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Dynamic Spectral Imaging: Improving Colposcopy

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Abstract

Purpose: Colposcopy occupies a key role in the prevention of cervical cancer by identifying preinvasive or invasive lesions. However, colposcopy is subjective and is responsible for 52% of screening failures. Dynamic spectral imaging (DSI) is based on the objective, quantitative assessment of the acetowhiteening effect. This study compared DSI with colposcopy.

Experimental Design: Women referred for colposcopy were examined simultaneously with colposcopy and DSI using a precommercial DySIS model (FPC-03) in an international, multicenter trial. The colposcopy impression and DySIS values were compared with consensus histology reports of biopsies. Subjects were recruited to a training group and subsequently to a test group. Measures were taken to avoid verification bias.

Results: The training and test groups comprised 82 and 308 eligible women, respectively. A cutoff value to identify high-grade disease was selected from the results of the training group and data from previous work. Receiver operator curve analysis of the test data showed an area under the curve of 0.844. DySIS detected 62.9% more high-grade cases than colposcopy (57 versus 35, \( P = 0.0001 \)). DySIS exceeded end points approved by the Food and Drug Administration for similar studies, with increments in the true positive rate of 22/308 (7.1%; lower 95% CL, 4.5% versus 2%) and in the false positive rate of 32/308 (10.4%; upper 95% CL, 14.7% versus 15%).

Conclusions: DySIS is more sensitive than colposcopy in detecting high-grade lesions and can provide improved guidance for biopsy. The results are obtained in a user-independent fashion, making it suitable for use by nursing personnel.

The prevention of cervical cancer is a major health care issue throughout the World. In Europe, cytology screening has reduced the incidence and mortality to historically low levels but the more recent reversal of these changes in some European countries indicates the need to improve the quality of the program (1). Although immunization against some high-risk types of human papillomavirus may reduce the incidence of cervical cancer in the future, it will be essential to maintain a high-quality screening program to detect lesions not prevented by vaccination. In one study, vaccination reduced high-grade cervical intraepithelial neoplasia (CIN) by only 27% in HPV16/HPV18-negative young women (2). The introduction of more sensitive screening tests will be crucial to provide the best cost-effectiveness ratio (3).

The management of women with abnormal screening results or suspicious symptoms is determined by colposcopy, but this is a subjective technique performed by highly trained personnel. Currently, approximately 124,000 women in England (4) and nearly 3 million women in the United States (3) are referred every year for colposcopy. However, the efficacy of the entire diagnostic chain is constrained by the low sensitivity of colposcopy (3, 5–9) and by low levels of intraobserver and interobserver agreement (10). As a result, colposcopy is responsible for 52% of screening failures, including missed lesions, unnecessarily repeated tests, and diagnostic delays (11).

To fully exploit the benefit of increased screening sensitivity, the performance of colposcopy must be improved (3). Dynamic Spectral Imaging (DSI) and the Dynamic Spectral Imaging system (DySIS), developed by C. Balas (12–15), has given promising results in initial studies of the quantitative measurement and mapping of the dynamic light-scattering characteristics of epithelium treated topically with acetic acid as used routinely in colposcopy. Acetic acid transiently alters the

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Note: This clinical investigation was set up and conducted in accordance with ISO 14155:1-2003 and the Declaration of Helsinki.

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The basis of colposcopy is the acetic acid–induced transient alteration of the light-scattering properties of abnormal epithelium such that it turns white. Acetowhiteness is observed in several conditions including cervical intraepithelial neoplasia, and in several physiologic and benign conditions. Discriminating between these conditions with conventional colposcopy is difficult and is the main reason for its poor performance.

Dynamic spectral imaging produces a user-independent, quantitative measurement and mapping of the effects of acetic acid. This promises greatly improved discrimination between high-grade cervical intraepithelial neoplasia (the precursors of cervical cancer) and lesions with little or no malignant potential. Replacing conventional colposcopy with dynamic spectral imaging—based instruments could greatly enhance the diagnostic stage of the cervical cancer prevention program, reducing missed lesions and diagnostic delays.

Translational Relevance

Approximately 3 million women are referred for colposcopy every year in the United States as part of the cervical cancer prevention program. The purpose of colposcopy is to identify preinvasive and early invasive cervical carcinoma. However, colposcopy is subjective and has low sensitivity (55-65%) and specificity (70-90%), and is responsible for 52% of screening failures, including missed lesions, unnecessarily repeated tests, and diagnostic delays. There is a pressing need to improve on this performance.

