPV	95.9	90.4-101.5	61.6	52.0-71.2	90.0	84.6-95.4
	66.0		66.0		89.5	

PPD: Positive Predictive Value NPD: Negative Predictive Value CI: Confidence Interval

Table 4

The Relationship Between Preoperative Grade and Other Postoperatively Determined Features

	Preoperative Grade						
	Grade 1		Grade 2		Grade 3		
	n	%	n	%	n	%	p
Tumor sizes							
• 2 Cm ≤	22	25.9	13	37.1	3	21.4	0.384
• 2 Cm >	63	74.1	22	62.9	11	78.6	
Myometrial Invasion							
• < 50 %	54	63.5	23	65.7	7	50	0.569
• ≥ 50 %	31	36.5	12	34.3	7	50	
LVS Invasion							
• (+)	10	11.8	7	20	4	28.6	0.198
• (-)	75	88.2	28	80	10	71.4	
Cervical Invasion							
• (+)	9	10.6	3	8.6	5	35.7	0.055
• (-)	76	89.4	32	91.4	9	64.3	
LN Metastasis °							
• (+)	7	9.7	2	6.5	2	15.4	0.661
• (-)	65	90.3	29	93.5	11	84.6	
Stage *							
• Stage 1	66	77.6	29	82.9	7	50	
• Stage 2	8	9.4	2	5.7	3	21.4	
• Stage 3	9	10.6	4	11.4	2	14.3	
• Stage 4	2	2.4	0	0	2	14.3	
Total	85	100	35	100	14	100	

** Chi-square analysis could not be performed. °A total of 116 patients who underwent lymph node dissection. LVS: Lymphovascular Space, LN: Lymph Node*

Final postoperative pathology confirmed the endometrioid type in 92.5% of patients (n = 124). The remaining 7.5% (n = 10) were diagnosed with non-endometrioid subtypes, including 4 serous, 1 mixed, 1 undifferentiated, and 4 carcinosarcomas.

Tumor characteristics revealed that 71.6% (n = 96) of patients had tumors larger than 2 cm. Lymphovascular space invasion (LVSI) was present in 15.7% (n = 21), and cervical stromal invasion was observed in 12.7% (n = 17) (Table I). The majority of patients were diagnosed at an early stage: 53.7% (n = 72) were Stage IA, 22.4% (n = 30) Stage IB, 9.7% (n = 13) Stage II, 11.2% (n = 15) Stage III, and 3.0% (n = 4) Stage IV.

Postoperative histopathological examination revealed grade upgrading in 35.8% of cases (n = 48). Among these, 36 patients (26.9%) were upgraded from Grade 1 to Grade 2 or 3, and 7 patients (5.2%) were upgraded directly to Grade 3. Only 4 patients were downgraded, none of whom were downgraded from Grade 3 to Grade 1.

Concordance between preoperative and postoperative grades was evaluated using Cohen's kappa coefficient, yielding a value of 0.383 ($p < 0.001$), indicating fair agreement (Table II).

Table 5

The Relationship Between Lymph Node Involvement and Postoperative Grade

	LN Involvement (+)		LN Involvement (-)		p
	n	%	n	%	
Preoperative Grade					
• Grade 1	7	63.6	65	61.9	
• Grade 2	2	18.2	29	27.6	0.661
• Grade 3	2	18.2	11	10.5	
Postoperative Grade*					
• Grade 1	0	0.0	35	33.3	
• Grade 2	4	36.4	54	51.4	
• Grade 3	7	63.6	16	15.2	
Total	11	100	105	100	

**Chi-square analysis could not be performed LN: Lymph node*

Table 6

Upgrade of Grade and Relationship with Other Pathology Outcomes

	Preoperative & Postoperative Grade				
	Non-Upgrade		Upgrade		
	n	%	n	%	P
Tumor Size					
• 2 Cm ≤	27	37.5	8	16.7	0.014
• 2 Cm >	45	62.5	40	83.3	
Myometrial Invasion					
• < 50 %	49	68.1	28	58.3	0.277
• ≥ 50 %	23	31.9	20	41.7	
LVS Invasion					
• Invasion (+)	9	12.5	8	16.7	0.521
• Invasion (-)	63	87.5	40	83.3	
Cervical Invasion **					
• Invasion (+)	9	12.5	3	6.3	0.358
• Invasion (-)	63	87.5	45	93.8	
LN Involvement **°					
• LN Involvement(+)	1	1.7	8	18.2	0.004
• LN Involvement(-)	58	98.3	36	81.8	
Stage					
• Stage 1	60	83.3	35	72.9	
• Stage 2	8	11.1	2	4.2	
• Stage 3	4	5.6	9	18.8	
• Stage 4	0	0.0	2	4.2	
Total	72	100.0	48	100.0	

**Patients with preoperative Grade 1 and Grade 2 are included (n:120).*
***Fisher exact, °Patients who underwent lymph node sampling were included (n:103).*

The sensitivity of preoperative biopsy for detecting Grade 1 tumors was 95.5% (95% CI: 89.3–101.6), with a negative predictive value of 95.9% (95% CI: 90.4–101.5). For Grade 3 tumors, sensitivity was 50.0% (95% CI: 30.0–70.0) and specificity was 98.2% (95% CI: 95.7–100.7). The lowest diagnostic sensitivity was

observed for Grade 2 tumors (42.4%, 95% CI: 30.5–54.3), with a negative predictive value of 61.6% (95% CI: 52.0–71.2). The highest accuracy rate was found in Grade 3 cases (89.5%) (Table III).

