Accuracy of Preoperative Curettage in Determining Tumor Type and Grade in Endometrial Cancer

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Objective: *To compare the accuracy of tumor grade and type in endometrial cancer between samples from preoperative curettage and postoperative hysterectomy specimens.*
Material and Method*: From January 2002 to June 2006, 98 women diagnosed with endometrial cancer and treated in the Department of Obstetrics and Gynecology, Siriraj Hospital were included. The comparisons of tumor types and grades were performed on both preoperative endometrial curettage and hysterectomy specimens; the relationships between the concordance rate and accuracy of types and grades were analyzed.*
Results: *Endometrial samples and the subsequent hysterectomy specimens from 98 patients were studied. After exclusion of benign endometrial tissue sampling and no residual tumor in hysterectomy specimen and preoperative diagnosis from endometrial biopsy, 86 patients were analyzed. The overall tumor type accuracy was 93.0% for endometrioid type. The comparative FIGO grades were analyzed between preoperative endometrial samplings and hysterectomy specimens. Accuracy was 74.0% for grade 1, 75.3% for grade 2 and 90.4% for grade 3. The accuracy for grade 3 tumors was significantly higher than for grade 1.*
Conclusion: *The authors should be careful in planning patient management based on the initial histological findings. It is important for clinicians to be aware that endometrial adenocarcinoma may show focal variation in tumor grade and to be aware of the limitation of examination of small tissue samples.*

Keywords: *Endometrial cancer, Tumor grade, Endometrioid, Cancer corpus, Curettage*

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Endometrial cancer is a common malignant tumor of the female genital tract. Nearly 90% of patients with an endometrial carcinoma presented with abnormal vaginal bleeding which leads to early diagnosis of endometrial carcinoma[1,2]. Prognostic factors among women with the disease include histology type, histology grade, stage, and race. Endometrial curettage is a classical standard approach in diagnosing endometrial cancer preoperatively.

In 1988, the International Federation of Obstetrics and Gynecology (FIGO) switched the staging system of endometrial cancer from clinical staging to surgical staging[3], which included peritoneal cytology, pelvic, and para-aortic lymphadenectomy. However, the extent of the surgical staging among women with low-risk endometrial carcinoma (grade 1 or 2 with no or minimal myometrial invasion) has been debated[4-7].

Although endometrial curettage is considered to be the most reliable procedure in the diagnostic workup, unfortunately, the determination of the aforementioned tumor characteristics are not always accurate, thus leading to either underestimation of the severity of the disease or, more rarely, overestimation, with direct influence on treatment planning. Since 1950, some studies have been shown that comparing the histopathologic findings of endometrial curettage with hysterectomy specimens endometrial curettage had a low-efficiency. For example, Stock et al[8] found that less than 50% of uterine cavity was curetted in 60% of cases and less than 25% was curetted in 16% of cases. Thus, the great discrepancy could be due to variation of uterine cavity, inefficient instruments, small

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samples, and inexperienced surgeons. Admittedly, blind operative procedures result in inadequate diagnosis.

A Medline search of the published data on this subject revealed that endometrial curettage had discrepancy concerning the final diagnosis for tumor type and grade ranging from 20.4% to 46%[10-15]. The aim of the present retrospective study was to find the diagnostic accuracy of the preoperative endometrial sampling in determining tumor type and grade in establishing the diagnosis of endometrial carcinoma in Siriraj Hospital.

Material and Method

The authors analyzed retrospectively the medical records of women with the final diagnosis of endometrial carcinoma, which underwent primary surgical procedures that at least included total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) at the Department of Obstetrics and Gynecology, Siriraj Hospital, between January 2002 and June 2006.

Exclusion criteria

1. Patients with the preoperative endometrial curettage were not reported or reviewed by the staff of the Department of Pathology at Siriraj Hospital.
2. Patients treated primarily with radiation therapy.
3. Patients who did not undergo total hysterectomy.
4. Cases that lost preoperative or post-operative histologic sections.
5. Patients whose preoperative diagnoses were from endometrial biopsy.
6. Patients who had the diagnosis of endometrial cancer after hysterectomy.
7. Patients who had no residual disease detected in the hysterectomy specimen

The medical records of the patients were reviewed and the following data were extracted: age, parity, menopausal status, body mass index, time period between preoperative endometrial curettage and hysterectomy, number of histologic slides of tumor from curettage, tumor grade, and histology.

