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

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Introduction

The present study was designed to assess the potential impact on cervical disease management that spectroscopic imaging would have if employed as a primary imaging test to triage women with negative Pap tests for cervical disease. The study endpoints included both sensitivity to detect biopsy proven cervical dysplasia, especially moderate and severe forms (CIN2+), as well as specificity to rule out cervical conditions that also had been ruled out for colposcopy and biopsy. The study population included women with a history of abnormal cervical cytology or other risk factors, such as previously unexplained histopathology of cervical dysplasia in need of follow-up.

Objective

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

Cervical Neoplasia Detection System (CNDS)

The device system (Guided Therapeutics, Inc. Norcross, GA, USA) used in the study is a noninvasive risk device by FDA standards that noninvasively and automatically scans the ectocervix and distal endocervix for disease related changes in fluorescence and reflectance spectra (see Figure 1). Alterations in fluorescence spectra are a marker of disease states associated with neoplasia, while alterations in reflectance and scattering are indicative of structural changes associated with neoplasia, such as epithelial thickening, nuclear size and content and angiogenesis. 1,2

A plurality of equally spaced points over a one-inch diameter area of the cervix was automatically scanned during a four-minute period using a filtered xenon arc lamp as an illumination source. For cervical tissue reflectance measurements, broadband spectral output ranging from about 350 to 900nm was used, where the center wavelength was tuned by software control to the cervix using the same xenon arc lamp. The resultant reflectance spectra were imaged onto the CCD camera and stored for analysis. For cervical tissue fluorescence measurements, light from the arc lamp was band pass filtered to limit exposure of the cervix to bands within the 380 to 520 nm range. These spectral bands are known to excite fluorophores associated with neoplastic processes as described above. Each of the fluorescence wavelengths were applied automatically under software control in a predetermined order and scan pattern. The resultant fluorescence spectral output of the cervical tissue was imaged onto a charge-coupled detector (CCD) and analyzed for changes and stored for processing and analysis.

Figure 1. CNDS Device

The system consists of two main physical components, the handheld unit and the base unit (Figure 1). The handheld unit is connected to the base unit via fiber optic cables for transmitting data and video to and from the base unit, which contains the xenon lamp, optical processing elements (filters and lenses) and the CCD camera on a rolling cart (CNDS Device). 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 demographic data.

Methods

Subjects meeting the inclusion criteria underwent spectroscopy of the cervix during their colposcopy visit. Spectroscopy measurements taken over four minutes were integrated by a cross-validated pattern recognition algorithm and compared with expert panel reviewed histopathology to yield sensitivity and specificity of cervical spectroscopy. After the spectroscopy measurements were taken, a Pap test was taken, followed by colposcopy and biopsy, if indicated.

Histopathology Quality Control

Each clinical site fixed tissue per current clinical practice. An additional slice adjacent to the specimen cut and into the clinical pathology lab of one of the authors (EW). If EW disagreed with the diagnosis of the clinical site pathologist, the slide was then sent to a third pathologist (SR). A case was considered disagreement when either the CNDS and EW agreed or two out of three diagnoses agreed (i.e., either benign, CIN1, CIN2+) or using the opposite disease grade for each case). A case was considered nonevaluable when all three pathologists disagreed.

Results

A total of 448 consecutive women from the four clinical sites met inclusion criteria, signed the consent form and were therefore eligible to participate in the study. Data could not be collected from 26 (5.8%) because they withdrew before the study could be completed. Median age of the 422 study participants was 27.7 (range 18-75) and 354 (84.1%) were under the age of 30 at the time of the study. Three hundred forty-five characterized themselves as African American, 141 as Caucasian and 4 as Asian American or other. Demographic data are summarized in Table 3 and Figure 3. No adverse events were reported.

All women underwent colposcopic examination and all but 42 had a Pap test result and valid histopathology available. Of the 587 subjects that had both the cervical biopsy result and/or colposcopic results, 15 cases could not be categorized because of a device or operator error. Thus sensitivity and specificity of the test was calculated for the remaining 572 evaluable subjects (see Table 2).

Sensitivity of cervical spectroscopy for CIN2+ lesions (n = 142) was 95.1% with a corresponding specificity of 74.7%. The 12% disagreement was mainly due to normal tissue (e.g., normal tissue, inflammation, CIN1) and agreed in 35 of 42 cases (83.3%) (see Table 2). The test also identified 75.0% of CIN1 lesions (n = 180) as positive. A secondary algo-
duc the number of CIN1 lesions as positive by spectroscopy, but without a significant reduction in sensitivity for CIN2+ lesions.

Several potential confounding factors (e.g., mucous, blood, patient motion, ambient light) were examined to determine their potential impact on the accuracy of the test (see Table 3). Excessive ambient light (e.g., strong examination light pointed directly at the lower genital tract) appeared to have the greatest effect, but no single factor contributed significantly to the results. When subjects with confounding factors were excluded, no significant change in sensitivity or specificity was reported (see Table 4).

Color enhanced maps of the cervix could be constructed from the spectroscopic data (see Figure 3).

Summary and Conclusions

Spectroscopy of the cervix has the potential to accurately detect moderate and high-grade cervical dysplasia while also reducing the false positive rate for benign cervixes. The test is relatively simple to implement, and if the present results are validated in pivotal clinical trials, could be utilized in practice. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure. If the present results are validated in pivotal clinical trials, the test would be a noninvasive and no adverse event procedure.

References


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