No statistically significant association was found between preoperative tumor grade and myometrial invasion (p = 0.569), lymph node metastasis (p = 0.661), LVSI (p = 0.198), cervical invasion (p = 0.055), or tumor size (p = 0.384). When preoperative grade was compared with FIGO stage, 77.6% of patients with Grade 1 tumors were Stage I, while 50% of those with Grade 3 tumors were also Stage I. Due to the absence of Grade 2 patients in the Stage IV group, statistical analysis for that subgroup could not be performed (Table IV).

When final pathology grade was compared with lymph node status, 63.6% of patients with node-positive disease were classified as Grade 3. Conversely, 63.6% of patients with lymph node metastasis had been initially graded as Grade 1 on preoperative biopsy, although many of these cases were subsequently upgraded in the final pathology (Table V).

A significant association was observed between grade upgrading and both tumor size greater than 2 cm (p = 0.014) and lymph node metastasis (p = 0.004). No significant relationship was found between grade upgrading and myometrial invasion (p = 0.277), cervical invasion (p = 0.358), or LVSI (p = 0.521) (Table VI).

4. Discussion

Endometrial cancer is the most common gynecological malignancy in developed countries. Its incidence continues to increase due to aging populations and lifestyle-related factors such as obesity and diabetes.[1-3] Although most cases are diagnosed at an early stage and generally carry a favorable prognosis, the rising incidence and mortality rates point to ongoing challenges in achieving accurate diagnosis and optimal treatment.[2] While early-stage detection is often prompted by symptoms such as abnormal uterine bleeding, accurate preoperative staging is essential to determine the most appropriate surgical and adjuvant treatment strategies.

Preoperative endometrial biopsy, typically performed using pipelle or dilatation and curettage (D&C), is widely accepted for estimating tumor grade and guiding surgical planning.[6] However, biopsy samples may not always capture the full histological heterogeneity of the tumor, potentially resulting in the underestimation or overestimation of tumor grade. In our study, we observed a weak but statistically significant correlation between preoperative biopsy and final histopathological grade. The diagnostic accuracy was highest for Grade 3 tumors (89.5%) and substantially lower for Grades 1 and 2 (66.0%).

Lago et al. demonstrated that concordance between biopsy and final pathology was highest in Grade 3 tumors (89.8%) and lower in Grade 1 (74.7%) and Grade 2 (73.2%) tumors.[14]. Our results showed a comparable pattern, with Grade 2 being the most frequently discordant category (73.1%). These discrepancies may be due to sampling limitations, particularly in tumors exhibiting focal solid growth or histological heterogeneity.

A significant association was observed between grade upgrading and both tumor size > 2 cm (p = 0.014) and lymph node metastasis (p = 0.004). No significant relationship was found between grade upgrading and myometrial invasion (p = 0.277), cervical invasion (p = 0.358), or LVSI (p = 0.521). These findings are summarized in Table VI, which presents the relationship between grade upgrading and various pathological features. They are consistent with previous reports indicating that tumor size and nodal involvement are key markers of aggressiveness in endometrial cancer.[13,15] Goksedef et al. similarly noted that discrepancies between biopsy and final pathology were more common in cases with larger tumors and deeper myometrial invasion.[15] Likewise, Lee et al. demonstrated a strong association between higher tumor grade and lymph node metastasis.[13]

A notable finding in our study was that 63.6% of patients with lymph node metastasis had been initially classified as Grade 1 based on preoperative biopsy. This suggests that relying solely on preoperative biopsy grade may underestimate true oncologic risk. Even among patients considered low-risk, comprehensive surgical staging including lymph node evaluation may be warranted. Additional preoperative assessment tools, such as magnetic resonance imaging (MRI) or intraoperative sentinel lymph node mapping, should be considered to improve risk stratification and optimize surgical planning.[16]

Our study also had limitations. Statistical analysis for Stage 4 patients could not be performed due to the absence of preoperative Grade 2 cases in this subgroup. This limitation may be related to referral patterns or selection bias inherent in retrospective study designs. Future multicenter prospective studies with larger sample sizes are needed to further explore the relationship between biopsy grade and final pathology, particularly in advanced-stage disease.

Although preoperative biopsy remains a valuable diagnostic tool, it should not be used in isolation. An integrated approach that combines histological evaluation, imaging, and intraoperative findings is essential to enhance diagnostic precision and guide individualized treatment decisions.

In conclusion, while preoperative endometrial sampling provides important preliminary information, its limited predictive value, particularly in low-grade tumors, underscores the need for supplementary diagnostic strategies. Prospective studies that incorporate radiologic and molecular data alongside biopsy results are essential to improve preoperative assessment in patients with endometrial cancer.

5. Conclusion

This study demonstrated that the concordance between preoperative endometrial biopsy and final histopathological findings in endometrioid-type endometrial cancer was limited, particularly for Grade 1 and 2 tumors. While preoperative biopsy remains a valuable diagnostic tool, it may not accurately reflect the final pathology in a significant proportion of patients. Notably, 63.6% of patients with lymph node metastasis were initially classified as Grade 1, highlighting the potential for risk underestimation.

These findings emphasize the need to incorporate additional diagnostic modalities, such as advanced imaging and intraoperative assessment, into the preoperative evaluation process. Relying solely on biopsy results may lead to inappropriate treatment decisions, including inadequate surgical staging. To improve risk stratification and optimize clinical outcomes, future research should focus on prospective, multicenter studies that integrate histopathological data with radiologic and molecular assessment tools.

Statement of ethics

Ethical approval was obtained from the Istanbul Training and Research Hospital Clinical Research Ethics Committee. (Date:18.01.2019/No:1642).

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

Concept (EŞ, CA), Design (EŞ, CA), Data Collection and/or Processing (EŞ, CA, FFV), Analysis and/or Interpretation (EŞ, CA, FFV)

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