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Accuracy of Pre-operative Endometrial Sampling for the Detection of High Grade Endometrial Cancer

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ABSTRACT

Objective: To assess the accuracy of endometrial sampling for detection of high grade endometrial cancer.

Materials and Methods: This study was a diagnostic test. One hundred and five endometrial cancer patients who underwent surgery in Phramongkutklao hospital between October 2009 and June 2014 were reviewed. Preoperative histology from endometrial sampling was compared with postoperative pathology. Sensitivity, specificity, PPV, NPV and likelihood ratio to diagnose endometrial cancer were analysed.

Results: A total of 105 patients, 31 patients were high grade endometrial cancer and 74 patients were low grade endometrial cancer. The accuracy of endometrial sampling for detection of high grade endometrial cancer revealed 91.67% sensitivity, 87.1% specificity, 73.33% PPV, 96.4% NPV, 7.10 likelihood ratio positive and 0.0957 likelihood ratio negative. Moreover, we found the sensitivity, specificity, PPV, NPV, likelihood ratio positive and likelihood ratio negative of fractional curettage were 72.68%, 93.02%, 82.35%, 88.89%, 10.6 and 0.283, respectively.

Conclusion: Endometrial sampling is accurate for the diagnosis of high grade endometrial cancer and can be utilized in patients with suspected malignancy-related abnormal uterine bleeding.

Keywords: Endometrial sampling, endometrial cancer, fractional curettage

Introduction

Endometrial cancer is the third most common gynecologic malignancy in Thailand with the incidence of 2.8 per 100,000 people per year[1]. The common presentation is abnormal uterine bleeding, in which, obtaining of endometrial tissue is fundamental in order to determine the cause. Endometrial tissue can be obtained by several techniques, including fractional curettage, endometrial sampling, or hysteroscopic biopsy[2]. In the past, fractional curettage was considered the only optimum method, however it requires hospitalization that not only is inconvenient but also causes delayed in diagnosis, especially in small hospital with limited inpatient units. Nowadays, endometrial sampling is considered as acceptable substitution of the fractional curettage because it is less invasive, highly sensitive and specific, and does not require hospitalization[3-8].

The diagnosis of endometrial cancer is based solely on tissue pathology. Low-grade cancer is

diagnosed when the pathology reports grade 1 or 2 endometrioid adenocarcinoma[7]. Low-grade carcinoma is usually associated with less than half of the myometrial invasion, less than 10% of pelvic and para-aortic lymph node metastasis, and more than 90% five-year survival rate[9, 10]. But high grade cancer is on the contrary. Since the diagnosis is based on histological morphology, the adequacy of tissue obtained from endometrial sampling is of major concern. Previous study suggested the high sensitivity and specificity of the endometrial sampling in detection of endometrial cancer[11-13]. Unfortunately, there is insufficient data on its accuracy for detection of high-grade endometrial cancer[7]. Surgical staging with extensive removal of tumor bulk remains the core treatment of endometrial cancer. Nonetheless, if low-grade cancer is confirmed, disease confined to the uterine fundus, no lymphovascular space invasion, no lymph node metastases, the patient can only undergo less invasive total abdominal hysterectomy with bilateral salpingo-oophorectomy[9].

Accurate tumor grading is empirical for the selection of appropriate surgical intervention before extra-uterine spread occurs and for early referral to gynecologic oncologist. Thus, the purpose of this study was to evaluate the accuracy of preoperative endometrial sampling for the histological diagnosis of endometrial carcinoma compared to the standard post-operative pathology and compare the accuracy between endometrial sampling and fractional curettage, using a cross sectional study of patients with endometrial cancer who had received treatment at Phramongkutklao hospital.

Materials and Methods

The study design was diagnostic test. The medical record of 120 patients who were diagnosed with endometrial cancer and underwent surgery at Department of obstetrics and gynecology, Phramongkutklao hospital between October 2009 and June 2014 were reviewed. Fifteen people were excluded either because the two primary cancer was presented, the tumor was inoperable, the pathological report before surgery was not available, or the diagnosis was made by hysteroscopic biopsy. The final 105 patients who met the selection criteria were further divided into fractional curettage group and endometrial sampling group. Preoperative histology was compared with the postoperative pathology and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio were calculated.

Definition

- Endometrial sampling is the procedure in which the endometrial tissue is collected with comprised only endocell or endometrial aspirator.