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Materials and Methods

Study design and participants. The study was a prospective, multicenter, nonrandomized, paired clinical trial. It was conducted in collaboration with Imperial College, London, United Kingdom and the First Gynecological Clinic of the Athens Medical School, Athens, Greece. The trial took place in the colposcopy clinics of Hammersmith Hospital and St Mary’s Hospital, London, United Kingdom, and at the Alexandra Hospital, Athens, Greece. The protocol of the study was approved by the relevant ethics committees.

Consecutive women referred to these colposcopy clinics because of an abnormal cervical smear or symptoms suggesting the possibility of cervical neoplasia were invited to participate in this study. The inclusion criteria were a cervical smear showing squamous or glandular cell dyskaryosis or borderline nuclear change (ASCUS or AGUS); or symptoms of postcoital bleeding, postmenopausal bleeding, or intermenstrual bleeding. All subjects gave written, informed consent. The exclusion criteria were self-referring women without an abnormal smear, an inadequate or an inflammatory smear, any other clinical indication for referral to colposcopy, pregnancy, previous pelvic radiotherapy, or any woman for whom any prolongation of the examination was thought to be inadvisable.

Procedures. The DySIS instrument enables the user to perform both standard colposcopy and DSI examination and mapping of every image pixel of the cervix. The optical head provides uniform illumination with a focused and collimated white light-emitting diode, and imaging with magnification optics coupled to a 1,024 × 768, 8-bit/channel digital color CCD camera (Fig. 1A). The camera is interfaced with a computer and control electronics unit and with a TFF monitor for image and data display. To reduce surface reflections that might obscure the acetowhiteness effect, linear polarizers are placed in both the imaging and illumination pathways, with their polarization axes perpendicular to each other. The optical head has a typical working distance of 25 cm and does not come in contact with the tissue. It captures images from a 23 mm × 20 mm area, including the transformation zone of the cervix.

In the precommercial model used in this study, the optical head was mounted on a mechanical arm to position and stabilize it, and locked onto an extension shaft attached to the speculum, to ensure a stable field-of-view during imaging acquisition. A syringe was used to spray 2 mL of 3% acetic acid onto the cervix through a nozzle mounted on the extension shaft. After capturing a reference image, application of acetic acid starts the image-capturing procedure automatically. A series of images is then captured automatically every 5 s for 240 s and stored in the computer and control electronics unit. The software performs automatic image alignment with pixel accuracy to compensate for movement during the scan. Changes in the diffuse reflectance over time are calculated for every image pixel, approximately corresponding to the area occupied by a single cell. Parameters such as the diffuse reflectance versus time integral are calculated through curve modeling and fitting and their spatial distribution is displayed as a PseudoColor Map (PCM) overlaid onto the image of the cervix (Fig. 1C). Diffuse reflectance versus time curves and their integral value (termed the CB parameter) can be displayed for every pixel selected by the operator (Fig. 1D). Exploratory clinical studies showed that the CB parameter was optimal for discriminating high-grade CIN. The operator can annotate atypical areas on the PCM or the reference image as colored circles to guide biopsy sampling (Fig. 1C). DySIS includes a database to store clinical details with the images and data collected during the examination. This facilitates objective follow-up.

In this study, the DySIS examination was done by one colposcopist while a second did a colposcopic assessment using a separate video monitor displaying the images of the cervix captured by the DySIS system but without the DySIS CB curves and PCM. Ferris and colleagues have shown that diagnostic accuracy is maintained when colposcopic images are viewed on a separate monitor by a colposcopist who is not able to direct the colposcopic examination or request enlarged images of specific lesions (16). Lugol’s iodine was not used in that study. Both colposcopists had access to the woman’s history and the reason for referral. All colposcopists who participated in the trial were experienced practitioners. The U.K. colposcopists were all accredited by the British Society for Colposcopy and Cervical Pathology and had at least 2 years experience in busy clinics. The Greek colposcopists were similarly experienced. Most colposcopists in all three sites had more than 5 years’ experience and several had more than 10 years experience—some substantially more. The DySIS device was operated by the colposcopy staff without technical assistance.

