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Original Research

Concordance of preoperative and postoperative histological grades in endometrioid type endometrial cancer

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Summary

Purpose of Investigation: To investigate concordance between grades determined by endometrial sampling and final pathology, and factors affecting this concordance, in endometrioid type endometrial cancer. *Materials and Methods:* In this retrospective study, 330 endometrioid type endometrial cancer patients were enrolled. For evaluating the concordance between histological grades in preoperative and postoperative pathology reports, Kappa statistic and comparative analyses were performed. *Results:* In 230 of 330 (69.7%) patients, the endometrial sampling-determined grade was in concordance with the final histological grade. The concordance was minimal according to the Kappa statistic in all patients ($K = 0.390$; 95% confidence interval = 0.666-0.047; $p < 0.01$). There was no significant correlation between diabetes mellitus, cancer antigen (Ca) 125, and Ca 19-9 status, and grade concordance ($p = 0.86$, $p = 0.715$, $p = 0.774$, respectively). *Conclusion:* In endometrioid type endometrial cancer, concordance between preoperative and postoperative histological grades was minimal. Therefore, histological grading by preoperative sampling alone is insufficient for decision-making in pelvic lymphadenectomy.

Key words: Dilatation and curettage; Endometrial neoplasms; Endometrium; Biopsy.

Introduction

In endometrioid type endometrial cancer, which is usually diagnosed at an early stage, concordance between the preoperative and the final histological grades has strong implications for morbidity and mortality related to insufficient surgery and unnecessary lymphadenectomy.

In several studies, it was stated that lymphadenectomy may be avoided in patients with a low risk of lymph node metastasis, as it may cause intraoperative large vessel and nerve injuries, postoperative deep vein thrombosis, or lymphedema in legs [1, 2]. On the other hand, surgical staging including lymphadenectomy may confer survival benefits in high-risk patients [3]. In several oncology centres, endometrial sampling is used for definitive prediction of the final pathological result, and surgical staging decisions are based on the preoperative biopsy [4, 5].

In this study, the authors' objective was to determine the concordance between these two pathological results by comparative analysis of the histological grade of the endometrial sampling material obtained from endometrioid type endometrial cancer tissue and the histological grade obtained after hysterectomy, and to identify factors affecting this concordance.

Materials and Methods

In this retrospective cohort study, 330 patients diagnosed with endometrioid type endometrial cancer after examination of endometrial samples and who underwent total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic-para-aortic lymphadenectomy at the Izmir Ataturk Training and Research Hospital between 01 January, 2008 and 31 May, 2018 were included. Ethics committee approval was obtained from our institution before the study started (#221/2018). They were divided into two groups according to the concordance between preoperative and postoperative histological grades; these groups were compared for clinical features and staging. The patients were surgically treated at least one month after the endometrial sampling. All preoperative and postoperative histological examinations were performed at the pathology clinic of this hospital. International Federation of Gynecology and Obstetrics (FIGO) classification was used for the histological grading [6]. Only patients with endometrioid type endometrial cancer as detected by endometrial sampling, and whose histological grade was recorded in the pathology report, were included in the study. Patients who previously underwent pelvic radiation therapy and had other concomitant histologically diagnosed cancers, were excluded from the study.

The concordance between histological grades in the endometrial sampling and final pathological report was analysed using the frequency-based Kappa (K) statistic and with a confidence interval (CI) of 95%. This method was chosen for its reliability. The generally accepted Cohen's Kappa interpretation values as presented in Table 1 were used for the determination of the concordance level with the K-value [7]. Categorical data were expressed as numbers, means, and percentages. Chi-square test and Fisher's exact test were used for the analysis of

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Table 1. — *Cohen's Kappa interpretation values.*

K-value	Level of agreement	% of data that are reliable
0 – 0.20	None	0 – 4
0.21 – 0.39	Minimal	4 – 15
0.40 – 0.59	Weak	15 – 35
0.60 – 0.79	Moderate	35 – 63
0.80 – 0.90	Strong	64 – 81
Above 0.90	Almost perfect	82 – 100

Table 2. — *The distribution of patients according to the preoperative and postoperative grade.*

	Preoperative		Postoperative	
Grade	n	%	n	%
1	235	71.2	194	58.8
2	78	23.6	113	34.2
3	17	5.2	23	7.0

Table 3. — *The patient distribution according to the concordance between grades related to tumour diameter and myometrial invasion.*

