자궁목세포진에서의 AutoPap Primary Screening System with Location-Guided Screening의 민감도 검사

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= Abstract =

Sensitivity of AutoPap Primary Screening System with Location-Guided Screening in Uterine Cervical Cytology

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Objective: The sensitivity of the AutoPap Primary Screening System with Location-Guided Screening (AutoPap LGS) for identifying atypical cells in cervicovaginal smears was evaluated. Methods: Two hundred forty one slides with atypical cervical cytology randomly sampled were rescreened both manually and by the AutoPap LGS. The AutoPap LGS localized the atypical cells as 15 fields of view(FOVs), which were reexamined by manual review. The sensitivity was also evaluated in accordance with the cellularity of the smears. Results: The AutoPap LGS successfully processed 232 out of 241 slides. The sensitivity of the AutoPap LGS identifying the atypical cells in successfully processed slides was 97.4%(226/232). The false negative rate was 2.6%(6/232). There was no false negative case in high grade squamous intraepithelial lesion (HSIL) or squamous cell carcinoma(SCC) smears in the AutoPap LGS. The FOVs localized the diagnostic-atypical cells in 97.8%(221/226). The number of diagnostic-atypical FOVs was increased in higher-degree of atypical cytology. The AutoPap LGS localized the atypical cells in 100% of adequately cellular smears and in 92.5% even in low cellular smears. Conclusion: The AutoPap LGS showed relatively good sensitivity to detect atypical cells. It can be a valuable system to localize atypical cells, especially in HSIL or cancer slides, even in smears with low cellularity.

Key words: AutoPap primary screening system with location-guided screening, Sensitivity, Cervical smear, Screening

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INTRODUCTION

The AutoPap Primary Screening System (Tripath Imaging, Inc., Burlington, North Carolina, U.S.A.) is an automated device, which was designed for initial screening of conventional cervical smears and, more recently, thin-layer specimens. The AutoPap System was approved by the U.S. Food and Drug Administration (FDA) as a method for quality control.[1,2] Its use in primary screening has been suggested and the evaluation of the effectiveness of the AutoPap Primary Screening System in the screening of cervical cytology was recently endorsed by the International Academy of Cytology.[3] The AutoPap Primary Screening System is the only system approved by the U.S. FDA for primary screening of Pap smears. The system classifies smears as No Further Review (smears can be judged with confidence as being within normal limits without being evaluated by a cytologist), Review (smears with a greater likelihood of abnormality and need to be reviewed manually), or Process Review/ Rerun (smears need to be reviewed manually because of technical problems). In addition to overall slide classification, the AutoPap Primary Screening System with Location-Guided Screening (AutoPap LGS) also provides PapMap, which is a printed map of the slide that contains up to 15 circles. Each circle is 2.5 mm in diameter, equivalent to one 10× objective microscopic visual field, and independent of microscope type. One such circle is referred to as a 'field of view (FOV)'.

In this study, the sensitivity of the AutoPap LGS for identifying abnormal cells in smears with known atypical cytology was estimated. In addition, the feasibility of the FOVs of the AutoPap LGS as well as that in low or adequately cellular smears was evaluated.

MATERIALS AND METHODS

Two hundred forty one smear slides randomly sampled from a file of atypical cytology slides, which were diagnosed as atypical squamous cells of undetermined significance (ASCUS) and more degree of epithelial cell abnormalities in cervicovaginal smears, obtained for one year were rescreened both by the AutoPap LGS and by manual method. They were composed of 63 ASCUS, 9 atypical glandular cells of undetermined significance (AGUS), 79 low-grade squamous intraepithelial lesions (LSIL), 76 high-grade squamous intraepithelial lesions (HSIL), 11 squamous cell carcinomas (SCC), and 3 adenocarcinomas (AC).

Two hundreds thirty two of 241 atypical cervical cytology cases were successfully processed (No Further Review or Review) by the AutoPap LGS. For each slide classified as Review, the AutoPap LGS provided 15 FOV locations of potentially abnormal cells.

For the manual rescreening, experienced cytotechnologists screened the smear without information of the previous diagnosis or its outcome on the AutoPap LGS. After that, the diagnosis was compared with the previous original diagnosis. If the two diagnoses agreed, the diagnosis was used as the study reference diagnosis. If the two diagnoses disagreed, the slide was adjudicated by two cytopathologists, who finally agreed each other and then assigned a study reference diagnosis to the smear. The cytologic criteria for ASCUS and AGUS were referred to the Bethesda system.[4] Among 241 atypical cervical cytology cases, cervical biopsy or conization procedure was taken in 162 cases, and the atypical cells found in cervicovaginal smears were confirmed histologically in 149 cases out of 162 cases.