During data acquisition, the second colposcopist completed a colposcopic form and marked the areas on a diagram the areas for biopsy. The DySIS user was guided by the PCM and marked the areas with the highest CB values with a colored circle (Fig. 1C). Both also selected sites
that did not seem to contain CIN in order to reduce verification bias (17). The PCM and the chosen biopsy points were then turned off and the independent colposcopist indicated the colposcopy biopsy points on the image which were marked with a circle of a different color. Thereafter, the PCM was toggled on again, making both sets of biopsy points visible. The DySIS user took biopsies from all these points (Fig. 2). When the selected sites coincided, a single biopsy sample was collected. The software stored a video of the biopsy sampling procedure to confirm that the sample was taken from the correct location.

The initial histologic report was provided by institutional pathologists. All diagnostic biopsies and any subsequent treatment or follow-up biopsies were evaluated independently by two accredited histopathologists (C.H. Buckley and K. Pavlakis) not associated with the hospital in which the biopsies had been taken or originally assessed. C.H. Buckley reviewed the U.K. biopsies and K. Perryman reviewed the Alexandra biopsies. Any differences were resolved by a third histopathologist. Two (R. Dina and V. Healy) of the three reviewers who provided the third opinion when there was disagreement between the first two reports were from the U.K. institutions taking part but they reviewed only material from the other hospital. Only 16.5% of biopsies needed to be sent for a third opinion. Histopathologists were unaware of the DySIS result and the histopathology reports of the other pathologists. The final diagnosis was determined by the majority opinion.

Data management and statistical analysis. The DySIS cutoff value used to identify high-grade disease was to be decided from the data from the first 100 subjects and the experience of earlier studies (training group). The accuracy of this cutoff value was to be compared with colposcopy in the remaining patients (test group).

The original power calculation was based on a meta-analysis of eight studies suggesting that the sensitivity and specificity of colposcopy in diagnosing high-grade CIN were 79% and 67%, respectively (18). To
show that the sensitivity of DySIS was not more than 9 percentage points less than colposcopy would require 293 subjects, and that DySIS improved on the 67% specificity of colposcopy to 80% would require 143 subjects (80% power, 5% alpha, 20% correlation coefficient for failure between paired values). In view of these figures, the study aimed to recruit 300 eligible subjects to the test group. Data published after these calculations were done suggested lower sensitivity for colposcopy with values of 50% to 65% when the prevalence of high-grade CIN is low (5–9, 19, 20). These new data suggested that the power of the study would be greater than first calculated.

All the results were delivered to the principal investigator and entered in the study database (Lotus Approach, IBM) before being sent to Forth Photonics. The primary study end points were the incremental DySIS test characteristics over conventional colposcopy using histology as a reference. The estimates of sensitivity and specificity of the different tests were made more reliable because the risk of verification bias was reduced by taking random biopsies from what was believed not to be CIN and including follow-up or treatment biopsy results (17). Receiver operator characteristic curve analysis was used to choose an appropriate cutoff value from the training group and to evaluate the overall performance of DySIS in the test group. Fisher’s exact test with two-sided P values was used to evaluate the differences in the number of cases correctly identified by the different tests. The analysis was done by the principal investigator using StatsDirect version 2.6.5.

During the course of this trial, the U.S. Food and Drug Administration approved study end points for electro-optical devices positioned as an adjunct to colposcopy. These were that the device should produce an increment in the true positive rate greater than 2 percentage points as measured from the lower 95% confidence interval (21). The increment was defined as the number of true positive subjects additional to colposcopy divided by the total number of subjects. The device should also produce an increment in the false positive rate less than 15 percentage points as measured from the upper 95% confidence interval. The increment was defined as the number of false positive subjects additional to colposcopy divided by the total number of subjects. Performance characteristics of DySIS were also compared with these end points.

Role of the funding source. The study was funded by Forth Photonics who contributed to the study design and the writing of the report. The collection and collation of the data were supervised by the principal investigator and corresponding author. The analysis of data was undertaken by the principal investigator. The decision to submit the report for publication was taken jointly by all the authors.

Results

In all, 529 women were recruited to the trial during the period May 2004 to July 2005. Of these, 82 eligible women were recruited to the training group from May to July 2004. A receiver operator characteristic curve of these data and from previous work was used to choose a cutoff value of 553 CB units to be employed in the main part of the study.

