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ORIGINAL ARTICLE

Dilatation and curettage in endometrial cancer. What is the correlation with hysterectomy histology? A 14 years retrospective cohort study

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Summary

Purpose: *The aim of the present study is to evaluate the concordance between preoperative endometrial sampling histopathology performed by conventional dilatation and curettage (D&C) and final histopathological diagnosis after total hysterectomy concerning tumor grade and subtype in patients with endometrial cancer (EC).*

Methods: *In this comparative retrospective study, 203 women with endometrial cancer were included who underwent at first dilatation and curettage and then total hysterectomy. The preoperative histopathological report obtained by dilatation and curettage was compared with the final histopathology after total hysterectomy to assess the accuracy of endometrial sampling.*

Results: *Comparison of preoperative with postoperative histopathological results showed an overall 5.9% and 10.9% discordance regarding endometrial cancer histological subtype and grade, respectively. Six (4.9%) of the patients with preoperative grade 1 were grade 2 and 1 (0.8%) was found to be grade 3. Three (8.3%) of the patients with preoperative grade 2 were found to be grade 3 after hysterectomy. Discordance is higher for endometrioid endometrial cancer grade 2 (25%) compared with grade 1 (5.7%) and 3 (18.8%).*

Conclusion: *Patients should be informed and consent for the potential discrepancy between the pre and postoperative histopathological features of malignancy. This discrepancy may result in either under or overtreatment. Thus, it should be accounted for when counseling for a major operation.*

Key words: *endometrial cancer, dilatation and curettage (D&C), grade, diagnostic accuracy, preoperative evaluation, postoperative evaluation*

Introduction

Endometrial cancer is the most common malignancy of the female genital tract in the developed countries, with an incidence of 11.1 per 100.000 women [1].

The lifetime endometrial cancer risk is approximately 2.9%, and it is most frequently diagnosed among women aged 55-64 years. Because its clinical manifestation is postmenopausal bleeding in more than 90% of cases, it is diagnosed early, and the survival is good. 5-year overall survival of endometrioid endometrial cancer ranges from 75% to 86% [2]. The cause of postmenopausal bleeding is endometrial cancer in 4.9% to 11.5% of the cases [3-6].

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There are two subtypes of endometrial cancer (endometrioid and non-endometrioid), although the genomic categorization has subdivided the tumors according to their molecular profiling [7]. There are two distinct types of endometrial cancer. The most common is Type 1, which is mostly endometrioid adenocarcinoma characterized by K-ras and PTEN loss or mutation and defects in the mismatch repair (MMR) system. Alternatively, Type 2 lesions comprise the minority and are associated with a relatively poor prognosis. Type II tumors show aneuploidy, p53 mutations, and overexpression of HER-2/neu.

The most widely used histologic grading system for endometrial carcinoma is the three-grade International Federation of Gynecology and Obstetrics (FIGO) system. This histologic grading system is based on both architectural (proportion of solid growth) and cytonuclear criteria. According to current practice standards, endometrioid endometrial cancers (EECs) are assigned a FIGO grade based on the degree of glandular differentiation. Grade 1 tumors exhibit ≤5% solid non-glandular, non-squamous growth, grade 2 tumors from 6% to 50%, and grade 3 tumors >50%. The presence of marked cytologic atypia increases the grade level [8]. FIGO grading has been found to have significant predictive value, although the reproducibility of pathologic diagnosis of Grade 2 is limited by significant interobserver variability.

Since the adoption of the surgical staging of endometrial cancer grading becomes a significant preoperative factor in guiding the extent of surgery, the accuracy of endometrial sampling is of great importance. Endometrial sampling can be performed by hysteroscopic biopsy, D&C, or office aspiration (pipelle). Discordances in histologic subtype or grading between preoperative and final diagnosis can lead to inadequate staging and sometimes either under or overtreatment with subsequent associated morbidity and mortality [9,10].

The tissue sample obtained by endometrial biopsy is often not adequate and makes the diagnosis challenging. Inadequate tissue sample is the main factor that can lead to discordances in histological subtypes or grading between pre and postoperative diagnosis [11,12].

Furthermore, another reason that may lead to discordance between preoperative endometrial sampling and the final specimen is that only the superficial part of the tumor, protruding into the endometrial cavity, is scrapped during curettage. In contrast, a tumor that lies deeper may have different histologic and molecular characteristics from the biopsy sample [13].

The present retrospective study aimed to assess the correlation and the discordance between the endometrial histology obtained by conventional dilatation and curettage (D&C) and the final diagnosis of tumor grade and subtype in patients with endometrial cancer (EC) after surgical treatment in the 2nd Department Obstetrics and Gynecology, Aristotle University, Thessaloniki, Hippokratio General Hospital.

Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

From January 2003 to December 2017, 203 patients who underwent surgery for endometrial cancer in the 2nd Department Obstetrics and Gynecology, Hippokratio General Hospital, were retrospectively reviewed. All individual participants provided signed informed consent and underwent D&C because of abnormal pre and postmenopausal uterine bleeding. The indication for surgical treatment was EC diagnosed by the histology obtained from D&C. All uterine specimens were sent to the department of pathology for histological examination. The final histopathology results were compared with the preoperative results. Chi-square and Cohen's kappa value was performed to assess the agreement of tumor subtypes and grades pre and postoperatively [14,15]. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy rates were calculated for all preoperatively assessed grades. McNemar's test was performed to evaluate the potential relationship between menopausal status and discordance of grade pre and postoperatively. All statistical analyses were performed using SPSS 25.

Results

The clinical records from 203 patients with EC over 14 years were evaluated. The mean age of the patients was 62.2±0.8 years (min: 27, max: 85), and the vast majority of the patients were postmenopausal (n=168, 82.8%). The final histopathology demonstrated that the most frequent subtype was endometrioid type endometrial cancer (n=180, 88.7%), followed by serous-papillary in 10 (4.9%), then mucinous in 6 (3%), clear cell in 4 (2%) and mixed serous-undifferentiated-endometrioid 1 (0.5%), mixed clear cell-endometrioid 1 (0.5%), and mixed serous–endometrioid in 1 (0.5%). Table 1 summarizes the subtypes of EC diagnosed at D&C and the final histology report after hysterectomy. The overall concordance of the preoperative histologic subtype was 94.1%. Cohen's kappa value for assessing the concordance

Table 1. Histological subtype at dilatation and curettage and at final histology

Hysterectomy Histology	*Dilatation and Curettage Histology*							*Total*
	Endometrioid	*Serous-Papillary*	*Clear cell*	*Mixed cell (carcinosarcoma)*	*Mixed cell (Endometrioid, clear cell)*	*Mixed cell (Endometrioid, mucinous)*	*Mixed cell (Endometrioid, serous, clear cell)*	
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Endometrioid	175 (86.2)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	180 (88.7)
Serous-Papillary	1 (0.5)	8 (3.9)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (4.9)
Clear cell	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)
Mixed cell (Endometrioid, serous, undifferentiated)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Mixed cell (Endometrioid, clear cell)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)
Mixed cell (Endometrioid, mucinous)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	6 (3.0)
Mixed cell (Endometrioid, serous)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Total	179 (88.2)	9 (4.4)	6 (3.0)	2 (1.0)	2 (1.0)	4 (2.0)	1 (0.5)	203 (100.0)

Table 2. Tumor grade of endometrioid EC at D&C and at final histology

Grade	*Postoperative grade*			*Total*
	1	*2*	*3*	
	n (%)	*n (%)*	*n (%)*	*n (%)*
Preoperative grade				
1	116 (66.3)	6 (3.4)	1 (0.6)	123 (70.3)
2	6 (3.4)	27 (15.4)	3 (1.7)	36 (20.6)
3	0 (0.0)	3 (1.7)	13 (7.4)	16 (9.1)
Total	122 (69.7)	36 (20.6)	17 (9.7)	175 (100.0)

between pre and postoperative histologic subtype was 0.73 (substantial agreement) with p<0.001 and 95% CI: 0.6-0.86.

In the final histopathology, most of the patients with endometrioid EC had grade 1 disease (n=122, 69.7%), while 36 patients had grade 2 (20.6%) and 17 (9.7%) patients had grade 3 EC. Comparing the D&C and the final hysterectomy report, there were 10 (5.7%) cases of upgrading and 9 (5.1%) cases of downgrading. Six (4.9%) of the patients with preoperative grade 1 were grade 2 and 1 (0.8%) was found to be grade 3. Three (8.3%) of the patients with preoperative grade 2 were found to be grade 3 after hysterectomy. Table 2 summarizes the tumor grade of EC at D&C and final histology report. The overall concordance of preoperative histologic grade evaluation was 89.1%. Cohen's kappa value for assessing the concordance between pre and postoperative tumor grade was 0.76 (substantial agreement) with p<0.001 and 95% CI: 0.66-0.86. The preoperative grade assessment accuracy rates with endometrial sampling were 92.6%, 89.7%, and 96% for grades 1, 2, and 3, respectively (Figure 1). Discordance was higher for endometrioid endometrial cancer Grade 2 (25%) compared with Grade 1 (5.7%) and 3 (18.8%). Sensitivity, specificity, PPV, and NPV rates of the preoperative prediction are summarized in Table 3. Among the preoperatively assessed grades, grade 1 had a higher sensitivity (95.1%) and lower specificity (86.8%) rates than grades 2 and 3.