All of the curettage and hysterectomy sections were re-examined and graded by one of the authors, (CL), a consultant gynecologic pathologist at the Department of Pathology, Siriraj Hospital, who was blinded to the original reports. In those cases, the authors found discrepancy between the original report and reviewed report. Another gynecologic pathologist (TC) who was blinded to the discrepancy reports re-evaluated. Agreement in two out of three diagnoses is a final diagnosis. In those cases in which a discrepancy occurred in all reports, a team reevaluation was performed in order to achieve a final diagnosis.

Most specimens were graded according to the WHO classification whereby both architectural and nuclear features were examined to generate an overall tumor grade[16].

Grade 1 means 5% or less of a non-squamous or non-morular solid growth pattern, grade 2 has 6-50% of non-squamous or non-morular solid growth pattern, and grade 3 has more than 50% of a non-squamous or non-morular solid growth pattern. Bizarre nuclear atypia should raise the grade by one (*i.e.* from 1 to 2 or 2 to 3). According to the current reporting guidelines from the Royal College of Pathologists[17], serous papillary and clear cell carcinomas are high-grade tumors and should not be assigned a FIGO grade. Only pure endometrioid type had to be graded using FIGO Grading.

Data were analyzed by SPSS software (version 11.5). Student's t test was used to evaluate means of continuous variables. Two-tailed statistical analysis was used for all analyses. Proportions were compared using the χ^2 test or Fisher's Exact test where appropriate.

The present study was approved by the Siriraj Ethics Committee.

Results

Between January 2002 and June 2006 there were 295 patients diagnosed with endometrial cancer but only 98 with preoperative and postoperative histologic sections. Four patients with preoperative diagnoses were from endometrial biopsy. Five patients had the diagnosis of endometrial cancer after hysterectomy including one case of inactive endometrium with myoma uteri, one case of proliferative endometrium with myoma uteri, one case of atypical endometrial hyperplasia, and two cases of endometrial hyperplasia without atypia by initial preoperative endometrial curettage examination (upgraded to grade 1 endometrioid adenocarcinoma by hysterectomy specimens). Three patients had no residual disease detected in the hysterectomy specimen. All situations were excluded from further analysis.

The 86 patients' demographic data are shown in Table 1. The mean age ($\pm$ SD) was 57.6 $\pm$ 10.4 (range

28-79) years. The most common presenting symptom was abnormal uterine bleeding (93.0%); 67 (77.9%) women who were in postmenopausal state and the mean interval between the last menstrual period and diagnosis was 10.9 ± 7.91 years. Of all patients, three had previous breast cancers and 16 had a medical history of diabetes mellitus. The gravidity ranged between 0 and 11 but 31(36.0%) patients had never been pregnant. The mean duration between initial sampling and hysterectomy was 6.5 weeks.

Fifteen specimens from ten patients needed re-evaluation for grading. It included five patients with both their endometrial curettage and hysterectomy specimens and five with the endometrial curetting only.

Tumor type and grade of both curettage and the hysterectomy specimens are summarized in Table 2.

Of the 86 preoperative tissue samples studied, 77 (89.5%) patients had pure endometrioid type, and nine (10.5%) had uncommon types or mixed carcinomas (Table3). At the final diagnosis, 87.2% (75/86) of the patients were reported to have pure endometrioid adenocarcinoma, and 12.8% (11/86) had uncommon types or mixed carcinomas. The accuracy of diagnosis between all preoperative endometrial curettage and hysterectomy specimens were 93.0% (80/86) for endometrioid and uncommon type. The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of the endometrial curettage for endometrioid types was 97.3 (73/75), 63.6 (7/11), 77.8 (7/9) and 94.8% (73/77) respectively.

The comparison of grades between all biopsy samples and hysterectomy specimens is shown in Table 4. The overall concordance rates were 64.1% for grade 1, 75.0% for grade 2, and 83.3% for grade 3. The concordance was higher for grade 3 than for grade 1. There were 35.9% of patients upgraded from grade 1 to grade 2-3 and 10.7% from grade 2 to grade 3. On the other hand, there were 14.3% downgraded from grade 2 and 16.7% from grade 3. The accuracy was 74.0% (54/73) for grade 1, 75.3% (55/73) for grade 2 and 90.4% (66/73) for grade 3. The test's accuracy as well as specificity increased with increasing tumor grade.