Subsequently, 447 women were recruited to the test group between August 2004 and July 2005. From this number, 139 women were excluded, leaving 308 women eligible. Software problems in the initial months of the trial resulted in 15 women being excluded. No biopsy was taken from 23 women. The view of the cervix was unsatisfactory in 45 women, largely due to the size and design of the speculae initially adapted for the instrument. Of the remaining excluded women, 6 were not eligible, 5% acetic acid was used in 1, a data form was lost in 1, biopsy slides from 5 were lost before review, blood or mucus obscured part of the cervix in 1, biopsies were taken from the wrong point in 3, and excessive movement prevented a reliable

### Table 1. Performance characteristics of DySIS, colposcopy, and referral smear

<table>
<thead>
<tr>
<th></th>
<th>Cytology, no. (rate %)</th>
<th>Colposcopy, no. (rate %)</th>
<th>DSI, no. (rate %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>38 (12.5)</td>
<td>35 (11.4)</td>
<td>57 (18.5)</td>
</tr>
<tr>
<td>False positive</td>
<td>33 (10.9)</td>
<td>25 (8.1)</td>
<td>57 (18.5)</td>
</tr>
<tr>
<td>True negative</td>
<td>199 (65.7)</td>
<td>211 (68.5)</td>
<td>179 (58.1)</td>
</tr>
<tr>
<td>False negative</td>
<td>33 (10.9)</td>
<td>37 (12.0)</td>
<td>15 (4.8)</td>
</tr>
<tr>
<td>Sensitivity (95% CI)</td>
<td>0.53 (0.41–0.65)</td>
<td>0.49 (0.37–0.61)</td>
<td>0.79 (0.68–0.88)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>0.86 (0.81–0.90)</td>
<td>0.89 (0.85–0.93)</td>
<td>0.76 (0.70–0.81)</td>
</tr>
<tr>
<td>Diagnostic OR</td>
<td>6.88</td>
<td>7.91</td>
<td>11.81</td>
</tr>
</tbody>
</table>

Fig. 2. A punch biopsy is taken from the area marked by the purple circle (A). The biopsy site can be seen (bottom) with the purple circle superimposed (B), confirming an accurate biopsy.

Table 1. Performance characteristics of DySIS, colposcopy, and referral smear

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measurement in 2. Problems with the application of acetic acid affected 37 women. This occurred almost exclusively at Hammersmith due to a batch of faulty disposable nozzles through which the acetic acid was delivered. No adverse events were reported. The few device failures resulted in either a cancelled examination or unsaved data. In no case did they present a danger to the patient. Colposcopy was described as unsatisfactory in 65 cases because the squamocolumnar junction was not clearly visible. These women were not excluded from the study.

The median age was 37 years (upper and lower quartiles, 29-46). Only 12 women were included because of symptoms. The remaining 296 had abnormal smears. A total of 603 punch biopsies were suitable for comparison with the DySIS data. Of these, 102 were high-grade disease or worse. Treatment biopsies from 86 women and follow-up biopsies from 15 women were included. Two review visit biopsies and three treatment biopsies were excluded because they were not reviewed. These exclusions did not alter the final diagnosis in any case. In all, 72 (23.4%) of the 308 women were found to have high-grade disease or worse. Of these, 43 had CIN III, 1 had adenocarcinoma in situ, and two had microinvasive squamous cell carcinoma. No women with clinically apparent cancer were included.

It was assumed that normal practice would include taking biopsies from lesions thought to be CIN I and from areas with CB values of 500 to 552 CB units. High-grade disease was found in 10 women as a result of 155 such biopsies from 122 women. Verification bias was reduced by random biopsies taken from 115 sites thought by the colposcopist to be normal, metaplasia, or human papillomavirus infection or with CB values less than 500, and 101 treatment or follow-up biopsies. These identified 10 of the women with high-grade disease: 9 of the 37 cases of false negative colposcopy and 4 of the 15 cases of false negative DySIS (there were three cases with both false negative colposcopy and false negative DySIS).

The performance of DySIS in identifying high-grade CIN or invasion was assessed on a per patient basis with a receiver operator characteristic curve. The area under the curve was 0.844 (95% confidence intervals, 0.797-0.892), indicating a good overall performance. Using the CB cutoff value of 553, DySIS detected significantly more high-grade cases than either colposcopy (57 versus 35; Fisher’s exact two-sided test, \( P = 0.0001 \)) or referral cytology (57 versus 38; Fisher’s exact two-sided test, \( P = 0.0013 \); Table 1). With a diagnostic odds ratio of 11.8, the overall performance of DySIS is better than colposcopy and cytology (7.9 and 6.9, respectively). The sensitivities of colposcopy and DySIS were 48.6% and 79.2%, respectively. If the cases of high-grade disease detected by biopsies taken to limit verification bias were excluded, the sensitivities would have seemed to be 55.6% and 83.8%, respectively. DySIS met the Food and Drug Administration criteria with an increment in the true positive rate of 22/308 (7.1%; lower 95% CI, 4.5% versus 2%); and an increase in the false positive rate of 32/308 (10.4%; upper 95% CI, 14.7% versus 15%). These values are not affected by verification bias.

