Spectroscopic Imaging as a Triage Test for Cervical Disease: A Prospective Multicenter Clinical Trial

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■ **Abstract**

Objective. The objective of the study was to evaluate the potential safety and effectiveness of tissue spectroscopy for the diagnosis of cervical cancer in a prospective multicenter study of women scheduled for colposcopy on the basis of an abnormal Pap test or other risk factor.

Materials and Methods. Five hundred seventy-two women underwent spectroscopy of the cervix during their colposcopy visit. Spectroscopy measurements taken over a scan period of 4 minutes and 30 seconds were integrated by a cross-validated pattern recognition model and compared with biopsy results to yield sensitivity and specificity of cervical spectroscopy.

Results. The median age of subjects enrolled in the study was 27.7 years. The sensitivity of cervical spectroscopy was 95.1% with a corresponding 55.2% specificity for benign lesions. Several potential confounding factors (eg, mucous, blood, patient motion, ambient light) were examined to determine their potential impact on the accuracy of the test. Ambient light seemed to have the greatest effect, but no single factor contributed significantly to the results. The subjects did not experience any adverse events from undergoing the test.

Conclusions. Spectroscopy of the cervix has the potential to accurately detect cervical moderate and high-grade dysplasia while also reducing the false-positive rate for benign cervices. The test is relatively simple to implement and was well accepted by subjects enrolled in the study. ■

Key Words: spectroscopy, cervical neoplasia, cancer diagnosis

Within the last decade, the management of cervical disease has undergone a number of significant changes. Whereas the Pap test, followed by colposcopically-directed biopsies when indicated, has been the mainstay of disease management since the 1960s, the publication of new data regarding the efficacy of this strategy and the acceptance of new technology have altered the landscape considerably and presented new challenges and opportunities to further optimize the detection of the disease and the reduction of false-positive results.

Currently, approximately 60% of all Pap tests conducted in the United States are liquid-based smears (1). This has resulted in a higher rate of disease detection and in an increase in the number of low-grade cervical

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intraepithelial neoplasia (CIN 1) and nondysplastic cases referred to colposcopy and biopsy because of the higher pickup rate for low-grade lesions (2–4).

In addition, recent studies, such as the landmark ASCUS LSIL Triage Study (ALTS) (5–10), indicate the need for new technology by showing that colposcopy is significantly less sensitive than previously thought (ie, 53%, a level corroborated by another recent study (11). Although ALTS also indicated that human papillomavirus (HPV) testing is a viable and even preferred alternative to follow-up Pap testing for patients with atypical squamous cells of undetermined significance (ASCUS), there was no value found for the use of HPV in triaging women with low-grade squamous intraepithelial lesion (LSIL) Pap results because the vast majority in this group was HPV positive, regardless of whether they actually had dysplasia or not. Thus, the overall result is that even with the improvements in cervical dysplasia detection afforded by thin-layer cytology and HPV testing, the likelihood of a woman with an ASCUS or LSIL Pap test result having significant cervical disease is only about 25%, and the current management strategy of sending ASCUS/HPV-positive women and women with LSIL to colposcopy would still miss about 30% to 40% of all CIN 3 disease (9–11).

The technology evaluated in the present study relies on the combination of both tissue fluorescence and reflectance characteristics. Naturally occurring fluorophores in tissue, such as tryptophan, collagen, elastin, the reduced form of nicotinamide adenine dinucleotide (NADH), and the oxidized form of flavin adenine dinucleotide FAD, emit light that is redshifted in response to a particular wavelength of excitatory light. Biochemically, NADH/FAD are known to play a role in cellular energy metabolism (12), and their concentration ratio is altered in malignant tissue [13]. Collagen and elastin are structural proteins that autofluoresce and are associated with cross-links (14–16). In tissue reflectance, certain types of tissue absorb and scatter light differentially. For example, increased blood perfusion (eg, angiogenesis), nuclear size and content, and epithelial thickening are hallmarks of cancer that alter light absorption and scattering (17–19).