- Low-grade endometrial cancer included endometrioid adenocarcinoma grade 1 or 2

- High-grade endometrial cancer included endometrioid adenocarcinoma grade 3 or non-endometrioid cancer such as carcinosarcoma (CS), uterine papillary serous carcinoma (UPSC), clear cell carcinoma (CCC), mucinous carcinoma and mixed seromucinous carcinoma

- Standard diagnosis is made from tissue pathology after surgical staging.

Inclusion criteria

- Women who were diagnosed endometrial cancer and underwent surgery at Phramongkutklao hospital between October 2009 and June 2014.

- Presence of pathological report prior to surgical staging.

Exclusion criteria

- Patient with two primary cancers.

- Absence of pathological report prior to surgical staging

Results

Among 105 patients, preoperative tissue diagnosed by endometrial sampling 43 patients, of those with endometrial sampling were postoperative high grade cancer 12 patients. Sixty-two patients were diagnosed by fractional curettage, of these 62 patients, 19 patients were diagnosed as postoperative high grade cancer. The remaining patients were low grade cancer.

The age of the enrolled patients was between 38 and 84 years old, with the average of 58.7 years old (mean±SD, 58.71±9.86). Fourteen patients had abnormal Pap smear, accounting for 13.33% of total. The underlying diseases and parity were demonstrated in Table 1.

Table 1. Demographic data

	N = 105	%
Age (years, mean±SD)	38-84	58.71±9.86
DM type 2	21	20.00
Hypertension	56	53.33
Dyslipidemia	34	32.38
Pap smear		
None	15	14.29
Negative for malignancy	76	72.38
Premalignant lesion	8	7.62
Malignant lesion	6	5.71
Parity*		
None	33	32.67
1	7	6.93
2	23	22.77
≥ 3	38	37.62
Method		
Fractional curettage	62	59.05
Endocell	38	36.19
Endometrial aspirator	5	4.76

* 4 patients had no data
N = Number of patient

The final histology revealed 92 patients with endometrioid adenocarcinoma (32, 42, and 18 of grade1, 2, and 3, respectively), 5 patients with carcinosarcoma, 1 patient with uterine papillary serous carcinoma, 2 patients with clear cell carcinoma, and 5 patients with other histology (4 patients with mucinous carcinoma, 1 patients with mixed seromucinous carcinoma) (Table 2).

Comparison between the pre-operative histology and the final pathology was demonstrated in Table 2 and 3. Thirty-one out of 105 patients had postoperative high-grade cancer. The overall sensitivity and specificity for detection of high-grade cancer in Phramongkutklao hospital from both endometrial sampling and curettage were 80.65% and 90.54%, respectively. The positive predictive value (PPV) was 78.13%. In 31 high-grade endometrial cancer patients, 6 were underestimated prior to the surgery. Thus, the negative predictive value (NPV) was 91.78%. The likelihood ratio positive and negative were 8.53 and 0.214 respectively.

Table 2. Preoperative pathology compared with final pathology

Pre-operative pathology	Final pathology							Total
	G1 EA	G2 EA	G3 EA	CS	UPSC	CCC	Others	
G1 EA	28	19	1	0	0	0	0	48
G2 EA	3	17	5	0	0	0	0	25
G3 EA	0	2	7	0	0	0	0	9
CS	0	0	1	4	0	0	0	5
UPSC	0	1	0	1	1	0	0	3
CCC	0	0	0	0	0	2	0	2
Others	1	3	4	0	0	0	5	13
Total	**32**	**42**	**18**	**5**	**1**	**2**	**5**	**105**

G1 EA—grade 1 endometrioid adenocarcinoma, G2 EA—grade 2 endometrioid adenocarcinoma, G3 EA—grade 3 endometrioid adenocarcinoma, CS—carcinosarcoma, UPSC—uterine papillary serous carcinoma, CCC—clear cell carcinoma, others—mucinous carcinoma, mixed seromucinous carcinoma

Table 3. Preoperative pathology from endometrial sampling and fractional curettage compared with final pathology classified by tumor-grading

Pre-operative	Final pathology		Total
	HG	LG	
All device			
HG	25	7	32
LG	6	67	73
Endometrial sampling			
HG	11	4	15
LG	1	27	28
Fractional curettage			
HG	14	3	17
LG	5	40	45
Total	**31**	**74**	**105**