Grade				Tumour diameter, cm				Myometrial invasion			
				≤ 2		> 2		< 50%		≥ 50%	
D&C	Final	n	%	n	%	n	%	n	%	n	%
1	1	170	72.3	92	54.1	78	45.9	131	77.1	39	22.9
1	2	58	24.7	17	29.3	41	70.7	30	51.7	28	48.3
1	3	7	3.0	2	28.6	5	71.4	2	28.6	5	71.4
2	2	50	64.1	17	34.0	33	66.0	22	44.0	28	56.0
2	3	6	7.7	1	16.7	5	83.3	3	50.0	3	50.0
2	1	22	28.2	9	40.9	13	59.1	14	63.6	8	36.4
3	3	10	58.8	8	80.0	2	20.0	2	20.0	8	80.0
3	2	5	29.4	4	80.0	1	20.0	2	40.0	3	60.0
3	1	2	11.8	0	0	2	100	2	100	0	0
X	X	230	69.7	111	48.3	119	51.7	155	67.4	75	32.6
X	Y	100	30.3	32	32.0	68	68.0	53	53.0	47	47.0
T	T	330	100	143	43.3	187	56.7	208	63.0	122	37.0

X: any grade, Y: any grade other than X, T: total.

Table 4. — *Patient distribution based on risk level and lower uterine segment involvement according to concordance between preoperative and postoperative histological grades.*

Grade				Lower uterine segment involvement				Risk level			
D&C	Final	n	%	No		Yes		Low risk		High risk	
				n	%	n	%	n	%	n	%
1	1	170	72.3	149	87.6	21	12.4	79	46.5	91	53.5
1	2	58	24.7	43	74.1	15	25.9	14	24.1	44	75.9
1	3	7	3.0	3	42.9	4	57.1	0	0	7	100
2	2	50	64.1	36	72.0	14	28.0	9	18.0	41	82.0
2	3	6	7.7	4	66.7	2	33.3	0	0	6	100
2	1	22	28.2	18	81.8	4	18.2	6	27.3	16	72.7
3	3	10	58.8	5	50.0	5	50.0	0	0	10	100
3	2	5	29.4	5	100	0	0	1	20.0	4	80.0
3	1	2	11.8	2	100	0	0	2	100	0	0
X	X	230	69.7	190	82.6	40	17.4	88	38.3	142	61.7
X	Y	100	30.3	75	75.0	25	25.0	23	23.0	77	77.0
T	T	330	100	265	80.3	65	19.7	111	33.6	219	66.4

X: any grade, Y: any grade other than X, T: total.

comparative data. All calculations were performed using the SPSS version 24.0 software.

Results

The records of a total of 330 patients with endometrioid type endometrial cancer who fulfilled the inclusion criteria, were accessed from the hospital archives. The average age of the patients was 59.9 ± 9.7 years. Endometrial sampling was performed with dilatation and curettage (D&C) in all patients. The distribution of the patients according to the preoperative and postoperative grade results is listed in Table 2.

The concordance between preoperative and postoperative histological grades was minimal in the Kappa statistical analysis (95% CI, 0.666–0.047; $p < 0.01$), which was performed for all grades (*K*-value = 0.390).

Table 5. — *Grade concordance and association with diabetes mellitus status, and to cancer antigen (Ca) 125 and Ca 19-9 levels.*

Grade				Diabetes mellitus				Ca 125						Ca 19-9					
D&C	Final	n	%	No		Yes		None		Normal		High		None		Normal		High	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	1	170	72.3	69	40.6	101	59.4	92	54.1	70	41.2	8	4.7	69	40.6	87	51.2	14	8.2
1	2	58	24.7	22	37.9	36	62.1	29	50	22	37.9	7	12.1	25	43.1	28	48.3	5	8.6
1	3	7	3.0	2	28.6	5	71.4	2	28.6	4	57.1	1	14.3	0	0	4	57.1	3	42.9
2	2	50	64.1	18	36.0	32	64.0	25	50.0	17	34.0	8	16.0	20	40.0	3	50.0	11	50
2	3	6	7.7	0	0	6	100	2	33.3	3	50.0	1	16.7	22	44.0	3	50.0	9	40.9
2	1	22	28.2	13	59.1	9	40.9	14	63.6	7	31.8	1	4.5	8	16.0	0	0	2	9.1
3	3	10	58.8	5	50.0	5	50.0	2	20.0	4	40.0	4	40.0	4	40.0	4	40.0	2	20.0
3	2	5	29.4	1	20.0	4	80.0	4	80.0	1	20.0	0	0	2	40.0	1	20.0	2	40.0
3	1	2	11.8	1	50.0	1	50.0	0	0	2	100	0	0	0	0	2	100	0	0
X	X	230	69.7	92	40.0	138	60.0	119	51.7	91	39.6	20	8.7	93	40.0	113	49.1	24	10.4
X	Y	100	30.3	39	39.0	61	61.0	51	51.0	39	39.0	10	10.0	41	41.0	47	47.0	12	12.0
T	T	330	100	131	39.7	199	60.3	170	51.5	130	39.4	30	9.1	134	40.6	160	48.5	36	10.9

X: any grade, Y: any grade other than X, T: total.