The smears, which had been processed on the AutoPap LGS, were also evaluated manually to be determined how many FOVs contained 'diagnostic-atypical' or 'nondiagnostic-atypical' cells. The 'diagnostic-atypical' FOV was defined as FOV contained atypical cells, on which based the diagnoses could be made. The 'nondiagnostic-atypical' FOV was assigned when the FOV contained atypical cells, but which were short to be an evidence of making a diagnosis.

The cellularity of smears was also evaluated (low cellular or adequately cellular). The low cellular smear was defined as a slide containing less than 15 atypical cell clusters, and the adequately cellular smear, 15 or more atypical cell clusters.

Table 1. The AutoPap LGS classification of atypical cytology slides

AutoPap LGS classification	Numbers of slides (%)
No Further Review	6 (2.5%)
Review	226 (93.8%)
Process Review/Rerun	9 (3.7%)
Total	241 (100%)

AutoPap LGS: the AutoPap Primary Screening System with Location-Guided Screening

RESULTS

Among 241 atypical cervical cytology slides rescreened by AutoPap LGS, 232 slides were successfully processed. AutoPap LGS classified 232 successfully processed slides as 6 'No Further Review' and 226 'Review' (Table 1). Nine cases were classified as 'Process Review/Rerun', which failed to provide the results of primary screening due to physical characteristics such as broken or misplaced cover slides or technical defects. The false negative rate of the AutoPap LGS in successfully processed slides was 2.6% (6/232). Six cases classified as 'No further Review' by AutoPap LGS were re-evaluated manually. They were diagnosed as ASCUS (1 case), AGUS (1 case) or LSIL (4 cases) in manual review (Fig. 1). There was neither HSIL nor cancer slides on false negative performance. The sensitivity of Auto-Pap LGS to detect atypicalities ('Review') in successfully processed slides was 97.4% (226/232). Cytologic diagnoses on manual review of 226 'Review' slides were as follows: 62 ASCUS, 8 AGUS, 71 LSIL, 71 HSIL, 11 SCC, and 3 AC.

In 226 'Review' slides, the AutoPap LGS detected atypical cells through FOV in 224 slides: at least one 'diagnostic-atypical' FOV present in 221 slides, and 'nondiagnostic-atypical' FOV only in 3 slides (Table 2). The sensitivity of AutoPap LGS to detect at least one diagnostic-atypical FOV was 97.8% (221/226). The sensitivity for identifying atypical cells through FOV, whether they were diagnostic-atypical or nondiagnostic-atypical, was 99.1% (224/226). The AutoPap LGS could not localize atypical cells through FOV in two slides, which contained 2 to 3 atypical cells at the outside areas
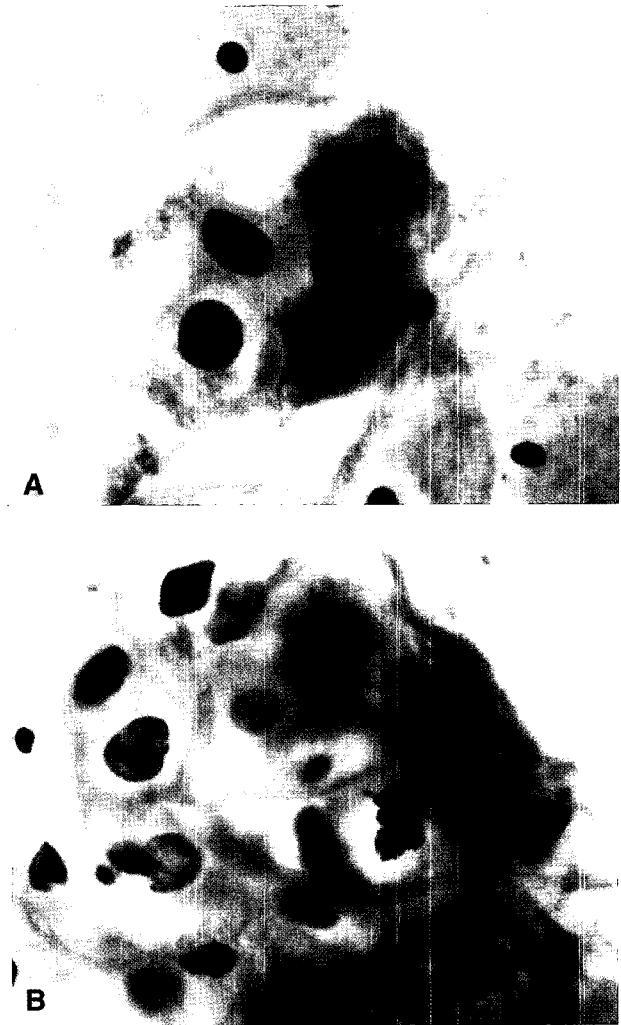

Fig. 1. The atypical cells classified as No Further Review by the AutoPap LGS. These smears were diagnosed as atypical squamous cells of undetermined significance (A) and low grade squamous intraepithelial lesion (B) in manual review. (Papanicolau)

of FOV. They were diagnosed as ASCUS (1 case) and LSIL (1 case) in manual review (Fig. 1).

