

Preliminary experimental results from multi-center clinical trials for detection of cervical precancerous lesions using the CerviscanTM system: a novel full-field evoked tissue fluorescence based imaging instrument

A. K. Dattamajumdar¹, D. Wells¹, J. Parnell¹, J.T. Lewis¹, D. Ganguly¹ and T.C. Wright Jr.²
¹LifeSpex, Inc., Bothell, WA 98021, ²Columbia University, New York, NY 10032

Abstract- Cervical cancer is an important cause of death in women worldwide, accounting for 190,000 deaths annually. Women are currently screened for cervical cancer using Pap smear – an imperfect technology with poor sensitivity and specificity. Furthermore, 5-10% of the Pap smear studies result in uncertain findings called ASCUS. These patients are subjected to repeat Pap smears to determine women who need further examination by colposcopy. LifeSpex, Inc. is developing the CerviscanTM system – a novel, full-field multi-spectral tissue fluorescence imaging system that is designed to detect cervical precancerous lesions (i.e. SIL) in real-time. We report preliminary results from a multi-center trial for evaluating the performance of CerviscanTM system. A study population of 67 subjects, in three clinical sites in the US and Canada, each underwent three procedures i.e. (a) repeat liquid-based Pap smear, (b) CerviscanTM exam, and (c) colposcopy directed biopsy exam (gold standard). Fifty-two patients for whom data from all three exams were available (i.e. 78% of the patients enrolled) are included in this preliminary analysis. A multivariate classification algorithm has been trained using data from 228 regions (82 SIL, 146 NonSIL) in 42 women. Results are reported on an independent test set of 70 regions (25 SIL, 45 NonSIL) in 10 women. The CerviscanTM system correctly identified 21/25 SIL and 42/45 NonSIL regions, giving a sensitivity of 84% and specificity of 93.3%. The CerviscanTM system correctly resolved 5/7 ‘ASCUS+LoSIL’ calls made by repeat liquid-based cytology. Furthermore, the CerviscanTM system detected 2 patients with precancerous lesions that had been missed by the repeat liquid-based cytology. The CerviscanTM system detects precancerous lesions with higher accuracy than repeat liquid-based Pap smear and locates lesion in real-time. The CerviscanTM system has the potential of providing a tool that permits better patient management.

I. INTRODUCTION

Cervical cancer is an important cause of death in women worldwide, accounting for 190,000 deaths annually. Women are currently screened for cervical cancer using Pap smear – an imperfect technology with 58% sensitivity and 69% specificity [1]. Furthermore, 5-10% of the Pap smear studies result in uncertain findings called “Atypical Squamous Cells of Undetermined Significance” or ASCUS. These patients are subjected to repeat Pap smears at 3-9 month intervals to determine whether these women need further examination by an expert procedure called colposcopy. This lack of immediate feedback from ASCUS readings leads to anxiety for these women.

Cervical tissue fluoresces when excited at spectral regions in the Ultraviolet-Visible (UV-Vis) region. As the health of the cervical tissue changes from normal healthy tissue towards cancerous tissue, the fluorescence response of the cervical tissue varies in overall intensity and spectral content. This evoked fluorescence change as the tissue state changes

is the basis of LifeSpex Inc.’s evoked tissue fluorescence (ETFTM) technology for cervical cancer screening [2]. LifeSpex Inc. is developing a multi-spectral tissue fluorescence imaging system (CerviscanTM) for detecting cervical squamous intraepithelial lesions (SILs) with high accuracy. The goal is to provide an instrument that can be used to triage women whose Pap smears have been read as ASCUS/LoSIL to determine which women need further examination by colposcopy.

In the implementation of LifeSpex’ ETFTM technology for cervical cancer screening (i.e. CerviscanTM), the cervix is excited at multiple spectral regions in the UV-Vis spectrum using a combination of Xenon lamp and excitation bandpass filters. This process ensures that vast majority of the bio-fluorophores involved in cervical malignancies are excited. The incident energy is irradiated on a 507 mm² area of the ectocervix via a disposable tissue contact element. The ETFTM emitted as a result of these multiple excitations are processed for a robust determination of the health of the cervical tissue. The CerviscanTM ETFTM data is four dimensional in nature i.e. two spatial dimensions and two wavelength dimensions (excitation and emission spectral regions).

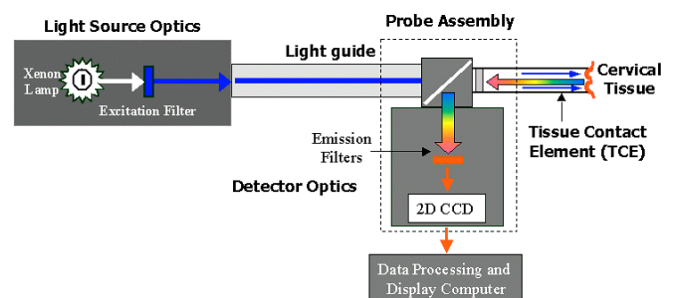


Fig 1. Multi-spectral tissue fluorescence imaging system (CerviscanTM) for detecting cervical squamous intraepithelial lesions.