Table 6. — *The distribution of the patients who underwent lymphadenectomy, according to the grade concordance*

Grade				Lymphadenectomy									
D&C	Final	n	%	None		Negative		Pelvic		Pelvic & para-aortic		Para-aortic	
				n	%	n	%	n	%	n	%	n	%
1	1	170	72.3	9	5.3	156	91.7	1	0.6	4	2.4	0	0
1	2	58	24.7	6	10.3	38	65.5	7	12.1	7	12.1	0	0
1	3	7	3.0	0	0	6	85.7	0	0	1	14.3	0	0
2	2	50	64.1	1	2.0	39	78.0	5	10.0	3	6.0	2	4.0
2	3	6	7.7	0	0	5	83.3	1	16.7	0	0	0	0
2	1	22	28.2	0	0	22	100	0	0	0	0	0	0
3	3	10	58.8	0	0	6	60.0	0	0	4	100	0	0
3	2	5	29.4	0	0	5	100	0	0	0	0	0	0
3	1	2	11.8	0	0	2	100	0	0	0	0	0	0
X	X	230	69.7	10	4.3	201	87.4	6	2.6	11	4.8	2	0.9
X	Y	100	30.3	6	6.0	78	78	8	8.0	8	8.0	0	0
T	T	330	100	16	4.8	279	84.5	14	4.2	19	5.8	2	0.6

X: any grade, Y: any grade other than X, T: total.

In the patient group with a tumour diameter of ≤ 2 cm, grade concordance was significantly strong ($p < 0.05$). Likewise, grade concordance was also significantly strong in the patient group with myometrial invasion (MI) less than 50% ($p = 0.013$). The patient distribution according to the concordance between grades related to the tumour diameter and MI is listed in Table 3.

The significant correlation between tumour diameter and MI, and grade concordance was significantly stronger in low-risk patients (final grade 1 or 2, MI < 50% and tumour diameter ≤ 2 cm) compared to that in high-risk patients (final Grade 3, MI ≥ 50% and tumour diameter > 2 cm) ($p < 0.05$). However, a similar correlation was not observed between grade concordance and lower uterine segment involvement ($p > 0.05$). The distribution of the risk level and lower uterine segment involvement is listed according to grade concordance in Table 4.

All patients without a previous diagnosis of diabetes mellitus (DM) were screened for this condition. Although 199 of the 330 participating patients (60.3%) had DM, there was no significant correlation between grade concordance and DM ($p > 0.05$). Cancer antigen (Ca) 125 and Ca 19-9 levels were not measured in every patient, but in cases where measurements were performed, no significant correlation was detected between grade concordance and these parameters ($p > 0.05$). The data on grade concordance and DM, Ca 125, and Ca 19-9 parameters are shown in Table 5.

Only 16 of the participating 330 patients (4.8%) did not undergo lymphadenectomy. However, 279 (84.5%) patients who underwent lymphadenectomy had a negative malignancy result in their pathology report. Patients with findings of metastasis in their pathology report (n = 35; 10.6%) were divided into three groups considering only positive pelvic, pelvic, and paraaortic, and only paraaortic metastasis; however, statistical analysis of these groups could not be performed due to insufficient number of patients in these groups. The distribution of patients who underwent lymphadenectomy according to grade concordance is summarized in Table 6.

Table 7. — *Results from previous studies on agreement rate by tumour grade.*

Study	Agreement rate by tumour Grade, %			
	G1	G2	G3	Total
Garcia *et al.* [13]	62	56	79	64
Helpman *et al.* [12]	78	59	68	71
Mitchard & Hirschowitz [8]	45	60	76	65
Petersen *et al.* [9]	60	71	84	69
Cilesiz Goksedef *et al.* [11]	64	66	58	64
Karateke *et al.* [10]	58	51	84	61

Discussion

In the present study, the rate of concordance between preoperative and postoperative grades was 69.7%. This rate is consistent with the rates reported in the literature, i.e., 61% to 71% (Table 7) [8-13].