McNemar's test was performed to assess whether menopausal status affected the accuracy of D&C and the concordance between pre and postoperative histological results. Statistical analysis showed that discordance regarding subtype of the tumor and grade were significantly higher (p<0.001) among postmenopausal women compared with premenopausal women with EC (Table 4).

Table 3. Sensitivity, specificity, PPV, NPV, PLR, NLR and accuracy for preoperative grade prediction

	Grade 1 %	*Grade 2* %	*Grade 3* %
Sensitivity	95.1	75	76.5
Specificity	86.8	93.5	98
PPV	94.3	75	81.3
NPV	88.5	93.5	97.5
PLR	7.2	11.6	40.3
NLR	0.1	0.3	0.2
Accuracy	92.6	89.7	96

PPV: positive predictive value, NPV: negative predictive value, PLR: positive likelihood ratio, NLR: negative likelihood ratio

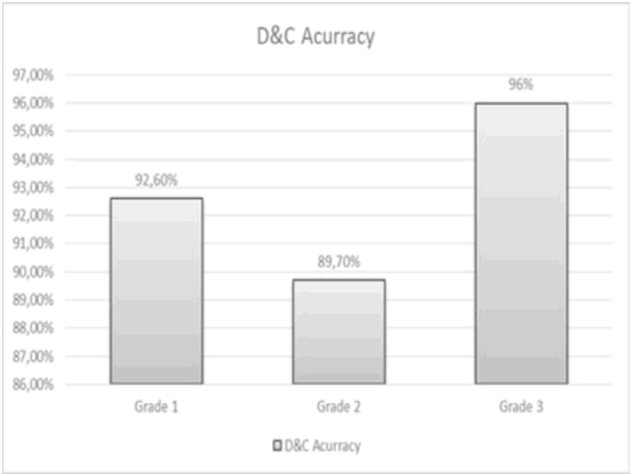

Figure 1. Diagnostic accuracy of D&C for each Grade of endometrioid endometrial cancer.

Table 4. Menopausal status and histological subtype discordance

Menopausal status		*Agreement*		*Total*
		Yes	*No*	
Menopause				
No	Count	35	0	35
	% of Total	17.2%	0%	17.2%
Yes	Count	156	12	168
	% of Total	76.8%	5.9%	82.8%
Total	Count	191	12	203
	% of Total	94.1%	5.9%	100.0%
McNemar test	p<0.001			

Discussion

Our study showed that the preoperative histologic subtype and tumor grade's overall accuracy rate were 94.1% and 89.1%, respectively (Table 1). The highest discordance between pre and postoperative histology was found in grade 2 tumors (25%). Overall, 10 cases (5.7%) were upgraded, and 9 (5.1%) were downgraded. About 14% of cases with an initial diagnosis of endometrioid cancer were other types, but only 1 (0.5%) Type II, a serous papillary tumor that needed more aggressive surgery, was missed by D&C. The other three mixed types (all endometrioid and mucinous) missed would not need a different surgical approach than endometrioid cancer. In our cases with endometrioid cancer (Table 2), grades 1 and 3 were more accurately diagnosed in D&C specimens than grade 2. As a result, only one patient was upgraded from grade 1 to grade 3 (0.8%). The accuracy of 96% suggests that undertreatment is a rare consequence of mistakes in grading. The six patients (3.4%) upgraded to grade 2 from grade 1 are also a small percentage with little clinical significance since the management of these two grades is similar.

The surgical approach for EC varies from simple total hysterectomy with bilateral oophorectomy to an extended procedure involving pelvic and para-aortic lymphadenectomy with or without omentectomy. Preoperative tumor grading, histologic subtype, and pre or intraoperative assessment of myometrial invasion depth determine whether lymph node dissection is necessary [10]. Besides subtype (serous papillary), it also determines the need for intraoperative omentectomy. The accuracy of preoperative endometrial sampling is of great importance, and the possible variance in the histological type and grade, even among expert pathologists, should be considered when informing patients about their surgical treatment strategy, with the risk for under or over treatment.

Patients in an office setting tolerate well endometrial biopsy with pipelle or the Vabra aspirator. The pipelle, a 3mm diameter flexible cannula, samples only 4% of the endometrial surface and has a 67-97 % sensitivity [16-18]. However, the Vabra aspirator samples around 40% of the endometrial surface but is more painful and expensive. Endometrial biopsy by D&C is superior regarding the amount of sampling from the endometrial surface, but anesthesia is always required and alone is not an adequate method for excluding endometrial malignancy in higher-risk groups [19]. The gold standard for endometrial investigation is the combination of hysteroscopy with histology reaching a sensitivity detection rate of almost 100% [20].