The number of diagnostic FOVs increased in higher-degree of atypical cytology (Table 3). Ten and more diagnostic-atypical FOVs were found in 37.2% ASCUS/AGUS, 45.3% LSIL, 67.6% HSIL, 100% SCC/AC, and all 15 diagnostic-atypical FOVs were found in 14.3% ASCUS/AGUS, 25.3% LSIL, 43.7% HSIL, and 92.9% SCC/AC. All 14 cancer cases with SCC or AC revealed the diagnostic-atypical FOV.

Among 226 "Review" slides, 67 slides were deter-

Table 2. The sensitivity of field of view in the AutoPap LGS stratified by the cytologic diagnoses

Cytologic diagnosis	No. of smears	No. of smears with diagnostic-atypical FOV	No. of smears with nondiagnostic-atypical FOV only	No. of smears with atypical cells not localized by FOV
ASCUS/AGUS	70	69 (98.6%)	0 (0%)	1 (1.4%)
LSIL	71	68 (95.8%)	2 (2.8%)	1 (1.4%)
HSIL	71	70 (98.6%)	1 (1.4%)	0 (0%)
SCC/AC	14	14 (100%)	0 (0%)	0 (0%)
Total	226	221 (97.8%)	3 (1.3%)	2 (0.9%)

AutoPap LGS; the AutoPap Primary Screening System with Location-Guided Screening
No.; numbers, FOV; field of view, ASCUS; atypical squamous cells of undetermined significance, AGUS; atypical glandular cells of undetermined significance, LSIL; low-grade squamous intraepithelial lesion, HSIL; high-grade squamous intraepithelial lesion, SCC; squamous cell carcinoma, AC; adenocarcinoma

Table 3. Numbers of diagnostic field of view in atypical smears

Cytologic Diagnosis	Numbers of diagnostic FOV					Total
	0	1-5	6-9	10-14	15	
ASCUS/AGUS	1 (1.4%)	13 (18.6%)	30 (42.9%)	16 (22.9%)	10 (14.3%)	70 (100%)
LSIL	3 (4.2%)	17 (23.9%)	19 (26.8%)	14 (20.0%)	18 (25.3%)	71 (100%)
HSIL	1 (1.4%)	5 (7.0%)	17 (23.9%)	17 (23.9%)	31 (43.7%)	71 (100%)
SCC/AC	0 (0%)	0 (0%)	0 (0%)	1 (7.1%)	13 (92.9%)	14 (100%)
Total	5 (2.2%)	35 (15.5%)	66 (29.2%)	48 (21.2%)	72 (31.9%)	226 (100%)

FOV; field of view, ASCUS; atypical squamous cells of undetermined significance, AGUS; atypical glandular cells of undetermined significance, LSIL; low-grade squamous intraepithelial lesion, HSIL; high-grade squamous intraepithelial lesion,
SCC; squamous cell carcinoma, AC; adenocarcinoma

mined to be low cellular smears, containing less than 15 abnormal cell clusters, of which large numbers (80.3%) were either ASCUS/AGUS or LSIL (Table 4). All cancer slides showed adequate cellularity. The sensitivity of the AutoPap LGS for detection diagnostic-atypical FOV in adequately cellular slides was 100%, while the sensitivity in low cellular smears was 92.5% (Table 5).

DISCUSSION

False negative outcomes make problems encompassing a delay or even curtailment of a chance for accurate diagnosis and adequate management. Aside from a sampling error, false negativity in the cytology laboratory results from the primary screening error including missing abnormal cells rather than interpretation error. To reduce false negativity and to increase the sensitivity of the primary screening, a need of the automated cytologic screening system has been raised. The AutoPap LGS is an independent computer scanning device implemented to assist and improve the practice of conventional cervical cytology by providing higher accuracy and time saving.[5,6] In this study, the sensitivity of the AutoPap LGS to detect atypicalities in successfully processed slides was 97.4% (226/232). This result was concordant to that in a recently reported study by Ronco et al., in which the AutoPap LGS showed good sensitivity (100% for squamous intraepithelial lesions and 80% for ASCUS).[7]

The AutoPap LGS showed false negative outcome (No Further Review) in 6 smears, which were diagnosed as ASCUS/AGUS (2 cases) or LSIL (4 cases) in manual review. The false negative rate in successfully processed slides was 2.6% (6/232). In a previous study about false negative cervical cytology, performed in our hospital, the