In the present study, the analysis of the concordance between preoperative endometrial sampling and postoperative final pathology assessment was interpreted with the Cohen's Kappa statistic, taking the numerical superiority of grade 1 lesions into consideration. The Kappa statistic, which was evaluated for all grades, revealed a minimal concordance between preoperative and postoperative histological grades (K-value = 0.39, $p < 0.01$), in agreement with a previous study which similarly assessed grade concordance with the Kappa statistic (minimal concordance; K-value = 0.221) [14].

Although the highest concordance rate was in the grade 1 group in this study and in the study conducted by Helpman *et al.* (78% and 72.3% respectively), in other studies, the highest concordance rate was observed in grade 3 patients [8-13]. Garcia *et al.* reported a concordance rate of 79%, and stated that preoperative grade 3 histology is a reliable finding regarding the decision on staging surgery [13]. In the present study, the high concordance in grade 1 patients also caused a significant grade concordance in the low-risk group (MI < 50% and tumour diameter ≤ 2 cm) ($p < 0.05$). In contrast, Wang *et al.* reported that grade concordance in a cohort of 218 patients with endometrial cancer was weaker in the grade 1 low-risk group (36.1%) [15]. However, in the same study, only 36 of total 97 patients with endometrial cancer were diagnosed with grade 1 disease at the preoperative stage (37.1%), which is in conflict with the results in the literature.

In the present study, 170 of 235 (72.3%) patients with grade 1 endometrioid type endometrial cancer were also grade 1 in the final pathology report, and 58 (24.7%) patients in this group were upgraded to grade 2. Nevertheless, patients whose grade was upgraded from preoperative grade 1 to postoperative grade 2, had MI < 50%, and a tumour diameter ≤ 2cm, did not need to undergo a relaparotomy for the staging surgery [1]. Therefore, a grade increase from grades 1 to 2 may not be important for low-risk patients. However, an upgrade to postoperative grade 3 points to a high-risk and to a necessity of lymphadenectomy and adjuvant treatment. In the present study, the grade was upgraded from grade 1 or 2 to grade 3 in only 13 (3.9%) of 314 (94.8%) patients. This rate was consistent with that reported by Garcia *et al.*, Cilesiz Goksedef *et al.*, and Helpman *et al.* (6.4%, 5.7%, and 5.6% respectively) [11-13]. In the present study, the final postoperative histological grades in 7 (3%) of 235 patients with a preoperative histological grade 1 (71.2%) were upgraded to grade 3, consistent with that reported in the literature. However, the up-grade rate from preoperative grade 2 to postoperative grade 3 in this study was inconsistent with that reported in the literature. In the present study, there was an upgrade to postoperative grade 3 in 6 (7.7%) of 78 (23.6%) patients, with a preoperative grade 2. In comparison, Garcia *et al.* reported such an upgrade in 8 of 50 (16%) patients, Helpman *et al.* in 20 of 125 (16%) patients, and Karateke *et al.* in 13 of 39 (31%) patients [10, 12, 13]. On the other hand, this upgrade rate was 13% and 11.4% in studies by Petersen *et al.* and Cilesiz Goksedef *et al.*, respectively [9, 11]. The variability in upgrade rates from histological preoperative grade 2 to histological postoperative grade 3 in the literature, which may lead to insufficient surgery, decreases the reliability of preoperative endometrial sampling with respect to the decision on staging surgery.

In the present study, five of the 17 preoperative grade 3 patients (29.4%) were downgraded to grade 2 and two of these patients (11.8%) were downgraded to grade 1. In other words, approximately 35% of the patients diagnosed with grade 3 disease preoperatively were downgraded in the final pathology report. This rate was consistent with the rates in the literature, which were reported to be between 8% and 42% [8, 10-13]. The downgrade rates in the final pathological reports are significant in the context of the morbidity and mortality rates related to unnecessary staging surgery. Thus the final histological grade may be both downgraded or upgraded depending partly on the limited tissue volume obtained during endometrial sampling, and partly on the conflicting interpretations of pathologists [12]. The FIGO grading system has been challenged due to the high discordance rates between the preoperative and post-operative histological grades in the literature, which has led investigators to seek new alternatives. One of the systems developed for this purpose and recommended by Scholten *et al.*, is a grading method which consists of two groups: a low-risk group constituted of FIGO grade 1 and 2 patients, and a high-risk group including patients with a solid tumour greater than 50% in addition to the presence of nuclear atypia (FIGO grade 3) [16]. This system seems to be clinically more advantageous with its high concordance rate of 85%, and is an important alternative to FIGO [17].

