นิพนธ์ต้นฉบับ

ความไวและความจำเพาะของการตรวจวินิจฉัยภาวะก่อนเป็นมะเร็งปากมดลูก ≥ HSIL ด้วยการตัดชิ้นเนื้อภายใต้กล้อง colposcope

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บทคัดย่อ

วัตถุประสงค์ : เพื่อศึกษาความไวและความจำเพาะของการตรวจวินิจฉัยภาวะก่อนเป็นมะเร็งปากมดลูก ≥ HSIL ด้วยการตัดชิ้นเนื้อภายใต้กล้อง colposcope

ชนิดของการวิจัย : การวิจัยเชิงพรรณนา

สถานที่ทำการวิจัย : กลุ่มงานสูติ – นรีเวชกรรม โรงพยาบาลมหาราชนครราชสีมา

วิธีการศึกษา : ผู้ที่เข้ารับการตรวจและตัดชิ้นเนื้อภายใต้กล้อง colposcope ที่โรงพยาบาลมหาราชนครราชสีมาตั้งแต่ มกราคม 2548 ถึง ธันวาคม 2550 เนื่องจากผลการตรวจ Pap smears ผิดปกติ ตามระบบ Bethesda system 2001 และได้รับการตรวจเพิ่มเติมเพื่อให้ได้ผลทางพยาธิวิทยาขั้นสุดท้ายจากการตัดปากมดลูกเป็นรูปกรวย หรือตัดมดลูกจำนวน 243 คน

ผลการวิจัย : การวินิจฉัยภาวะก่อนเป็นมะเร็งปากมดลูก ≥ HSIL ด้วยการตัดชิ้นเนื้อภายใต้กล้อง colposcope ในกลุ่มผู้ป่วยที่มีผล Pap smear ผิดปกติและได้รับการตรวจเพิ่มเติมด้วยการตัดปากมดลูกเป็นรูปกรวยหรือตัดมดลูก มีความไวร้อยละ 81.3 ความจำเพาะร้อยละ 100.0 โดยที่ผู้ป่วยมีอายุตั้งแต่ 21-84 ปี อายุเฉลี่ย 43.1 ปี (SD 10.1) ช่วงอายุที่พบมากที่สุด คือ 41-50 ปี คิดเป็นร้อยละ 35.8

สรุป : ผู้ป่วยที่มีผลการตัดชิ้นเนื้อภายใต้กล้อง colposcope เป็นระยะก่อนเป็นมะเร็งปากมดลูก ≥ HSIL ควรต้องทำการตัดปากมดลูกเป็นรูปกรวยเพื่อการวินิจฉัยและหวังการรักษาทุกราย ส่วนในกลุ่มที่เป็น ≤ LSIL หากไม่ได้ทำการตัดปากมดลูกเป็นรูปกรวยควรติดตามการรักษาอย่างใกล้ชิด

คำสำคัญ : ภาวะก่อนเป็นมะเร็งของปากมดลูก ≥ HSIL, การตัดชิ้นเนื้อภายใต้กล้อง colposcope, ความไว, ความจำเพาะ

Introduction

Cervical cancer is the second most common cancer in Thai women. The worldwide policy of cervical cancer prevention has focused on screening woman at risk by using Pap smear and early treatment on precancerous lesions because of its slowly progression to invasive cancer[1]. Pap smear programs or cytological screening programs have resulted in reducing incidence and mortality of cervical cancer in some countries that have higher screening quality and coverage. Pap smears was first introduced for screening precancerous lesion of cervix in 1948. In Thailand there is current national screening program[2], but Thai people still do not realize this problem, thus the incidence of cervical cancer is still high[2].