The tissue sample obtained by endometrial sampling is often not adequate and makes the diagnosis challenging, leading to discordances in histological subtypes or grading between pre and postoperative diagnosis [11,12]. Furthermore, another reason that may lead to discordance between preoperative endometrial sampling and the final specimen is that only the superficial part of the tumor, protruding into the endometrial cavity, is scrapped during curettage. However, the tumor that lies deeper may have different histologic and molecular characteristics from the biopsy sample [13]. A recent systematic review and meta-analysis demonstrated that pre and postoperative agreement for tumor grade depended on the method of endometrial sampling, with hysteroscopic biopsies showing a higher agreement than those obtained by D&C or by aspiration. Specifically, the agreement was 89%, 70%, and 73% for hysteroscopic biopsy, D&C, and office biopsy, respectively. Overall, this meta-analysis showed an agreement of 67% on the grade of preoperative endometrial sampling and post-hysterectomy histopathology finding. Agreement on histological subtypes was 95% and 81% for preoperative endometrioid and non-endometrioid carcinomas, respectively [9]. Compared to this meta-analysis, the accuracy rate of the current study where D&C was the only sampling method was higher with regard to tumor grade and similar for histological subtypes. However, this may happen because of the higher heterogeneity of the studies included in the meta-analysis (I^2=92%).

Statistics have shown that grade is the next more important prognostic factor in endometrioid carcinoma. But the real difference is between patients with EC grade1 and 2 compared to patients with EC grade 3 [21].

A small but significant statistical difference in survival of 5% between low-stage grades 1 and 2 ECs has not been demonstrated in all studies [22].

It is crucial during the pathologic diagnosis to exclude grade 3 and not distinguish between grades 1 and 2. In our series, most patients with grade 2 were allocated into grade 1, and very few patients were falsely allocated to grade 3 and had inadequate treatment. The morphological diagnosis of grade 2 has significant intraobserver variability, and many authorities favor the binary system [23].

Furthermore, the distinction between grades 1 and 2 is unimportant if a lymphadenectomy or sentinel node biopsy is part of the management protocol. Although grade 2 tumors have a higher risk of lymph node metastasis than grade 1 (6.6% vs. 11.6% in a series of 1544 patients), the significance is lost if there is myometrial invasion [24]. The use of preoperative tumor grade alone to select patients for lymphadenectomy does not reflect the complex interplay between the various pathologic parameters [25]. In the present study, 25% of patients allocated to grade 2 on D&C changed after the uterus's pathologic examination to lower grades.

It is well known that older patients have a more commonly worse prognosis due to higher risk tumors and deep invasion [26].

A limitation of the present study is the retrospective character of the analysis. The results were also obtained by D&C, as hysteroscopy was not always available in our department during the first years of the study period. Another limitation is the lack of data on the patients' outcome and the absence of cross-examination of the endometrial sample.

On the other hand, our study's strength is the large sample size. All tissue samples were examined by an expert pathologist (D.M.), and there was no interobserver variation in results. Moreover, all preoperative specimens were collected with the same method (D&C), eliminating the variations in accuracy between the various biopsy approaches.

In conclusion, our study highlights preoperative risk stratification difficulties based on pathologic findings to manage the appropriate surgical treatment. It also indicates the difficulties in the assignment of grade 2 EC. Borderline cases or cases that clinical diagnosis and imaging results are discordant should be discussed and resolved in a consensus meeting. However, a downgrading of tumors is less common, and the consequences of inadequate surgery less severe.

As proposed by the Cancer Genome Atlas, molecular classification and immunohistochemical biomarkers might improve the preoperative differentiation between high- and low-risk tumors [27-29]. Therefore, further studies are needed to evaluate whether the combination of morphologic grade and type with biomarkers may improve the preoperative risk assessment in EC care.

Author contributions

Anastasios Liberis: project development, study design, data collection, analysis of data and writing the manuscript (original draft); Evangelia Mareti: data collection, statistical analysis, writing and approving the manuscript, Georgios Pratilas: project development, review and approving the manuscript; Stamatios Petousis: study review and approving the manuscript; Angelos Daniilidis: reviewing and

approving the manuscript, Anastasia Vatopoulou: review and approving the manuscript, supervision; Konstantinos Pantazis: study review and approving the manuscript; Fotios Chatzinikolaou: study review and approving the manuscript, supervision; Dimosthenis Miliaras: project administration, data collection, study review and approving the manuscript; Konstantinos Dinas: project development, study design, data collection, supervision, reviewing and approving the manuscript (original draft).

Conflict of interests

The authors declare no conflict of interests.

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