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ความแม่นยำของการวินิจฉัย Cervical glandular lesions โดยการรายงานผลแบบเบเทสดา 2001

นิภา กาญจนาวิโรจน์กุล[1], ลัคกุล ยานากิฮาระ[2], รจนา ม่วงเล็ก[2]
[1]ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์ศูนย์รังสิต
[2]งานพยาธิวิทยา โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ มหาวิทยาลัยธรรมศาสตร์ศูนย์รังสิต

Diagnostic Accuracy of Cervical Glandular Lesions by the 2001 Bethesda System

Nipa Kanjanavirojkul[1], Lakkakul Yanagihara[2], Rotchana Muanglek[2]
[1]Department of Pathology, Faculty of Medicine
[2]Division of Pathology, Thammasat University Hospital, Thammasat University, Thailand

วัตถุประสงค์: เพื่อวิเคราะห์ความแม่นยำของการตรวจทางเซลล์วิทยา ในการวินิจฉัย cervical glandular lesions ด้วยการเทียบผลการวินิจฉัยแป๊บสเมียร์กับชิ้นเนื้อ
วิธีการ: แป๊บสเมียร์ของสตรีจำนวน 35,520 รายที่มีการตรวจคัดกรองแล้วรายงานผลด้วยระบบเบเทสดา 2001 ผลการวินิจฉัยเป็น glandular lesions จำนวน 163 ราย (0.5 เปอร์เซ็นต์) จำนวนเพียง 99 ราย (0.3 เปอร์เซ็นต์) ที่มีผลการวินิจฉัยชิ้นเนื้อซึ่งถือเป็นมาตรฐานการวินิจฉัยสุดท้าย เพื่อหาค่าความไว ความจำเพาะ ความแม่นยำ ค่าพยากรณ์บวกและค่าพยากรณ์ลบของการตรวจแป๊บสเมียร์
ผลการศึกษา: ผลการวินิจฉัยแป๊บสเมียร์เป็น atypical glandular cell (AGC) 49.5 เปอร์เซ็นต์ AGC-favor neoplasm 14.1 เปอร์เซ็นต์ adenocarcinoma in situ (AIS) 3 เปอร์เซ็นต์ adenocarcinoma (ADCA) 17.2 เปอร์เซ็นต์ และ glandular with squamous lesion 16.1 เปอร์เซ็นต์ ผลการวินิจฉัยชิ้นเนื้อเป็น benign cellular change (BCC) 58.6 เปอร์เซ็นต์ AIS 5.1 เปอร์เซ็นต์ ADCA 19.2 เปอร์เซ็นต์ การติดเชื้อฮิวแมนแปปปิวโลมาไวรัส หรือ cervical intraepithelial neoplasia 15.2 เปอร์เซ็นต์ และมะเร็งชนิดอื่น 2 เปอร์เซ็นต์ ค่าความไวของกลุ่ม AGC, AGC-favor neoplasm, AIS, ADCA และ mixed lesion เป็น 72.4, 50, 60, 79 และ 100 เปอร์เซ็นต์ตามลำดับ ค่าความเฉพาะของกลุ่ม AGC, AGC- favor neoplasm, AIS, ADCA และ mixed lesion เป็น 82.9, 88.2, 100, 97.5 และ 93.3 เปอร์เซ็นต์ตามลำดับ ค่าความถูกต้องของกลุ่ม AGC, AGC- favor neoplasm, AIS,

Objective: To analyze the diagnostic accuracy of cytologic examinations for the diagnosis of cervical glandular lesions through the correlation between cytologic and histologic findings.
Methods: Pap smears of 35,520 women were screened according to the 2001 Bethesda criteria. In 163 cases (0.5%) were diagnosed as glandular lesions. Only 99 cases (0.3%) had histologic specimens. Histologic results were used as the gold standard for calculations of sensitivity, specificity, accuracy, positive predictive value and negative predictive value of Pap smears.
Results: Pap smears were diagnosed as atypical glandular cell (AGC) 49.5%, AGC-favor neoplasm 14.1%, adenocarcinoma in situ (AIS) 3%, adenocarcinoma (ADCA) 17.2% and the glandular with squamous lesion 16.1%. The histologic examination revealed benign cellular change (BCC) 58.6%, AIS 5.1%, ADCA 19.2%, human papillomavirus or cervical intraepithelial neoplasia 15.2% and other neoplasia 2%. The sensitivity of AGC, AGC-favor neoplasm, AIS, ADCA and mixed lesion were 72.4%, 50%, 60%, 79% and 100%, respectively. The specificity of AGC, AGC-favor neoplasm, AIS, ADCA and mixed lesion were 82.9%, 88.2%, 100%, 97.5% and 93.3%, respectively. The accuracy of AGC, AGC-favor neoplasm, AIS, ADCA and mixed lesion were 76.8%, 85.9%, 98%, 93.9% and 93.9%, respectively.