As previously mentioned, collection of endometrial tissue for pre-operative histology was performed either by fractional curettage or endometrial sampling. Since our study focused on the benefit of endometrial sampling compared to the conventional method, we divided the patients into 2 groups for analysis. Endometrial sampling revealed 91.67% sensitivity, 87.1% specificity, 73.33% positive predictive value (PPV), 96.43% negative predictive value (NPV), 7.10 likelihood ratio positive and 0.0957 likelihood ratio negative for detection of high-grade endometrial cancer. The sensitivity, specificity, PPV and NPV of fractional curettage for high-grade cancer detection were 73.68%, 93.02%, 82.35% and 88.89% respectively. The likelihood ratio positive and negative of fractional curettage were 10.6 and 0.283 respectively (Table 4).

Table 4. Comparison of the accuracy of endometrial sampling versus fractional curettage for detection of high grade endometrial cancer

	Endometrial sampling N = 43	Fractional curettage N = 62	Total N = 105
Sensitivity of detecting HG (as confirmed by final histology)	91.67 %	73.68 %	80.65 %
Specificity of detecting HG (as confirmed by final histology)	0	0	1
Positive predictive value	73.33 %	82.35 %	78.13 %
Negative predictive value	96.43 %	88.89 %	91.78 %
Accuracy			
Likelihood ratio positive	7.10	10.60	8.53
Likelihood ratio negative	0.0957	0.283	0.214

HG—high grade tumor

Table 5 depicts the discordance between final pathology and endometrial sampling or fractional curettage. Endometrial sampling resulted in underestimation of tumor grading in 1 out of 6 patients (2.32%), while 5 patients were underestimated by fractional curettage. Of seven pre-operative samples that were reported as higher grade than the final histology, 4 out of 7 (9.3%) were diagnosed by endometrial sampling.

Table 5. Comparison of the accuracy of endometrial sampling versus fractional curettage for detection of high grade endometrial cancer

	Total N = 105	Endometrial sampling N = 43	Fractional curettage N = 62
Lower grade than final pathology	6 (5.71 %)	1 (2.32 %)	5 (8.06 %)
Higher grade than final pathology	7 (6.67 %)	4 (9.3 %)	3 (4.84 %)

Discussion

The diagnosis of endometrial cancer is based on the histological morphology. Thus, accurate initial tumor grading is empirical for selection of appropriate surgical intervention and early referral to gynecologic oncologist. Previous study suggested the high sensitivity and specificity of the endometrial sampling in detection of endometrial cancer[11-13]. However, there is insufficient data on its accuracy for detection of high-grade cancer[7]. As a result, this study focuses on the accuracy of endometrial sampling for detection of high-grade cancer to facilitate the planning of proper surgical interventions and compare the accuracy between endometrial sampling and fractional curettage. Several aspects include sensitivity, specificity, negative predictive value (NPV), or positive predictive value (PPV) of the method were analysed.

Sensitivity of endometrial sampling to detect high-grade endometrial cancer

Our study revealed the overall sensitivity of pre-operative histology for detection of high-grade endometrial cancer was 80.65%. Endometrial sampling

was more sensitive than fractional curettage in detecting of high-grade cancer, with the sensitivity of 91.67% compared to 73.68%. Interestingly, our result was dissimilar to the previous study by Gloria et.al, in which, the sensitivity of fractional curettage was as high as 92.3% while that for endometrial sampling was 85.7%[7]. Discrepancy of the results might be caused by various factors, including patient backgrounds (eg. race, age), type of tumor, and device variations.

The lower sensitivity of endometrial sampling in the previous study which was conducted in the similar fashion as our study might be due to the dominance of non-endometrioid cancer, different instrument use. However, it is not great different between the studies. Endocell and endometrial aspirator were used in our study while pipelle was used in the previous study for endometrial sampling.

In 31 samples from patients with final diagnosis of high-grade endometrial carcinoma in our study, 6 samples were underestimated, of which, 5 of those were obtained by fractional curettage. All of the 6 patients had grade 3 endometrioid adenocarcinoma while the pre-operative histology reported as endometrioid grade 1 or 2. The accuracy was 100% in non-endometrioid group.

The lower sensitivity of fractional curettage in our study might be caused by 55 out of 62 patients that from fractional curettage were not done in Phramongkutklao hospital, so we cannot review the pathological report or repeated procedure. Only 1 out of 7 samples from fractional curettage in our hospital could not detect high grade cancer.

Positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio of endometrial sampling to detect high-grade endometrial cancer

Our study demonstrated PPV 82.35% of fractional curettage and 73.33% of endometrial sampling, similar to the previous study by Huang GS, et al[7]. While NPV and likelihood ratio of endometrial sampling for detecting high-grade endometrial cancer had not been previously described. In this study demonstrated 96.43% PPV and 7.10 positive likelihood ratio. The NPV (96.4%) and negative likelihood ratio (0.0957) of endometrial sampling were higher than fractional curettage. Thus, endometrial sampling may be used as the initial procedure for evaluating abnormal uterine bleeding in outpatient unit. Nonetheless, when high-grade malignancy was suspected from clinical presentation, fractional curettage should be used due to the higher PPV and positive likelihood ratio (Table 4).

As a result, we suggested the use of endometrial sampling as the procedure of choice for abnormal uterine bleeding in outpatient unit when the malignancy is also suspected. Pathological report from endometrial sampling was reliable and accurate enough for detecting high-grade endometrial cancer for planning of appropriate surgery. However, we should keep in mind on the possibility of more advanced staging from final pathology than the preoperative pathological report.

Limitation

Limitation of our study was inadequate cases of endometrial sampling. In the future, we recommend to expand the study into multi-centers collaboration to increase the study population.

Conclusion

In summary, our study demonstrated that endometrial sampling was highly accurate in detection of high-grade endometrial cancer and could be utilized in patients with suspected malignancy-related abnormal uterine bleeding. Moreover, we demonstrated the strong correlation between the histology from endometrial sampling and the final pathology that was useful for preoperative counseling, referral decision, and proper surgical management.

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ความแม่นยำของการใช้เครื่องมือดูดเซลล์เยื่อบุโพรงมดลูกมาตรวจทางพยาธิวิทยา สำหรับการวินิจฉัยมะเร็งเยื่อบุโพรงมดลูกชนิดรุนแรง

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วัตถุประสงค์ *: เพื่อศึกษาหาความแม่นยำของการใช้เครื่องมือดูดเซลล์เยื่อบุโพรงมดลูกมาตรวจทางพยาธิวิทยา สำหรับการวินิจฉัยมะเร็งเยื่อบุโพรงมดลูกชนิดรุนแรง*

วิธีการศึกษา *: การศึกษาวิจัยแบบตัดขวาง โดยสืบค้นประวัติผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกที่ได้รับการผ่าตัดในโรงพยาบาลพระมงกุฎเกล้า ตั้งแต่ตุลาคม 2552 ถึง มิถุนายน 2557 จำนวน 105 คน และนำผลการตรวจทางพยาธิวิทยาก่อนผ่าตัดมาเปรียบเทียบกับผลตรวจชิ้นเนื้อหลังผ่าตัด คำนวณหาค่าความไว ความจำเพาะ และค่าพยากรณ์บวกของเครื่องมือที่ใช้วินิจฉัยโรคเยื่อบุโพรงมดลูกก่อนผ่าตัด*

ผลการศึกษา *: จากผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกจำนวน 105 ราย แบ่งเป็นผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกชนิดรุนแรงจำนวน 31 ราย และชนิดไม่รุนแรง จำนวน 74 ราย พบว่าเครื่องมือดูดเซลล์เยื่อบุโพรงมดลูกสามารถทำนายโรคมะเร็งเยื่อบุโพรงมดลูกชนิดรุนแรงได้โดยมีค่าความไวร้อยละ 91.67, ความจำเพาะร้อยละ 87.1 และค่าพยากรณ์บวกร้อยละ 73.33 นอกเหนือจากนี้ยังพบว่าการขูดมดลูกสามารถทำนายโรคมะเร็งเยื่อบุโพรงมดลูกชนิดรุนแรงได้โดยมีค่าความไวร้อยละ 72.68, ความจำเพาะร้อยละ 93.02 และค่าพยากรณ์บวกร้อยละ 82.35*

สรุป *: เครื่องมือดูดเซลล์เยื่อบุโพรงมดลูกน่าจะเป็นทางเลือกที่ดีสำหรับการตรวจผู้ป่วยที่มีเลือดออกผิดปกติทางช่องคลอดและสงสัยมะเร็งเยื่อบุโพรงมดลูกเนื่องจากเป็นเครื่องมือที่มีความแม่นยำสูง*