A pilot study was performed to determine the safety and effectiveness of the CerviscanTM system when used as a triage tool in women with ASCUS or LSIL Pap smears. The specific aims of the study were to determine the performance of the CerviscanTM system for detection of SIL. The second goal of the study was to determine the performance of the CerviscanTM system as a triage tool to resolved which patients with ASCUS/LoSIL reads on their previous Pap smears need to examined further by colposcopists. Histopathology of colposcopy directed biopsies were the gold standard for these studies.

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II. METHODS AND MATERIALS

The instrument is currently undergoing multi-center clinical trials in the US and Canada. This report includes data from the first 52 consecutive patients in whom complete data is available representing 78% of all women enrolled in the trial. All women were referred for colposcopic evaluation on the basis of an abnormal Pap test. Women had a repeat liquid-based Pap test obtained and then were examined using the CerviscanTM device. A colposcopic examination that usually included a cervical biopsy was then performed. The colposcopists provided their impression of regions with and without squamous intraepithelial lesion. Cervical biopsies were diagnosed using a "consensus pathology" approach. The clinical procedure flow diagram is shown in Figure 2.

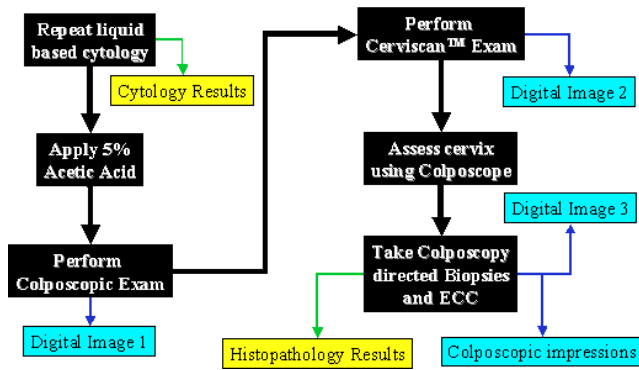


Fig 2. Flow diagram of the clinical procedure for evaluating the safety and effectiveness of the CerviscanTM system.

Data from 298 regions (97 biopsies) were analyzed from the 52 patients are included in this analysis. Patients were randomly assigned to be in either the training group (80% of all patients) or the testing group (20%). The partitioning of the data is shown in Table 1. The LifeSpex tissue classification algorithm uses a multivariate stochastic training algorithm to estimate the relation between the tissue state and fluorescence response. The clinical trial data has two components to it, viz., (1) ETFTM spectral data, and (2) histopathology of excised tissue samples (i.e. the "gold standard"). The algorithm was trained using proprietary methods to use the ETFTM spectral data to classify the cervical tissue into the tissue-states identified by histopathology. The iterative training process was stopped at a stage when the average RMS error of prediction was below a specified amount. The result of the training was a lookup table that contained classification coefficients, equations relating the coefficients and classification thresholds. The lookup table was applied independently to the testing set and the classification performance assessed.

TABLE 1
DATA FOR ANALYZING PERFORMANCE OF CERVISCANTM SYSTEM

Tissue Type	Number of Patients	Number of Regions	Number of NonSIL	Number of SIL
Training Group	42	228	146	82
Testing Group	10	70	45	25

The resulting algorithm model was applied to the ETFTM spectral data and a disease index map showing the SIL vs. NonSIL classification of the full-field image of the cervix was performed. These images were used to determine the presence and extent of precancerous lesions on the cervix. For each patient, the result of cytology on the repeat liquid-based Pap smear was compared with those from the colposcopy directed biopsy (i.e. gold standard) to determine the 'true status' of the subject's cervical tissue. A similar comparison was performed for the results of CerviscanTM system. These results were compared to determine the effectiveness of Cerviscan as a triage tool to effectively resolved those women whose Pap smears were read as ASCUS/LoSIL.

III. RESULTS

The results of applying the trained algorithm on a testing data set of 10 patients are shown in Figure 3. The instrument correctly identified 21 of the 25 SIL regions for a sensitivity of 84%, while 42 of the 45 NonSIL regions were correctly identified for a specificity of 93.3%. The results of applying the algorithm to one of the testing patients are shown in Figure 4. The left image shows a gray scale image of the cervix with the colposcopic impressions outlined in black. The subject has a large low-grade precancerous lesion (LoSIL). This was confirmed by three biopsy samples as shown in Figure 4. The right image shows the CerviscanTM output showing the presence and extent of the precancerous lesion in red superimposed on the gray-scale image of the cervix. As seen Figure 4, the CerviscanTM output tracks the colposcopist's impressions.