ADCA และ mixed lesion เป็น 76.8, 85.9, 98, 93.9 และ 93.9 เปอร์เซ็นต์ ตามลำดับ

สรุป: กลุ่ม AIS, ADCA และ mixed lesion มีความถูกต้องในการวินิจฉัยมากกว่า 90 เปอร์เซ็นต์ ส่วนกลุ่ม AGC และ AGC- favor neoplasm มีความถูกต้องน้อยกว่า ค่าความไวที่ต่ำในกลุ่ม AGC และ AGC- favor neoplasm เพราะขนาดรอยโรคที่เล็กหรือตำแหน่งอยู่ลึก ทำให้ยากในการเก็บตัวอย่างชิ้นเนื้อบริเวณรอยโรค ถึงแม้ว่าเกณฑ์ในการวินิจฉัย glandular lesions มีการตีพิมพ์แพร่หลายแต่ก็ยากในการวินิจฉัย glandular lesions ดังนั้นการศึกษาต่อไปจึงจำเป็นในการเพิ่มความสามารถของการวินิจฉัย glandular lesions

คำสำคัญ: แป๊ปสเมียร์ glandular lesions ระบบเบเทสดา 2001 ค่าความไว ความถูกต้อง

Conclusions: This study had high diagnostic accuracy more than 90% for AIS, ADCA and mixed lesion. AGC and AGC-favor neoplasm were less accurate than above lesions. The sensitivity was low in AGC and AGC-favor neoplasm because the histologic specimen from the small size lesion or deep location are difficulty in sampling the affected pathologic area. Although cytomorphologic criteria for diagnosis of glandular lesions have published, there was difficulty in interpreting glandular lesions. Further studies are need to increase diagnostic performance of glandular lesions.

Keywords: Pap smears, glandular lesions, the 2001 Bethesda system, sensitivity, accuracy

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Introduction

The Pap smears are used as a screening test for early detection of cervical cancers. Cervical glandular lesions are less frequent than the squamous epithelial lesions; however, the incidence of adenocarcinoma (ADCA) of the cervix has increased gradually in the last 2 decades,especially in younger women[1].

The term “atypical glandular cells of undetermined significance” (AGUS) was introduced in the 1988 Bethesda System (TBS)[2] and defined as morphologic changes in glandular cells beyond those suggestive of a benign reactive process,but insufficient for the interpretation of ADCA. In the TBS 2001, AGUS had been changed to “atypical glandular cells” (AGC), with the subclassifications “not otherwise specified” (NOS) and “favor neoplasm”. The cell type of origin, endocervical or endometrial, should be diagnosed whenever possible. Adenocarcinoma in situ (AIS) had been separated as another distinct category of diagnosis[3].

Many reports had been published on the accuracy of the Pap smears for squamous lesions but fewer reports for glandular lesions. The sensitivity diagnosis depends on the subtype of lesions. The sensitivity in endocervical ADCA was higher than endometrial ADCA[4]. Early detection of precursor lesions of squamous had decreased the incidence of squamous cell carcinoma, whereas many studies had shown that glandular lesions might be missed by Pap smears.[5,6]

The objective of this study is to analyze the diagnostic sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of cytologic examination for the diagnosis of cervical glandular lesions through the correlation between cytologic and histologic findings.