In the present study, all endometrial samplings were taken with dilatation & curettage (D&C). In some studies focused on the comparison between the sampling method and the concordance rate, D&C was considered superior to hysteroscopy [8, 13]. However, in another study

in which endometrial sampling was performed only with the hysteroscopic biopsy, the grade concordance was 80% and the concordance level was moderate according to the Kappa statistic (*K*-value = 0.64) [18]. In the present study, the authors also compared grade concordance with the presence of DM. It was present in 199 of 330 (60.3%) patients. However, there was no significant correlation between grade concordance and the presence of DM (p = 0.865). This was in agreement with two previous studies which found no significant correlation between grade concordance and the presence of DM [11, 15].

Uniquely, the present authors compared Ca 125 and Ca 19-9 levels with grade concordance, which was not included in any other study in the literature. Preoperative Ca 125 levels were measured in 200 of 330 participating patients (60.3%). The Ca 125 levels were higher than 35 U/ml (the accepted cut-off value) only in 30 (15%) of these patients, and there was no significant correlation of this parameter with grade concordance (p = 0.715). Likewise, Ca 19-9 levels were measured in 169 (51.2%) patients and 36 of them (21.3%) had levels higher than 39 U/ml, though there was no significant correlation with grade concordance (p = 0.774). Batista *et al.* recommended the use of elevated Ca 125 levels for the decision on lymphadenectomy in patients with grade 1 or 2 disease [14]. In the present study, 154 patients were tested for Ca 125 and underwent lymphadenectomy. Of these patients, 28 had Ca 125 levels higher than 35 U/ml (18.2%) and 13 (46.4%) had lymph node metastasis. Of 126 patients who had Ca 125 levels lower than 35 U/ml (81.8%), only 12 (9.5%) had lymph node metastasis ($p < 0.05$). Consequently, the authors believe that increased preoperative Ca 125 levels have a considerable value regarding the decision on lymphadenectomy. The authors also compared the Ca 19-9 levels with pathological results in patients who underwent lymphadenectomy. Only 33 of the 188 (17.6%) patients who had a Ca 19-9 measurement and underwent lymphadenectomy had a Ca 19-9 level higher than 35 U/ml; only seven of these patients (21.2%) had lymph node metastasis. There was no significant correlation between the Ca 19-9 levels and lymph node metastasis (p = 0.147).

Of 330 participating patients, 314 (95.2%) underwent pelvic and paraaortic lymphadenectomy, while 211 of these 314 patients (67.2%) were in the high-risk group, 35 of them (16.6%) had lymph node metastasis. The present authors did not observe lymph node metastasis in the low-risk patients in this study. A Study in the Treatment of Endometrial Cancer (ASTEC) which was a multi-centre study conducted in Europe 1,408 patients with early-stage endometrial cancer, the investigators concluded that routine pelvic lymphadenectomy should not be recommended for patients in an early stage [1]. Unnecessary lymphadenectomies may be prevented in the low-risk group following correct diagnosis of the histological grade with preoperative endometrial sampling. Mariani *et al.* from the Mayo Clinic Group conducted a study in which decisions on lymphadenectomy were made according to a model based on the preoperative endometrial sampling grade, MI, and tumour diameter evaluated after the intraoperative cervical canal incision. In that study, lymphadenectomy was avoided in more than 40% of the patients, though one case of lymph node metastasis was overlooked, the study model thus achieved a predictive value of 99% [3].

Since there was no explanation for lymphovascular area invasion in most of the final pathology reports that were derived from the present institution, a potential extension to this study would include a standardization of those reports. Moreover, in some reports, tumour size was not clearly defined. For the vaguely defined cases, the tumour size was determined by the authors of this study by referring to myometrial thickness and invasion rate. Additionally, in order to determine an alternative method to the FIGO histological grade system which can eliminate discrepancy of preoperative and postoperative grade in endometrial cancer, more prospective studies should be conducted. However, a consensus on reporting with the pathology unit is needed to be reached before beginning a prospective study about grade concordance in endometrial cancer.

Conclusion

In endometrioid type endometrial cancer, the concordance between preoperative (determined by endometrial sampling) and postoperative (final pathology report) histological grades is minimal. The upgrade from preoperative grade 1 to postoperative grade 3 is less common compared to the upgrade from preoperative grade 2 to postoperative grade 3. Therefore, a two-group histological grading system (low- and high-risk) should be implemented for the evaluation of preoperative endometrial sampling.

Conflict of Interest

The authors declare no competing interests.

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