The methods that have been used for native fluorescence and reflectance range from single-point probes (20–22) to systems that spectroscopically image the cervix using multiple fluorescence wavelengths (23), a single fluorescence wavelength in tandem with flood illumination for reflectance (24), multiple fluorescence wavelengths with flood illumination for reflectance (19), and multiple fluorescence wavelengths with structured illumination for reflectance (18, 25).

Thus, the present study was designed to assess the potential impact of tissue spectroscopy on cervical disease management if used as a precolposcopy triage test.

MATERIALS AND METHODS

Subjects

This study was designed to evaluate the sensitivity and specificity of fluorescence and reflectance imaging spectroscopy in women scheduled for colposcopy, most of whom were scheduled because of an abnormal Pap test, ASCUS, ASC-H (atypical squamous cells, cannot exclude HSIL [high-grade squamous intraepithelial lesion]), LSIL, or HSIL. Additional subjects were enrolled because they had risk factors, such as a history of cervical disease, and were therefore being followed up. The study endpoints included both sensitivity to detect biopsy-proven cervical dysplasia, especially moderate and severe forms (CIN 2+), and specificity to rule out normal and benign cervical conditions (eg, inflammation, metaplasia) that also had been scheduled for colposcopy and biopsy. The study population included women with a history of abnormal cervical cytology or other risk factors, such as previously documented histopathology of cervical dysplasia in need of follow-up.

A total of 648 women were enrolled consecutively during the years 2002 to 2004 across 4 clinical centers, which were large, academically affiliated centers with referral colposcopy clinics located in relatively urban environments, including Miami, Hartford, and Atlanta and Augusta, Georgia. Each site's institutional review board approved the study. The inclusion criteria were as follows: women aged 18 and older, able to give informed consent, a referral Pap test within 120 days of the study or on the day of the study, and having been scheduled for colposcopy. The exclusion criteria were as follows: pregnancy, radiation therapy for the urogenital tract, or current menstruation. In addition to having a Pap test on the day of the study, all subjects had the spectroscopic analysis, colposcopy and, when indicated, biopsy. In some cases, for example, when colposcopy was normal, a subject did not have a biopsy and the case was considered benign by expert colposcopy, unless the Pap result was HSIL, in which case the subject was referred to a diagnostic excisional procedure.

Procedure

All data were collected using the same prototype device. There were no additional cleaning steps taken, such as removal of cervical mucous, except for what current practice would indicate for a Pap test or colposcopy. Fluorescence and reflectance measurements were

collected before a Pap smear and colposcopy/biopsy. When the subject was released from the clinic, there was no further follow-up for study purposes. Investigators and subjects were blinded from the output of the device to ensure that its results during experimental evaluation would not influence patient treatment. The HPV results were not available for this study because the use of this test was not yet widespread in this population as a mechanism of referral to colposcopy.

Spectroscopic Imaging Device

The device system (Guided Therapeutics, Inc, Norcross, GA) used in the study is a nonsignificant risk device, in accordance with the Food and Drug Administration standards, that noninvasively collects and analyzes fluorescence and reflectance spectra from the cervix. No contrast agents, such as acetic acid, are applied to the cervix before taking the measurements. A plurality of equally spaced points over a 1-inch diameter area of the cervix was automatically scanned over a 4-minute period using a xenon arc lamp as an illumination source.

For cervical tissue fluorescence measurements, the light from the arc lamp was band-pass filtered to limit the exposure of the cervix to bands within the 300- to 500-nm range. These spectral bands are known to excite fluorophores associated with neoplastic processes as previously described. Each of the fluorescence wavelengths was applied automatically under software control in a predetermined order and scan pattern. The resultant fluorescent spectral output of the cervical tissue was imaged onto a charge-coupled device (CCD) camera and stored for processing and analysis.