Because of Pap smears has low sensitivity and this technique cannot identify the location of the lesions[3]. Colposcopic Directed Biopsy (CDB) is a standard for diagnosis of cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL)[4] At present, management algorithms are based on the colposcopic findings and the histology from biopsies. According to the literature, disagreement between diagnosis based on CDB and specimens obtained by Large Loop Excision Transformation Zone (LLETZ) had been reported[5-7]. Moreover, there were high numbers of underdiagnosis by CDB[8-10]. Women with greater level of severity identify by CDB may receive inadequate treatment, and have significantly higher risk of recurrence and development of invasive cancer. There were many reports of invasive disease being found in LLETZ specimens, which were previously unsuspected during colposcopy or undetected by CDB[7,11-14]. Sensitivity, specificity, or accuracy of CDB have the difference in each a report[12-16]. Therefore, the aims of this study were to determine sensitivity and specificity of CDB for detecing ≥ High grade cervical squamous intraepithelial lesion (HSIL).

Materials and methods

This study was approved by the Institutional Review Board of the Maharat Nakhon Ratchasima Hospital. Data was collected from January 2005 to December 2007. Only 243 from 620 patients, who had abnormal Pap smears, were included in this study (Figure 1.). All of the cases were obtained from Maharat Nakhon Ratchasima Hospital