The mean ages of the patients in the concordant and non-concordant groups were similar (56.2 and 57.0 years, respectively, p = 0.765). The mean BMI were similar in both groups (27.6 and 25.3, respectively, p = 0.066), as was the time interval between biopsy and hysterectomy (6.5 vs. 6.2 weeks, p = 0.705). The concordance rates were similar in menopause

Table 1. Patients' demographic data

Characteristics	
Age (years)	
Mean	57.6 ± 10.4
Range	28-79
Body mass index	
Mean	26.7
Range	17.3-46.6
	No. of patients (%)
Underlying disease	
No underlying	37 (43.0)
DM	13 (15.1)
DM + other disease	3 (3.5)
Hypertension	26 (30.2)
Breast cancer	3 (3.5)
Other	4 (4.7)
Menopausal status	
Pre-menopausal	19 (22.1%)
Postmenopausal	67 (77.9%)
Presenting symptom	
Abnormal uterine bleeding	80 (93.0%)
Abnormal Pap smear	5 (5.8%)
Other	1 (1.2%)

Table 2. Preoperative & postoperative tumor types and grades

D&C n	%	
Tumor histological type	86	
Endometrioid	77	89.5
Grade 1	40	
Grade 2	28	
Grade 3	9	
Clear-cell	5	5.8
Serous-papillary	2	2.3
Carcinosarcoma	1	1.2
Other mixed	1	1.2
Hysterectomy specimens		
Tumor histological type	86	
Endometrioid	75	87.2
Grade 1	30	
Grade 2	33	
Grade 3	12	
Clear-cell	5	5.3
Serous-papillary	3	3.5
Carcinosarcoma	2	2.3
Other mixed	1	1.2
No malignancy	3	3.1

Table 3. Comparison of tumor type between preoperative curettage and hysterectomy specimens

D&C	Hysterectomy		Total
	Endometrioid	Uncommon type	
Endometrioid	73	4	77
Uncommon type	2	7	9
Total	75	11	86

Table 4. Comparison of tumor grade between preoperative curettage and hysterectomy specimens

D&C		Hysterectomy (grading)			Total
		1	2	3	
Grading	1	25	11	3	39
	2	4	21	3	28
	3	1	0	5	6
Total		30	32	11	73

* Only the cases that show endometrioid subtype in both preoperative curettage and hysterectomy specimens

and pre-menopause (71.9% and 70%, respectively, p = 0.869), non anesthesia and with anesthesia groups (70.67% and 68.42%, respectively, p = 0.819), nulliparous and multiparous groups (71.4% and 71.4% respectively, p = 1), one slide sampling and two or more slides sampling (68.5% and 78.3% respectively, p = 0.386).

Discussion

Endometrial curettage remains the most widely used technique for the initial workup of abnormal uterine bleeding. It is a relatively simple procedure and considered as a gold-standard approach in the preoperative evaluation and therapeutic intervention of abnormal uterine bleeding patients. Unfortunately, because it is a blind method of endometrial sampling, there is always a risk of missing an abnormal site. In the relatively few published papers that have evaluated this, the reported discrepancy rates varied significantly from 20.4% to 46%[6-11]. The present study confirmed the previous reports (Table 5), discrepancy in tumor grades of endometrial cancer between preoperative endometrial curettage and hysterectomy specimen findings from various studies. The overall discrepancy of types and grades of endometrial cancer by D&C and hysterectomy specimens was 6.67% and 28.57%, respectively.

On preoperative endometrial pathological findings, five patients (out of 98, 5.1%) were diagnosed with benign endometrial sampling (2 normal endometrial samplings, 3 complex hyperplasia). Most of their endometrial cancers were grade 1 endometrial cancer (4 cases), and the other was grade 2 by hysterectomy specimen confirmation. Similar findings have been reported by Stefano Bettocchi et al[9] and George Vorgias et al[12]. This was a great discrepancy between the two diagnostic approaches, which suggested that 5.1% of patients could have escaped from endometrial cancer diagnosis. If not confirmed by hysterectomy specimen examination, those patients might have a delay in the appropriate treatment of the endometrial carcinoma, which may lead to an adverse impact on their health.

There were three patients shown to have endometrial carcinoma by endometrial curettage but the hysterectomy specimens were negative. The authors speculated that the three patients' lesions were minimally localized and in the early stage of

Table 5. Comparison of tumor grade based on D&C and hysterectomy specimens

References	Patients	Concordance (%)				Discordance (%)	Upgrade (%)	Downgrade (%)
		Grade 1-3 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)			
Mitchard J[13]	89	-	52.9	68.4	77.4	-	20.2	10.1
Vorgias G[12]	263	55.5	-	-	-	-	37.3	7.2
Obermair A[11]	137	-	78.8	-	-	-	20.4	0.7
Soothill PW[10]	117	-	51.7	43.9	60.0	54.0	-	-
Gamal h[14]	182	-	70.9	-	-	-	29.1	-
Wang X[15]	52	-	20.0	61.6	77.8	-	-	-
Our study	86	69.8	64.1	75.0	83.3	30.1	23.3	6.8

endometrial cancer, so the tiny tumor residues were evacuated by preoperative endometrial curettage.