Materials and Methods

During a period of 5 years (January 2007-December 2011), a total of 35,520 Pap smears in Thammasat University Hospital were screened for early detection of cervical cancer. Abnormal cervical glandular lesions diagnosed based on the TBS 2001 were reported as AGC, AGC-favor neoplasm, AIS, ADCA and mixed lesions (AGC with abnormal squamous and AGC-favor neoplasm with abnormal squamous). Pure abnormal squamous lesions were excluded from this study. A total of 163 cases (0.5%) were diagnosed as glandular lesions. Only 99 case (0.3%) had definitive histologic diagnosis as benign cellular changes (BCC), AIS, ADCA, human papillomavirus effect (HPV) with or without cervical intraepithelial neoplasia (CIN) and

other neoplasia. Histologic results were used as the gold standard for calculations of sensitivity, specificity, accuracy, PPV and NPV of Pap smears.

Results

Table 1 showed the correlation of cytologic and histologic diagnoses in 99 cases. In the histologic diagnosis of BCC were 58 cases, 42 cases were interpreted as AGC in cytology. The same histologic and cytologic diagnosis of AIS were 3 cases from total histologic diagnosis of AIS 5 cases. The cytologic evaluations of ADCA were 17 cases, 15 cases were diagnosed as ADCA in histology, one case as small cell carcinoma and one case as carcinosarcoma. The histologic diagnosis of HPV with or without CIN were 15 cases, 5 cases were interpreted as pure glandular lesions in Pap smears, 10 cases as mixed lesions.

The results of sensitivity, specificity, accuracy, PPV and NPV were shown in Table 2. The sensitivity varied from 50% to 100%, specificity from 82.9% to 100%, accuracy from 76.8% to 98%, PPV from 14.3% to 100% and NPV from 68% to 100%.

Table 1 Cytology versus histology

Cytology	Histology					Total
	BCC	AIS	ADCA	HPV/CIN	Other neoplasia**	
AGC	42	1	2	4	-	49 (49.5%)
AGC with abnormal squamous*	6	-	-	7	-	13 (13.1%)
AGC-favor neoplasm	10	1	2	1	-	14 (14.1%)
AGC-favor neoplasm with abnormal squamous*	-	-	-	3	-	3 (3.0%)
AIS	-	3	-	-	-	3 (3.0%)
ADCA	-	-	15	-	2	17 (17.2%)
Total	58 (58.6%)	5 (5.1%)	19 (19.2%)	15 (15.2%)	2 (2.0%)	99 (100%)

BCC : benign cellular changes, AIS : Adenocarcinoma in situ, ADCA : Adenocarcinoma, HPV : Human papillomavirus effect, CIN : cervical intraepithelial neoplasia

* Atypical squamous cells of undetermined significance (ASC-US), Atypical squamous cells-cannot exclude high - grade squamous intraepithelial lesion (ASC-H), HPV, CIN

**Small cell carcinoma and carcinosarcoma

Table 2 Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV)

	Pap smears diagnosis				
	AGC	AGC-favor neoplasm	AIS	ADCA	Mixed lesions*
Sensitivity (%)	72.4	50.0	60.0	79.0	100
Specificity (%)	82.9	88.2	100	97.5	93.3
Accuracy (%)	76.8	85.9	98.0	93.9	93.9
PPV (%)	14.3	21.4	100	88.2	62.5
NPV (%)	68.0	96.5	97.9	95.1	100

*AGC with abnormal squamous and AGC-favor neoplasm with abnormal squamous

Discussion

The results from literature for the sensitivity of Pap smears in interpretation of glandular lesions were varied from 38.6 - 87.1%[7-10], the mixed lesions were varied from 65.6 - 80%[7,8]. The sensitivity in this study were similar rate for AGC (72.4%), AGC favor neoplasm (50%), AIS (60%), ADCA (79%) but mixed lesions (100%) was higher rate than previous literatures. The specificity of AIS in this study was 100% and more than Renshaw et al. report (46.5%)[11]. Raab et al[9]. reported specificity of AGC (58%) which was less than our specificity (82.9%). Koss et al[12]. reported overall accuracy rate for detection of endometrial ADCA by endocervical sample to be 70%. Accuracy of ADCA (all type) in this study was 93.9%. The false negative rate (NPV) for endometrial ADCA was 67% in Salomao et al[13]. publication and it was lower than our NPV of ADCA (95.1%). Mitchell et al[14]. reported that the diagnosis of endometrial ADCA predicted the presence of disease (PPV) in only 28% of cases. PPV (88.2%) and NPV (95.1%) for ADCA in this study were higher than previous reports.