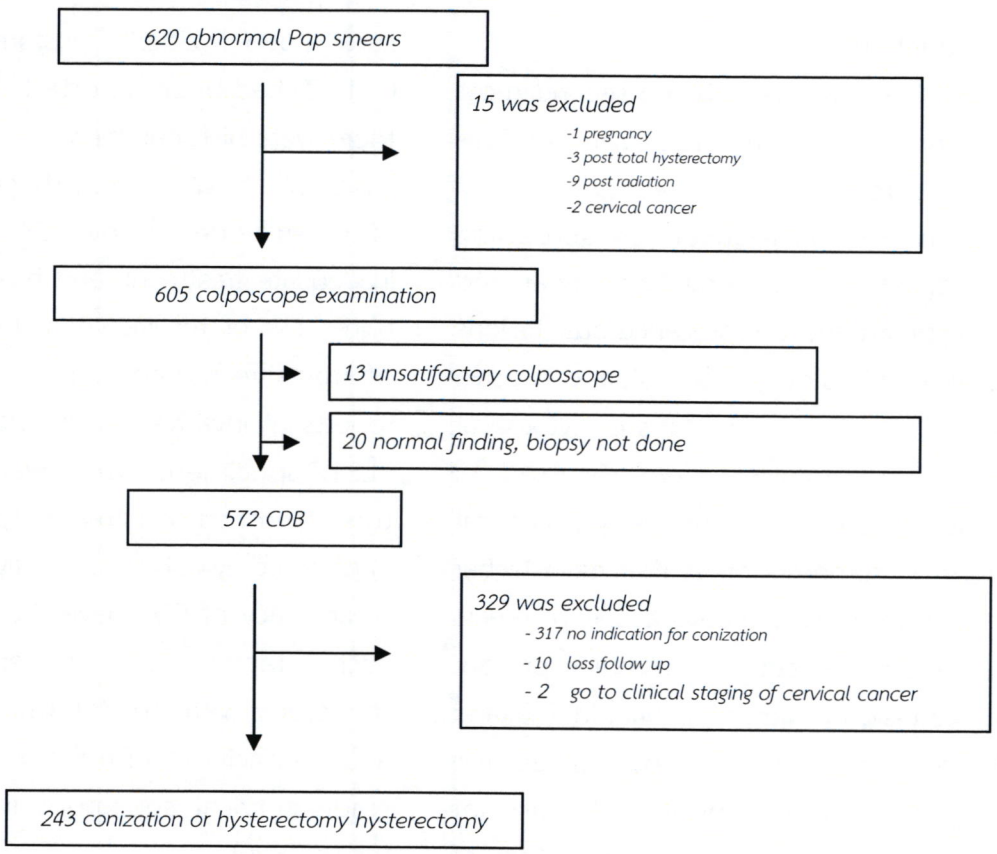

Figure1. Enrollment of patients

Cytological abnormality was classified by Bethesda system 2001 as ASCUS (Atypical squamous cells of undetermined significance) or worse. The indication for conization was utilized according to standard protocols. They were 1) diagnosis of microinvasive carcinoma or adenocarcinoma in situ that was obtained from CDB. 2) presence of results discrepancy between Pap smears and subsequence CDB and 3) therapeutic procedure for HSIL. CDB, conization and hysterectomy were done by gynecologists. Pathological reports of CDB and final diagnosis of HSIL or worse (≥ HSIL) were labeled as positive disease and reports of LSIL or less (≤ LSIL) were labeled as negative disease. The accuracy of CDB occurred when the diagnosis from CDB was the same with the final pathological diagnosis. If result of CDB was less than or equal to LSIL but final pathological diagnosis was HSIL or worse, it showed confliction and CDB would be interpreted as inaccuracy. The recorded data were hospital number, age, cytological diagnosis, pathological diagnosis from CDB and from conization or hysterectomy. Descriptive statistics, sensitivity, and specificity were reported in percentage.

Results

During the study period, 273 patients were eligible for the present study. (figure1). The mean age was 43.1 year (SD 10.1; range 21-84 years). Most (35.8 %) were in the age group of 41-50 years.

Table 1 showed the agreement of pathological diagnosis from CDB and conization or hysterectomy. Of the 243 women, CDB identified 60 (24.7%) with no evidence of SIL (no SIL), 35 (14.4%) with LSIL, 134 (55.1%) with HSIL, 1 (0.4%) with microinvasive (MIC), 13 (5.3%) with invasive. The exact agreement concurred in 167 out of 243 patients (68.7%). The overall rate at CDB was 7.4% and 23.9% undercall. This indicated moderate agreement and correlation between the results of CDB and conization or hysterectomy findings.

Table 1. Pathological diagnosis of CDB and conization or hysterectomy (n=243)

CDB	Conization or hysterectomy					Total	Exact agreement (%)
	No Squamous Intraepithelial Lesion	Low grade Squamous Intraepithelial Lesion	High grade Squamous Intraepithelial Lesion	Microinvasive cancer	Invasive cancer		
No Squamous Intraepithelial Lesion	40	12	7	0	1*	60	66.7
Low grade Squamous Intraepithelial Lesion	1	8	23	1	2*	35	22.9
High grade Squamous Intraepithelial Lesion	7	9	106	7	5 †	134	79.1
Microinvasive cancer	0	0	0	1	0	1	100
Invasive cancer	0	0	1	0	12	13	92.3

* Pathological report was adenocarcinoma

†Two patients of five patients were adenocarcinoma

Table 2 showed the comparison of pathological diagnosis from CDB and final diagnosis. The accuracy rate of CDB in comparison of final diagnosis was 76.1%. Accuracy rate was higher in women with invasive, MIC and HSIL (100%, 100% and 91% respectively). There were 8 cases of MIC and 8 cases of invasive carcinoma that were not diagnosed by CDB. Eight patients of MIC were diagnosed as HSIL 7 cases

and LSIL 1 case by CDB. Eight patients of invasive carcinoma (5 adenocarcinoma and 2 squamous cell carcinoma) were diagnosed as HSIL 5 cases, LSIL 2 cases and no SIL 1 case. The women with unexpected MIC group were 3.3% similar to unexpected invasion group.

Table 2 Pathological diagnosis of CDB and final diagnosis (n=243)

CDB	Final diagnosis					Total	Accuracy (%)
	No Squamous Intraepithelial Lesion	Low grade Squamous Intraepithelial Lesion	High grade Squamous Intraepithelial Lesion	Microinvasive cancer	Invasive cancer		
No Squamous Intraepithelial Lesion	40	12	7	0	1*	60	66.7
Low grade Squamous Intraepithelial Lesion	0	9	23	1	2*	35	25.7
High grade Squamous Intraepithelial Lesion	0	0	122	7	5†	134	91.0
Microinvasive cancer	0	0	0	1	0	1	100.0
Invasive cancer	0	0	0	0	13	13	100.0

* Pathological report was adenocarcinoma

†Two patients of five patients were adenocarcinoma

Comparison data between CDB and final diagnosis for detecting ≥ HSIL, when pathological reports as HSIL or worse (≥ HSIL) were labeled as positive disease and reports of LSIL or less (≤ LSIL) were labeled as negative disease. CDB for detected ≥ HSIL was 81.3% sensitivity, 100% specificity, 100% positive predictive value and 64.2% negative predictive value. (Table 3)