Four women were referred with AGUS Pap smear. One had adenocarcinoma in situ and one CIN III. Both of these had abnormal DySIS. The remaining two had only CIN I and neither had abnormal DySIS results. In this study, 28 women were over 50 years old. Of these, 9 were over 60 years. Of the 28 women over 50 years old, 8 had high-grade disease and 7 were detected by DySIS. Of the 20 without high-grade disease, 16 were correctly categorized by DySIS. Although women referred with only inflammatory changes in the smear were excluded, many had inflammatory changes on the cervix but a more marked cytologic picture. Cervicitis did not affect the interpretation as areas of high-grade CIN were clearly seen as distinct areas with high CB values.

**Discussion**

This trial used the precommercial DySIS model, FPC-03, and identified certain difficulties with this first prototype. Nevertheless, the process of correcting these unexpected difficulties provided an opportunity to improve the device, and despite these problems, DySIS performed well and illustrated the advantages of DSI and its clinical potential. The current commercial version of DySIS is expected to perform even better than the one used in this study because several technical problems have been identified and overcome.

The better sensitivity of DySIS improves the detection of high-grade disease and guides biopsy sampling (Fig. 3). DySIS showed a relative gain in sensitivity of 62.9% over colposcopy.

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Fig. 3. A, a high-grade biopsy taken from a white area on the PCM. B, a biopsy from a blue area on the PCM showing only viral changes and an inflammatory infiltrate in the stroma.
and exceeded study end points approved by the Food and Drug Administration for true positive and false positive rates (21). It might be thought that the results for colposcopy described here are not representative of those usually reported. However, the reported accuracy rates for colposcopy vary hugely. The factors that have the greatest potential effect on accuracy are the prevalence of disease, verification bias when no biopsies are taken from colposcopically negative sites on the cervix, inclusion of CIN I in the definition of abnormal, and whether the colposcopic impression or the biopsy is used as the end point. Had the data that reduced verification bias in this study been ignored, the sensitivity of colposcopy would have seemed to be 55.6% rather than 48.6%. The former rate compares favorably with studies of the accuracy of the colposcopic impression with a similar prevalence of disease, some of which have no correction for verification bias (5–9, 17, 19, 20, 22).

A variety of optical technologies have been evaluated clinically over the past two decades. Fourier transform IR spectroscopy and Raman spectroscopy have been applied mainly to smears or biopsy samples and are not well-suited to in vivo application (23–26). Optical coherence tomography has been used in vivo but postmenopausal women gave misleading results (27). In common with some other techniques, the instrument used had to be touched onto the cervix to take a measurement from one point in each quadrant in turn. Although not using optical technologies, two other instruments that take point measurements from the cervix have been investigated (28, 29). Both show promising results but are unable to allow visualization of the lesion, a problem inherent in all such devices. They are probably better suited to screening in low resource settings. Recently, two clinical studies have evaluated the performance of combined reflectance/fluorescence imaging spectroscopy in detecting high-grade CIN in vivo. Both of these, like DySIS, image the whole cervix. In one study, the imaging device was operating as an adjunct to conventional colposcopy and 22% more high-grade cases were detected compared with colposcopy (21). This may be compared with the 62.9% more cases detected by DySIS used as a stand-alone instrument. In the second study, the sensitivity of cervical spectroscopy was 95.1% but the specificity was a disappointing 55.2% (30). These poor results may be attributed to the fact that fluorescence and reflectance spectroscopy indicate changes in the stroma rather than the epithelium where the lesion is located.

DySIS clearly exceeds the performance of conventional colposcopy even when the latter is operated by experts. It provides an objective assessment and guidance for improving the biopsy sampling accuracy and therefore it is also highly suited for operation by nurses. These characteristics suggest the role of DySIS as a replacement for conventional colposcopy, holding the promise to improve the cost-effectiveness of the diagnostic chain. There is also the potential to apply this very promising technology to screening in low resource settings in which visual inspection with acetic acid (31) is currently under investigation.

Disclosure of Potential Conflicts of Interest

W.P. Soutter is a member of the speakers bureau of Forth Photonics. C. Balas has an ownership interest in Forth Photonics.

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