A high rate (28-54%) of CIN involving endocervical glands misinterpreted as glandular lesions on smears had been reported from Renshaw et al[11]. In present study the squamous lesions are missed from Pap smears 5 cases because AGC marked a few scattered dysplastic squamous cells. Squamous lesions involving with glandular extension may show architectural arrangements that resemble those of endocervical cells and groups. They may also acquire some of the nuclear and cytoplasmic features that are more characteristic to the cells of glandular origin and thus may be misclassified as AGC.

There are several reasons why screening for glandular lesions may not be as successful as for squamous lesions. One of the main reasons for the low sensitivity of glandular lesions is their location in the endocervical canal which is less well accessible for adequate cytological sampling. Furthermore, because of the relatively rarity of the disease, cytologists rarely gather sufficient experience with glandular neoplasm and leading to false negative diagnoses. The interpretation of glandular lesions are difficult as there is a high degree of intra and inter observer variation.

Conclusion

This study has high diagnostic accuracy more than 90% for AIS, ADCA and mixed lesions. AGC and AGC - favor neoplasm are less accurate than above lesions. The sensitivity is low in AGC and AGC - favor neoplasm. Although cytomorphologic criteria for diagnosis glandular lesions have been published, the diagnosis of glandular neoplasm are difficult. Continuous improvement in cervical sampling specimens and cytodiagnostic skills, better understanding of glandular precursors lesion and the classification of cytologic and histologic findings are expected to increase the performance of glandular lesions.

References

1. Waddell C. glandular prediction : The pride and the prejudice. Cytopathology 2004; 15:177-80.
2. National Cancer Institute Workshop : The 1988 Bethesda System for reporting cervical/vaginal diagnoses. JAMA 1989; 262:931-4.
3. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. Forum group Members; Bethesda 2001 Workshop : The 2001 Bethesda System : Terminology for reporting results of cervical cytology. JAMA 2002; 287:2114-9.
4. Raab SS. Can glandular lesions be diagnosed in Pap smear cytology? Diagn Cytopathol 2000; 23:127-33.
5. Sasieni P, Castanon A, Cuzick J. Screening and adenocarcinoma of the cervix. Int J Cancer 2009; 125:525-9.
6. Bray F, Carstensen B, Moller H, Zappa M, PrimicZakelj M, Lawrence G, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 2005; 14:2191-9.
7. Lee KR, Minter LI, Granter SR. Papanicolaou smear sensitivity for adenocarcinoma in situ of the cervix. A study of 34 cases. Am J Clin Pathol 1997; 107:30-5.
8. Schoolland M, Segal A, Allpress S, Miranda A, Frost FA, Sterrett GF. Adenocarcinoma in situ of the cervix; sensitivity of detection by cervical smear. Cancer (Cancer Cytopathol) 2002; 96:330-7.

9. Raab SS, Snider TE, Potts SA, MC Da niel HL, Robinson RA, Nelson DL et al. Atypical glandular cells of undetermined significance; diagnostic accuracy and interobserver variability using select cytologic criteria. Am J Clin Pathol 1997; 107:299-307.
10. Schorge JO, Saboorian MH, Hynan L, Ashfag R. ThinPap detection of cervical and endometrial adenocarcinoma. A Retrospective cohort study. Cancer (Cancer Cytopathol) 2002; 96:338-43.
11. Renshaw AA, Mody DR, Lozano RL, Volk EE, walsh MK, Davey DD et al. Detection of adenocarcinoma in situ of the cervix in Papanicolaou tests: Comparison of diagnostic accuracy with other high-grade lesions. Arch Pathol Lab Med 2004; 128:153-7.
12. Koss LG, Schreiber K, Oberlander SG, Moussouris HF, Lesser M. Detection of endometrial carcinoma and hyperplasia in asymptomatic women. Obstet Gynecol 1984; 64:1-11.
13. Salomao DR, Raab SS. Atypical glandular cells of undetermined significance, favor endometrial origin. Diagnostic criteria to separate benigns from malignant lesions. Acta Cytol 1998; 42:1212.
14. Mitchell H, Giles G, Medley G. Accuracy and survival benefic of cytological prediction of endometrial carcinoma on routine cervical smears. Int J Gynecol Pathol 1993; 12:34-40.