Table 3. Comparison data between CDB and final diagnosis for detected HSIL

CDB	Final Diagnosis		Total
	Positive	Negative	
Positive	148	0	148
Negative	34	61	95
Total	182	61	243

Discussion

Majority of the patients in this study were in the age group of 41-50 years (35.8%). Similar finding had been reported previously. Therefore, it would be beneficial to encourage and educate woman in this age group. From this study, we found that there were satisfactory colposcope 97.8% (592 cases from 605 cases) while the previous reports had shown only 74-80%[18-19]. This might be more experience of colposcopists.

Three hundred and seventeen patients from 572 patients (55.4%) whose underwent CDB were excluded from this study because Pap smears was ≤ LSIL and compatible with CDB so no indication for conization. While previous report was only 21%[17]. Possible reason included experience of colposcopists and early recognized of people to received routine check up for Pap smears. Therefore, we could not evaluate sensitivity and specificity of CDB in this group.

This study showed the exact agreement of CDB and conization or hysterectomy was 68.7% while previous reports was 35-90%[20-21]. The agreement was low in the no SIL and SIL group but it was better in MIC invasive and HSIL group. Possible reason for the low agreement in no SIL and LSIL group included failure of the colposcopist to take the biopsy at the most severe area, complete removal of a small low-grade lesions by CDB, inability to carefully inspected deep transformation zone, low sensitivity of CDB for detect cervical glandular neoplasia[22], high variability of gynecologist and pathologist in diagnosis of LSIL. The possible reason for the higher agreement in lesion of invasive, MIC and HSIL included the effect area was easier to be identified by colposcopist, persisted the large size lesion after taking CDB, residual lesion is not much affected by inflammatory reaction[23].

In this study, we found undercall rate at CDB was 23.8%. In no SIL groups was noted 33.3% and 74.3% in LSIL group. This is a worrisome finding because it could be under treatment. Previous studies showed 21-42% of HSIL that found in LSIL group from CDB[24]. From this study was 65.7%. This indicated disadvantage of using observational strategies to manage women with CDB was LSIL.

In the present study, we found 81.3% sensitivity and 100% specificity similar finding that reports in Thailand[10-11]. However, because of false negative rate was 18.7%, observational strategies in women with no SIL or LSIL by CDB may be disadvantage due to the possibility that a high grade lesion may be progression to invasive cancer. The most serious aspect is underdiagnosis of invasive carcinoma. Moreover 3 cases of invasive and 1 case of MIC were missed by CDB in these groups. Treatment with conization or hysterectomy might be appropriate than close follow up particularly in poor compliance patients.

However, we should concern that conization or hysterectomy might had serious complication (cervical stenosis, preterm delivery in subsequent pregnancies, excessive blood loss)[6], and patients must received anesthesia and hospitalization.

Because of 5 from 8 patients (62.5%) of invasive cancer that missed by CDB were adenocarcinoma, we can concluded that sensitivity of CDB for diagnosis cervical glandular neoplasia was rather low, similar finding to the previous report.[22] Therefore, we should concern about invasive cancer lesion in any patient that had abnormal glandular neoplasia on pap smear result and careful follow up.

The limitation of this study was the retrospective study, thus we lost several important data such as cytological sampling techniques (conventional Pap or liquid-based Prep), conization techniques (Loop electrosurgical excision procedure or cold knife conization) and examiners (staff, or residents). Secondly, colposcopic examination and pathological review were depended on doctor's experience; different doctor may define different result in same patient. Thirdly, we excluded patient, who had only provisional diagnosis from colposcope and CDB not done, and who had CDB compatible with Pap smear or no indication for conization. So selection bias might be occur. Further study should recruit more data mentioned above.

In summary, even though the sensitivity was rather low but the specificity was high. In our setting CDB is still clinical use. For Patients with HSIL or worsen from CDB should be promptly performing conization for early diagnosis and treatment. For patients with LSIL or lower from CDB should receive careful follow up, conization or hysterectomy is recommend in poor compliance patients.

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