In the present study, there was high sensitivity and accuracy of the endometrial curettage in determining endometrioid type and there was a 23.3% increase in tumor grade, 35.9% upgraded from grade1 to grade 2-3 and 10.7% from grade 2 to grade 3. On the other hand, there were 14.3% downgrade from grade 2 and 16.7% from grade 3. Previous studies demonstrated the same trends of higher concordance rates along with increasing tumor grades. The correlation was poorest with grade 1 endometrioid cancer, which was consistent with the present study[9,11]. The reasons for the discrepancy in grades between preoperative endometrial curettage and hysterectomy specimens may be associated with many factors. Obviously, hysterectomy specimens had more samples than endometrial curettage samples, so observing the variations in histological type, architectures and nuclear pleomorphism, became easier than the samples provided by endometrial curettage. In the downgrade group, it was possible that the more severe lesion had been removed by prior preoperative endometrial curettage and the clinician should consider in the further management according to the more severe histological grading. Grade 3 adenocarcinoma could contain areas of grades 1, 2 or 3 tumor tissue, but grade 1 adenocarcinoma only contain grade 1, it was reasonable why grade 1 diagnosed with preoperative endometrial curettage was most likely to be discordant with hysterectomy specimens. Regarding the preoperative role of preoperative endometrial curettage in endometrial cancer, there was a strong suggestion that an appropriate treatment should be considered in patients with a diagnosis of endometrial cancer performed by preoperative endometrial curettage, especially a well differentiated tumor, because of inaccurate information on tumor grades from preoperative endometrial curettage.

In conclusion, the present findings emphasized the need for caution in planning patient management based on the initial histological findings, especially for tumors reported as low grade on the initial biopsy. It is important for clinicians to be aware that endometrial adenocarcinoma may show focal variations in tumor grade and to be aware of the limitations of examination of small biopsy samples.

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Potential conflicts of interest

None

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ความแม่นยำของ เกรด และชนิดของเซลล์มะเร็งจากการขูดมดลูกในมะเร็งเยื่อบุโพรงมดลูก

อมรรัตน์ ธนชัยวิวัฒน์, ชัยยศ ธีรผกาวงศ์, ชัยรัตน์ ลีลาพัฒนดิษฐ์, เตือนใจ ช่วงสุวนิช

วัตถุประสงค์: *ศึกษาความแม่นยำของชนิดและเกรดของเนื้อเยื่อบุโพรงมดลูกในผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกที่ได้จากการขูดมดลูกเปรียบเทียบกับเนื้อเยื่อบุโพรงมดลูกที่ได้จากการตัดมดลูก*

วัสดุและวิธีการ: *ศึกษาเปรียบเทียบความแม่นยำและความคลาดเคลื่อนของชนิดและเกรดของเนื้อเยื่อบุโพรงมดลูกที่ได้จากการขูดมดลูกเปรียบเทียบกับเนื้อเยื่อบุโพรงมดลูกที่ได้จากการตัดมดลูกในผู้ป่วยมะเร็งเยื่อบุโพรงมดลูก 86 ราย ที่เข้ารับการรักษาด้วยการขูดมดลูก และผ่าตัดมดลูกที่ภาควิชาสูติศาสตร์และนรีเวชวิทยา โรงพยาบาลศิริราช ระหว่าง 1 มกราคม พ.ศ. 2545 ถึง 30 มิถุนายน พ.ศ. 2549*

ผลการศึกษา: *จากการวิเคราะห์ข้อมูลของผู้ป่วย 86 รายพบว่าความแม่นยำของเนื้อเยื่อเอ็นโดเมทริออยด์เท่ากับร้อยละ 93 และเมื่อแยกศึกษาตามเกรดของเนื้อเยื่อพบว่าความแม่นยำของเกรด 1, 2 และ 3 อยู่ที่ร้อยละ 74.0, 75.3 และ 90.4 ตามลำดับ*

สรุป: *เนื่องจากข้อจำกัดของปริมาณเนื้อเยื่อที่ได้จากการขูดมดลูก ชนิด และเกรดของเนื้อเยื่อบุโพรงมดลูก ที่ได้จากการขูดมดลูกในผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกอาจมีความคลาดเคลื่อนได้โดยเฉพาะเกรด 1 และ 2 การวางแผนการรักษาผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกโดยอ้างอิงเกรดและชนิดของเนื้อเยื่อบุโพรงมดลูกที่ได้จากการขูดมดลูกอย่างเดียวจึงมีโอกาสผิดพลาดได้*