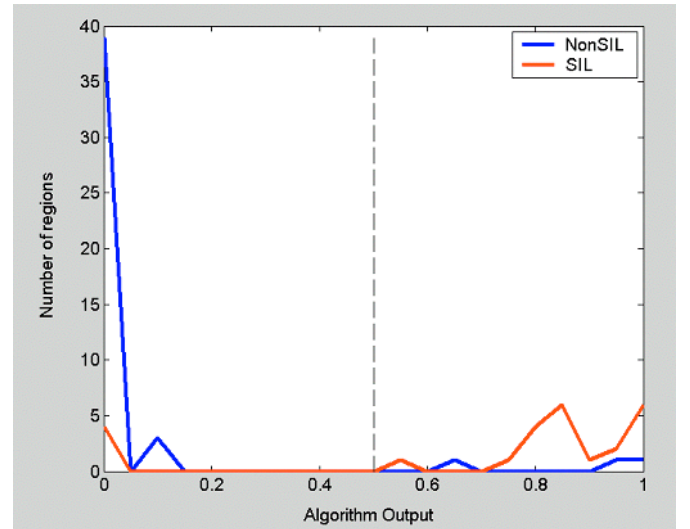


Fig 3. Results of applying SIL vs. NonSIL algorithm to independent testing data from 10 patients. The SIL regions (red plot) were separated from the NonSIL region with a 84% sensitivity and 93.3% specificity. The optimal classification threshold was determined from ROC analysis of training data.

The results of cytology analysis of the repeat liquid-based Pap smear are summarized in Table 2. Of the 10 patients in the testing set, 5 patients had uncertain findings (i.e. ASCUS), 2 patients had low grade precancerous lesions and

the remaining 3 subjects did not have any precancerous cervical tissue. Colposcopy directed biopsy (i.e. gold standard) showed that of the 5 patients with ASCUS, 3 had precancerous lesions and two did not have precancerous lesions. The two patients with low-grade precancerous lesions were confirmed by colposcopy directed biopsy. Of the three patients called to be normal by repeat Pap smear, two patients had low-grade precancerous lesions while one was normal as determined by colposcopy directed biopsy.

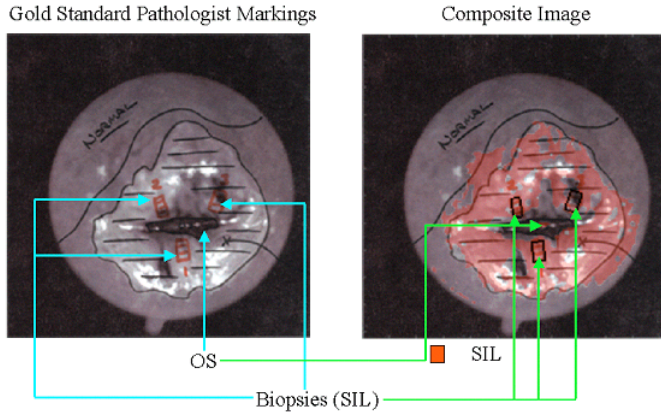


Fig 4. Result from Cerviscan™ examination of a patient in the test set. The left image shows a gray scale image of the cervix with the colposcopic impressions outlined in black. The right image shows the Cerviscan™ output showing the presence and extent of the precancerous lesion.

Cerviscan™ output correctly resolved three of five ASCUS cases correctly, while miscalling two cases to be normal. The two cases with low-grade precancerous lesions were called correctly. Significantly, the patients called to be normal by repeat Pap smear, were correctly determined by Cerviscan™ output to be two patients with low-grade precancerous lesions and one with normal cervical tissue.

TABLE II

COMPARISON OF PATIENT BASED RESULTS OF REPEAT LIQUID BASED CYTOLOGY, CERVISCAN™ SYSTEM AND COLPOSCOPY DIRECTED BIOPSY.

Liquid-based Repeat-Pap Cytology Results*	Gold Standard (Colposcopy directed Biopsy)*	Cerviscan™ system (correctly resolved cases)*
ASCUS: 5	3 SIL, 2 NonSIL	1 SIL, 2 NonSIL, (2 SIL cases miscalled)
LoSIL: 2	2 LoSIL	2 SIL
NonSIL: 3	2 SIL, 1 NonSIL	2 SIL, 1 NonSIL

*Results are shown in terms of number of patients

IV. CONCLUSIONS

Initial results from this multi-center trial indicate that the Cerviscan™ system detects precancerous cervical lesions with a high degree of sensitivity & specificity. The system presents a full field image of the cervix identifying regions of precancerous lesion, present on the visible portion of the cervix, in real-time. Furthermore, the Cerviscan™ system has the potential of being a valuable tool for triaging women whose Pap smear cytology results are of the ASCUS/LoSIL grade.

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