Accuracy of FocalPoint GS Imaging System in Detecting Squamous Intraepithelial Lesions

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ABSTRACT

Introduction: Recently, the Food and Drug Administration approved the use of the location guided imaging system FocalPoint GS (FPGS) to assist in the primary screening of SurePath Papanicolaou (Pap) tests. A few studies have demonstrated a significant decrease in screening time and a substantial increase in the detection of squamous abnormalities. The objective of the current prospective study is to analyze the accuracy of FPGS in detecting squamous intraepithelial lesions in the clinical setting.

Materials and Methods: All SurePath Pap tests being evaluated with the assistance of FPGS during 2011 were included in the current study. False negative cases that were discovered during quality control (QC) review were retrieved. The majority of the cases that were selected for QC review were high-risk i.e. cases with previous cervical abnormalities and/or positive HPV co-testing. Only false negative cases with the final diagnosis of low-grade squamous intraepithelial lesion (LSIL) or above were included. The original 10 fields of view (FOV) were then reviewed by a senior cytotechnologist to determine if any abnormal cells were present in any of the original 10 FOVs.

Results: A total of 66,863 SurePath Pap tests were evaluated with the assistance of the FPGS imaging system during the study period. A total of 9,762 (14.6%) underwent full manual QC review. Among these cases, 105 (1.1%) cases were reclassified as LSIL or above. No abnormal cells were present in the original FOVs in 15 (14.3%) out of the 105 false negative cases. All 15 cases were reclassified as LSIL; 7 were subsequently confirmed histologically; 2 additional cases tested positive for high-risk HPV. No HSIL cases were missed by FPGS imaging system.

Conclusions: On prospective analysis, based on the results of QC review of 9,762 cases, only a small number (15/9,762; 0.15%) of abnormal squamous cells/cell clusters were not presented in the 10 FOVs by the FPGS imaging system. It is reasonable to conclude that the FPGS imaging system is relatively sensitive in detecting clinically relevant squamous cell abnormalities.

INTRODUCTION

The FocalPoint GS imaging system (FPGS) is a Food and Drug Administration (FDA) location guided imaging system which is designed to detect and present cells or cells clusters of interest within 10 selected views or field of views (FOVs). [1] For each imaged slide, a cytotechnologist then reviews the 10 FOVs. If no abnormal cells are identified within the 10 FOVs and the slide is satisfactory for intepretation, the slide is classified as negative and no further review is required. If any potential abnormalities are identified in any of the FOVs, manual screening of the entire slide will be performed. The coordinates of the 10 FOVs selected by the imaging system are saved within the system and can be retrieved at a later time allowing the re-examination of the exact FOVs evaluated by the cytotechnologist at the time of initial screening.

Our laboratory implemented FPGS for the primary screening of SurePath Pap tests in May 2009. During our quality control processes, we noted that no abnormal cells were present within the 10 FOVs in cases initially interpreted as negative, but were reclassified as squamous intraepithelial lesions or above on rare occasion during our quality control processes. The goal of this prospective study was to analyze the accuracy of FPGS in identifying squamous intraepithelial lesions (SILs) in the clinical setting.

MATERIALS & METHODS

Our laboratory processes about 80,000 Pap tests annually. Evaluation was performed by a team of 14 cytotechnologists and 6 pathologists; the latter were all board certified in both anatomic pathology and cytopathology. The study population consisted of all SurePath pap tests processed in our laboratory between Jan 2011 and Dec 2011. All SurePath Pap tests were evaluated with the assistance of FPGS. According to the manufacturer's recommended protocol, FPGS selected 15% of the highest scoring negative slides for full-slide manual screening as part of quality control (QC). The QC rescreen was performed by cytotechnologists who had not previously reviewed the slides. In addition, full slide manual screening were also performed on Pap tests that 1) were interpreted as "negative of intraepithelial lesion or malignancy" that were tested positive for high risk HPV DNA by hybrid capture II (Qiagen, Gaithersburg MD), 2) were reported to have no endocervical component by FPGS, and 3) were selected based on high-risk factors because of previous abnormal cytology or biopsy, and patient history. False negatives were defined as cases initially interpreted as negative and were reclassified as squamous intraepithelial lesions (SIL) or above after QC rescreen and subsequently confirmed by a cytopathologist. A senior cytotechnologist would then review all false negative cases on the imager microscope to determine whether the abnormal cells were in the 10 original FOVs selected by the FPGS.

RESULTS

The study population consisted of 67,230 SurePath specimens, which accounted for 82.8% of the Pap tests processed in our laboratory in 2011. All SurePath Pap tests were imaged; 59,431 (88.4%) were reported as negative, 4,644 (6.9%) as ASC, 2,230 (3.3%) as LSIL, 154 (0.2%) as HSIL or above, and 140 (0.2%) as unsatisfactory. A total of 14,711 (24.8%) SurePath specimens initially classified as negative were subjected to QC review. During the QC review, 105 (0.71%) cases were reclassified as SIL or above. Thus, 4.4% (105/2384) of SIL+ cases reported were initially false negative cases. Among these cases, abnormal cells were not identified in the 10 FOVs in 15 (14.3%) cases. All 15 cases were reclassified as LSIL. HR-HPV testing was performed in 10 cases and was positive in 8 cases including 6 co-testing and 2 reflex testing. Histologic follow up was available in 9 cases; mild dysplasia/CIN I was noted in 7 cases; the remaining 2 cases were negative for dysplasia. No HSIL+ cases were missed by FPGS. In those cases in which FPGS failed to detect the LSIL cells, the average number of dysplastic squamous cells per slides was 19 (**Table 1**). **Figure 1** shows an example of a classic koilocyte (**A**, Pap stain; 400X), dysplastic cells (**B**, Pap stain; 400X), and cervical biopsy follow up of the same case (**C**, H&E stain; 200X).