For cervical tissue reflectance measurements, broadband spectral output ranging from about 350 to 900 nm was automatically applied under software control to the cervix using the same xenon arc lamp. The resultant reflectance spectral output from the cervical tissue was imaged onto the CCD camera and stored for processing and analysis. The combined fluorescence and reflectance information, determined by previous studies and measured from multiple points on the cervix, were combined in a multivariate regression analysis to produce a single index—standardized on a scale of 0 to 100, with the higher number indicating greater probability of CIN 2+ disease—for each subject. A threshold was set at approximately 95% sensitivity for CIN 2+ using the first half of the data collected; then, the resultant specificity corresponding to this threshold was calculated.

In addition to the fluorescence and reflectance spectroscopy channel, the cervical neoplasia detection system (CNDS) also contains a separate colposcopy-quality imaging channel for real-time imaging of the cervix for centering guidance while the contact tube is being placed inside the vagina, for allowing the images to be taken to document the placement of the device, and for appropriate centering of the cervix within the 1-inch diameter measurement area.

The other major component of the CNDS is a computer for control and data processing. This includes the capability for a diagnostic algorithm based on spectroscopic information measured from the cervix, calibration data, and other patient data, such as Pap results or patient demographic data. A photograph of the system is shown in Figure 1.

Histopathology Quality Control

Each clinical site fixed tissue in accordance with current clinical practice. An additional slide adjacent to the

Figure 1. Photograph of the Guided Therapeutic's Multimodal Hyperspectral Imaging System.

diagnostic slide was also cut and sent to the clinical pathology laboratory of one of the authors (E.W.). If E. W. disagreed with the diagnosis of the clinical site pathologist, the slide was then sent to a third pathologist (S.R.). A case was assigned to a diagnostic category when (1) the site and E.W. agreed, or (2) when 2 of 3 diagnoses agreed (ie, either benign, CIN 1, or CIN 2+, using the most severe disease grade for each case). A case was considered nonevaluable when all three pathologists disagreed.

RESULTS

A total of 648 consecutive women from the 4 clinical sites met the inclusion criteria, signed the consent form, and agreed to participate in the study. Data could not be collected from 19 subjects because they withdrew before the study could be completed, usually because it was determined that they did not actually meet the inclusion/exclusion criteria (eg, they were still menstruating). The median age of the 629 study participants was 27.7 years (range = 18–75 years); 354 (57.6%) were younger than 30 years at the time of the study. Three hundred forty-five characterized themselves as African American, 139 as Hispanic, 141 as white, and 4 as Asian American or other. The demographic data are summarized in Table 1.

Fifty-seven of the 629 subjects that completed the study were excluded from analysis either because they did not have valid Pap, histopathology, and/or colposcopy results available (n = 42), or because spectroscopic data could not be analyzed because of a device or operator error (n = 15). Thus, sensitivity and specificity of the CNDS test could be calculated for the remaining 572 evaluable subjects (Table 2).

Alternative thresholds based on the same algorithm could be set to reduce sensitivity and increase specificity. For example, reducing the sensitivity for CIN 2+ lesion from 95.1% to 91.5% results in an increase in specificity from 55.2% to 65.5%.

Table 1. Demographic Data for the 629 Study Subjects

Demographic	Category	Number	Percent
Age distribution	Median	27.7	–
	Range	18–75	–
	Less than age 30	354	57.6
	age 30 or older	275	42.4
Race distribution	African American	345	54.8
	White	141	22.4
	Hispanic	139	22.1
	Asian American or other	4	0.6

Table 2. Sensitivity and Specificity of Spectroscopy by Disease Category for All 572 Evaluable Subjetcs

All cases (N = 572)	Sensitivity		Specificity*
Disease	CIN2+	CIN1	No CIN
Number tested	142	180	250
Number correct	135	135	138
Percent correct	95.1	75.0	55.2
95% CI	91.55, 98.65	68.67, 81.33	49.04, 61.36

* Note: In 149 cases, biopsy was not performed because expert colposcopy indicated a normal cervix and the Pap test did not indicate dysplasia. Most of these cases were referred to colposcopy on the basis of other risk factors and are categorized as benign for the purposes of statistical analysis.