Table 4. Cytologic diagnosis of "Review" slides in different cellularity of smears

Cellularity	ASCUS/AGUS	LSIL	HSIL	SCC/AC	Total
Adequate	43 (61.4%)	44 (62.0%)	58 (82.0%)	14 (100%)	159 (70.4%)
Low	27 (38.6%)	27 (38.0%)	13 (18%)	0 (0%)	67 (29.6%)
Total	70 (100%)	71 (100%)	71 (100%)	14 (100%)	226 (100%)

ASCUS; atypical squamous cells of undetermined significance, AGUS; atypical glandular cells of undetermined significance, LSIL; low-grade squamous intraepithelial lesion, HSIL; high-grade squamous intraepithelial lesion, SCC; squamous cell carcinoma, AC; adenocarcinoma

Table 5. Sensitivity of the AutoPap LGS in different cellularity of the smears

Cytologic Diagnosis	No. of slides with FOV containing diagnostic atypical cells	
	Adequately cellular smears	Low cellular smears
ASCUS/AGUS	43/43 (100%)	26/27 (96.3%)
LSIL	44/44 (100%)	25/27 (92.6%)
HSIL	58/58 (100%)	11/13 (84.6%)
SCC/AC	14/14 (100%)	0/0 (0%)
Total	159/159 (100%)	62/67 (92.5%)

AutoPap LGS; the AutoPap Primary Screening System with Location-Guided Screening, No.; numbers, FOV; field of view, ASCUS; atypical squamous cells of undetermined significance, AGUS; atypical glandular cells of undetermined significance, LSIL; low-grade squamous intraepithelial lesion, HSIL; high-grade squamous intraepithelial lesion, SCC; squamous cell carcinoma, AC; adenocarcinoma

overall false negative rate including sampling error was 6%, and false negative rate in screening error was 1.4%.[8] Comparing the false negative rate in screening procedure of the AutoPap LGS in this study with that of manual method in that previous study, there was no superiority on the AutoPap LGS to the manual screening to decrease overall false negativity. However, there was no false negative case in HSIL or cancer smears in the AutoPap LGS. In contrast to this, false negative HSIL or SCC cases was 1.2% (12/1000 cases) in manual screening.[8] It is important not to miss HSIL or cancer in Pap screening test. In this point, the result that no case with HSIL or cancer was missed on the AutoPap LGS is worthy of attention, and suggests the superiority of the AutoPap LGS to the manual screening in high grade epithelial neoplastic lesions. The diagnostic-atypical cells were marked as FOVs by the AutoPap LGS in 221 out of 226 smears. Ten and more numbers of diagnostic FOVs were more frequent in higher degree of atypical cytologic diagnosis. In all cases but one with SCC and all 3 AC,

the AutoPap LGS provided diagnostic-atypical cells in all 15 FOV circles. This result also suggests the usefulness of the AutoPap LGS in high grade epithelial neoplastic lesions. Two atypical smears not detected as FOVs by the AutoPap LGS were composed of 1 ASCUS and 1 LSIL smears. In these cases, if reviewers examined only FOV circles, a false negative outcome would be made. To prevent these, it would be better that cytopathologists examine entire fields of the slides with a priority on FOVs rather than examine FOV circles only.

In smears with HSIL or SCC/AC, the adequately cellular cases were more frequent than that in ASCUS/AGUS or LSIL. This may be one factor contributing to the higher numbers of diagnostic-atypical FOVs in HSIL or SCC than in ASCUS or LSIL. In adequately cellular smears, all slides contained the diagnostic-atypical FOV. The sensitivity of the AutoPap LGS to localize the diagnostic-atypical cells in low cellular smears was slightly lower (92.5%) than the sensitivity of the AutoPap LGS to localize the diagnostic-atypical cells in

adequately cellular smears (100%). Either in low cellular or adequately cellular smears in this study, the sensitivity of AutoPap LGS to detect the diagnostic-atypical cells seemed to be higher than that of human screening in previous studies, in which the reported sensitivities were 57% to 83%.[9-12]

CONCLUSIONS

This study demonstrated as follows: The sensitivity of the AutoPap LGS to identify the atypical cells in successfully processed slides was 97.4%. The false negative rate of the AutoPap LGS was 2.6%. The sensitivity of the FOV in AutoPap LGS to select the diagnostic-atypical cells was 97.8%. The number of diagnostic-atypical FOVs increased in higher-degree of atypical cytology. In all adequately cellular smears the AutoPap LGS detected the diagnostic-atypical FOV. The AutoPap LGS can be a valuable system to localize abnormal cells, especially in HSIL or cancer cases.

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