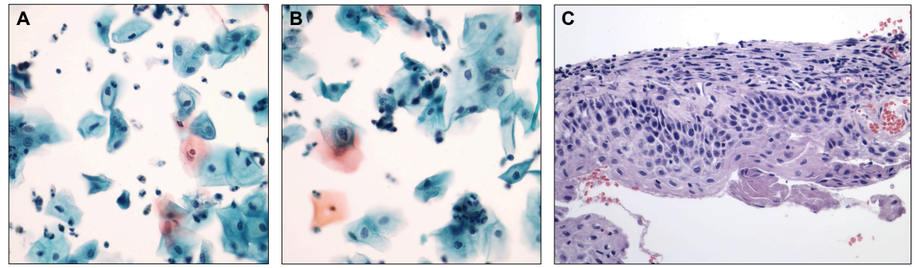

Figure 1. A case from our study showing classic koilocytes (**A**, Pap stain, 400X), and a dysplastic cell (**B**, Pap stain, 400X) missed by FPGS. The follow up cervical biopsy (**C**, H&E, 200X) confirms LSIL.

Table 1. Clinico-cytologic characteristics of 15 cases with HPV status and surgical follow up

Case No.	Age	Prior History of Abnormal Pap	Diagnosis	HPV result	Surgical Followup	Koilocyte #	Dysplastic Cell #
1	21	Yes	LSIL	NA	NA	8	36
2	47	No	LSIL	Positive	HPV	2	9
3	22	Yes	LSIL	NA	NA	5	15
4	25	Yes	LSIL	Positive	CIN I	3	25
5	27	Yes	LSIL	Positive	CIN I	1	7
6	49	Yes	LSIL	Negative	Negative	0	4
7	32	Yes	LSIL	Positive	CIN I	1	8
8	42	No	LSIL	Positive	CIN I	0	22
9	51	Yes	LSIL	Positive	NA	1	22
10	27	Yes	LSIL	Negative	NA	3	33
11	32	Yes	LSIL	Positive	NA	3	28
12	47	Yes	LSIL	NA	NA	1	11
13	36	Yes	LSIL	Positive	CIN I	2	52
14	31	Yes	LSIL	Positive	CIN I	5	28
15	25	Yes	LSIL	NA	CIN I	1	12

DISCUSSION

Since FocalPoint GS imaging system approval in 2008 by FDA, there have been only a few U.S. studies evaluating the performance of this system in detecting epithelial abnormalities.[2, 3] The clinical trial of FPGS was conducted in 4 diverse laboratories and included 12,313 SurePath Pap.[2] The result of clinical trial demonstrated an increase in sensitivity of detecting HSIL+ and LSIL+ lesions by 20% and 10%, respectively, using FPGS when compared with manual screening. The clinical trial also reported that 1 (7.6%) cancer, 3 (1.9%) HSIL, and 39 (6.8%) LSIL based on adjudicated diagnoses were classified as negative using FPGS, i.e. 5.7% (43/743) SIL+ cases were initially classified as negative using FPGS.[1, 2] The false negative "cancer" case was indicated for a full slide review by FPGS because of "insufficient squamous cellularity"; the slide was subsequently classified as "negative" by the cytotechnologist after the full-slide manual review. In a more recent study, our group reported that the false negative fraction decreased from 1.39% to 0.88% after the implementation of FPGS; this represented a 37% drop (student t-test, $p < 0.001$).[3] However, we did not separate cases that were related to the failure of the imaging system to locate the diagnostically relevant cells in the 10 FOVs from those due to interpretation errors. In the current study, we reported that 105 (0.71%) case, that were initially classified as negative by the primary screening technologists, were reclassified as SIL or above during QC review. Thus, the estimated false negative fraction (EFNF) of the current study is comparable to the result of our previous study and was approximately of half the rate (1.39%) reported before the implementation of FPGS and identical QC rescreening methods in our laboratory.[3] Since not all negative cases undergo QC rescreening and the selection was biased toward high-risk cases, the actual false negative rate may be actually lower from the estimate. It is interesting to point out that 2 of the 15 cases were selected for QC review because they were tested positive for high risk HPV as part of the cotesting. A recent study pointed out that the inclusion of negative Pap Slides tested positive for high risk HPV in the QC review resulted in a significant increase in the detection of SIL than routine QC review that did not include such cases.[4]

In 15 (14.3%) cases, dysplastic squamous cells were found outside the 10 FOVs, i.e. automated location errors, accounting for 0.1% of all cases under QC review. Because 25% of our negative cases were selected for rescreening, the estimated actual false negative rate for SIL as a result of automated location error was 2.5% (59/2,384). The remaining false negative cases were due to interpretative errors of the primary screeners.

Our results showed that only a small percentage of false negative cases were due to location errors, i.e. abnormal cells were not detected and present in the original 10 FOVs by the FPGS, indicating that the sensitivity of FPGS detecting potentially abnormal cells in the 10 FOVs is comparable or may be more superior to manual screening.

CONCLUSIONS

- In the current study estimated actual false negative rate for SIL as a result of automated location error was of FPGS system was 2.5% (59/2,384).
- Sensitivity of FPGS detecting potentially abnormal cells in the 10 FOVs is comparable or may be more superior to manual screening.

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