Previous work by this group has indicated that several factors may interfere with spectroscopic measurements of the cervix, either by obscuring the tissue of interest or affecting the wavelength and/or intensity of light emitted or reflected by the tissue. We investigated the effects of 6 potential interferences: mucous, blood, specular reflection, ambient light (usually a strong examination light pointed directly at the lower genital area), poor centering of the cervical os in the visual field, and physical movement of the cervix or device during the course of data collection to determine whether any of these influenced the device's spectrographic results. With assistance from one of the site investigators (D.F.), the cases were prospectively categorized with no knowledge of spectroscopic, Pap, colposcopic, or histopathologic diagnoses as either having a significant amount of interfering factors (ie, >25% of the cervix affected and/or the os not visible after spectroscopic measurements were taken using the device's imaging channel; n = 62) or having less than 25% of the cervix affected by interfering factors (n = 510). The results of the 510 cases with cervices free from significant mucous, blood, specular reflection, ambient light, physical motion, and/or poor centering of the os are shown in Table 3.

A comparison of Tables 2 and 3 shows only slight improvement when the 62 cases with potentially

Table 3. Sensitivity and Specificity by Disease Category for 510 Subjects with No Interfering Factors (Unaffected Cases)

All cases (n = 510)	Sensitivity		Specificity*
Disease	CIN2+	CIN1	No CIN
Number tested	133	151	226
Number correct	127	119	128
Percent correct	95.5	78.8	56.6
95% CI	91.98, 99,02	72.28, 85.32	50.14, 63.06

* Note: In 135 cases, biopsy was not performed because expert colposcopy indicated a normal cervix and the Pap test did not indicate dysplasia. Most of these cases were referred to colposcopy on the basis of other risk factors and are categorized as benign for the purposes of statistical analysis.

affected cervices are removed from analysis, suggesting that spectroscopic measurements and the interpretive algorithm used to produce the test result are relatively robust.

Ambient light seemed to have the greatest confounding effect on the spectroscopic measurements and usually occurred when an intense examination light was inadvertently directed at the patient (Table 4).

Excessive ambient light seemed to reduce the specificity of the test, whereas one case of CIN 2+ was missed when excessive motion was observed. Because sample sizes are relatively small in each category, caution must be used when drawing any conclusions.

Two hundred fifty-five of the subjects had an endocervical curettage in addition to a biopsy performed during their study visit. Of these endocervical curettages, 9 were positive for CIN 2+ disease, but each was found in conjunction with CIN 2+ disease on the ectocervix; thus, it was not possible to ascertain whether cervical spectroscopy could detect disease limited to the endocervix.

The diagnostic algorithm used to generate sensitivity and specificity was cross validated by randomly partitioning the data in half, with the first half serving as a training set for the algorithm and the second half serving as the prospective data set. When this is done, there is no reduction in performance, again indicating the robustness of the method. There was also no evidence that practice with the test made any real difference in performance. A comparison of sensitivity and specificity for the first 25 subjects tested and the last 25 subjects at each site showed only small differences in performance that were not statistically significant (95.1% sensitivity and 61.4% specificity for the first 100 cases pooled across the sites versus 96.9% sensitivity and 44.0% specificity for the last 100 cases pooled across the sites). As expected and shown in previous work with a similar device [18], none of the demographic variables, such as age or race, were found to significantly influence the test result.

There was some evidence that the device's output correlated to some degree with the severity of dysplasia. For example, to separate CIN 3 from CIN 1, a threshold could be set whereby approximately half of the CIN 1 cases fell below the set threshold (ie, the specificity for ruling out CIN 3+ is 50%). At this threshold, the sensitivity for CIN 3 cases was still 93%. Using the same threshold, however, the device's algorithm had slightly more difficulty in separating CIN 2 cases from CIN 1 cases; at 50% specificity for CIN 1, the sensitivity for CIN 2 was reduced to 85%.

Table 4. Sensitivity and Specificity of Cases with Potentially Interfering Factors

	Number			Sensitivity		Specificity
Interfering Factor	CIN2+	CIN1	No CIN	CIN2+	CIN1	No CIN
Excessive ambient light	4	10	6	100	50.0	16.7
Excessive motion	4	12	10	75.0	70.0	70.0
Other*	1	7	8	57.1	57.1	25.0
Total	9	29	24	55.2	55.2	41.7

* Includes no or poor contact with cervix (n = 5), poor centering, (n = 2), excessive mucous and/or blood (n = 9).

DISCUSSION

To be accepted into the clinical mainstream, the new technology should not only show improved performance over existing technologies but should also be cost effective and convenient to use. Medical spectroscopy has advanced recently in part because of technical improvements in imaging and signal acquisition hardware. Historically, however, such systems have been expensive and inconvenient.

The results from this study are consistent with previous studies and show that the device is capable of detecting more than 95% of CIN 2+, with a corresponding specificity for benign cervices of 55% in a population of women scheduled for colposcopy. The same algorithm used for distinguishing CIN 2+ disease from benign cases classified approximately 75% of CIN 1 cases as positive. However, the use of a secondary algorithm could separate 93% of the CIN 3+ and 85% of the CIN 2 lesions from approximately half of the CIN 1 lesions. With a sensitivity for CIN 2+ disease greater than 95% and a corresponding specificity for benign cervices of 55%, if applied to a population with 20% prevalence of CIN 2+ disease, the negative predictive value of the test would be approximately 98%. For CIN 3+, with a prevalence of about 10%, the negative predictive value would be approximately 99%.

As previously discussed, the advent of new screening tests is expected to increase the number of women scheduled for colposcopy and biopsy. The problem will be exacerbated if HPV testing is adopted to screen women aged 30 and older, for whom its use is currently approved by the Food and Drug Administration. Colposcopic examination is time consuming, expensive, and with lower-than-expected sensitivity, as shown by the ALTS results. In contrast, spectroscopic examination of the cervix

is relatively convenient to implement, especially when compared with colposcopy. The total time of data collection for these prototype devices was about 4 minutes and 30 seconds, including the collection of some additional spectroscopic information solely for research purposes. A new version of the device currently undergoing clinical pilot testing reduces this time by more than half. In patient acceptance, Ferris et al. (25) has recently published the results of an exit poll in which women were tested with the same device used in the present study, along with colposcopy and the Pap test during the same visit, and then were asked for their impressions. More than 96% of the women favored the spectrographic test as a method for locating the presence of disease and reducing the number of biopsies. Moreover, 81% wanted the new test to replace the Pap test and 87% would recommend the test to a friend.

The device provides video feedback for positioning and is self focusing with the contact tube in place. In some cases during the present study, the device was operated by a nurse or a physician's assistant, a design goal that also has the potential for cost savings.

To be a complete test, especially for primary screening, any new technology must address the sampling of the endocervical canal (26). For a triage application, where the algorithm can combine both quantified spectroscopic data and a numerical score corresponding to the severity of the Pap result, the smear can provide information regarding abnormal endocervical and ectocervical cells as long as appropriate technique is used in collecting the sample. However, instead of endocervical cell collection, cervical screening by spectroscopy will need to measure the endocervix. The work on this is already underway and two of the investigators (L.T. and L.F.) have collected pilot data with a small, dedicated spectroscopic probe that can access the endocervix. Further work on integrating the endocervical probe with the system described in this report is indicated and currently underway. In the present study, all 9 subjects with endocervical biopsy-proven CIN 2+ disease had abnormal findings on the ectocervix also; thus, it was not possible to determine whether cervical spectroscopy could detect CIN 2+ limited only to the endocervix.

In terms of cost effectiveness, the design of the present instrument uses an arc lamp, instead of a laser as the illumination source, and a consumer grade CCD camera and electronics, which lends itself to a low-cost instrument affordable to ob-gyns even in small practices. From the point of view of the payer, new technology must also demonstrate cost savings to the health care system. If the present results are maintained in pivotal clinical trials and in actual commercial use, a significant reduction in the number of unnecessary follow-up tests, colposcopies, and biopsies could be expected. Moreover, any technology with more accurate or earlier detection would potentially save treatment costs.

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