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Multimodal hyperspectroscopy as a triage test for cervical neoplasia: Pivotal clinical trial results

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HIGHLIGHTS

- Prospective study effectively demonstrates cervical spectroscopy triage high risk women.
- Cervical spectroscopy detected 36.4% more CIN2+ than tests used under current guidelines.
- Cervical spectroscopy could reduce unnecessary referrals of women with normal pathology by 40%.

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ABSTRACT

Objective. To prospectively evaluate a new non invasive device that combines fluorescence and reflectance spectroscopy in a population in women at risk for cervical dysplasia.

Methods. A total of 1607 women were evaluated with multimodal hyperspectroscopy (MHS), a painless test with extremely high spectral resolution. Subjects who were referred to colposcopy based on abnormal screening tests or other referral criteria underwent the MHS test and also had a sample taken for additional cytology and presence of high risk human papilloma virus (HPV) prior to undergoing biopsy.

Results. Sensitivity of MHS for cervical intraepithelial neoplasia (CIN) 2+ was 91.3% (252/276). Specificity, or the potential reduction in referrals to colposcopy and biopsy, was 38.9% (222/570) for women with normal or benign histology and 30.3% (182/601) for women with CIN1 histology. Two year follow-up data, collected for a subgroup of 804 women, revealed 67 interval CIN2+ that originally were diagnosed at enrollment as normal or CIN1. MHS identified 60 of these (89.6%) as positive for CIN2+ prior to their discovery during the two year follow-up period.

Conclusions. MHS provides an immediate result at the point of care. Recently, the limitations of cytology have become more obvious and as a consequence greater emphasis is being placed on HPV testing for cervical cancer screening, creating a need for an inexpensive, convenient and accurate test to reduce false positive referrals to colposcopy and increase the yield of CIN2+ at biopsy. MHS appears to have many of the attributes necessary for such an application.

Introduction

Management of women with abnormal cervical cytology and/or high risk human papillomavirus (HPV) subtypes remains a challenge. Recent years have seen the advent of numerous new technologies, re-assessments of old technologies and new guidelines for the management of cervical disease. Chief among these has been the emergence of HPV testing and the re-assessment of colposcopy as the

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gold standard imaging technique for assessing the need for further management. Ironically, as HPV testing has redefined the risk for cervical neoplasia, it also has focused attention on the need to effectively control the morbidity and costs associated with managing it. This has led to new recommendations, including the virtual elimination of screening and follow-up testing for adolescent women and extended screening intervals for most other women [1,2].

We report here the results of a clinical study that evaluated the potential of multimodal hyperspectroscopy (MHS) to effectively triage women at risk for moderate and high grade dysplasia. MHS is the concurrent use of multiple types of tissue spectroscopy, whereby specific wavelengths of light are focused on the cervix and the response of cells and cellular structures, as manifested in the reflected light, is resolved spectrally and imaged onto a high resolution sensor. The primary goal of this study was to provide a prospective evaluation of the sensitivity and specificity of MHS for the detection of moderate and high grade dysplasia and, using this information, provides insights for how this new test could be used to improve care for women at risk for these conditions.

Materials and methods

Tissue spectroscopy has been evaluated in many clinical trials for detecting neoplasia of the cervix [3–7], lung [8], gastrointestinal tract [9–11], and skin [12]. These earlier systems typically utilized a single excitation wavelength or a single spectroscopic mode [8,13–15]. In contrast, the system evaluated in the present study combined fluorescence and reflectance spectroscopy in a cost effective device that can be easily operated by trained medical personnel. The advantage of combining spectroscopic modes is that fluorescence spectroscopy identifies metabolic changes associated with neoplasia, while reflectance spectroscopy indicates the presence of structural changes within tissue that are indicative of neoplasia [14,16–21].

Two prototype systems that collected and analyzed spectroscopic data in the same way were used and each consisted of three major components; 1) a base unit that includes the light source, power supply, computer and monitor; 2) a handheld unit, which contains the optical systems and 3) the sight tube, a hollow tube that was inserted into the vagina through a speculum and whose distal end encompassed the cervix. Learning the procedure took about two or three cases. Women tolerated the procedure well and no adverse events were reported.

The study procedure consisted of the following: After obtaining informed consent, the subject was prepared as for a standard pelvic examination. If excessive mucus or blood was observed on the cervix, it was removed with saline, but no acetic acid was applied. The MHS device was calibrated and the sight tube was inserted through the speculum, using a live video feed, until the distal end of the tube was in place, with the os visible and focused in the field of view. Spectroscopic measurements were then made automatically under software control. Scan time was approximately 4.5 min for the earlier prototype system and 1 min for the newer system. After the scan was completed, a second video image was obtained to ensure that the os was still in view and the cervix had not moved significantly. The sight tube was then removed and colposcopy with acetic acid was performed. To reduce verification bias, Lugol's solution was used when acetic acid did not reveal a lesion and endocervical curettage was performed on all subjects that had referral cytology of LSIL or HSIL. Biopsy specimens were sent to the local pathologist for diagnosis, as well as to two additional, blinded pathologists for diagnosis. If the first additional pathologist agreed with the diagnosis of the local pathologist, then for each individual biopsy specimen, this served as the gold standard pathology diagnosis. If the first additional pathologist disagreed with the local pathologist, then the biopsy specimen was sent to a second additional pathologist. This second pathologist served as the “tie breaker” with the final gold standard diagnosis based on the majority (two out of three) opinion. If all three pathologists disagreed (i.e., normal vs. CIN1 vs. CIN2+), the case was not used for analysis.

This multicenter study employed a single arm design whereby each woman served as her own control, undergoing MHS and evaluation according to current management guidelines. Physicians, support personnel, subjects and the histopathology QA team were blinded to the results of the MHS test. Women were eligible for the study if they required evaluation for either an abnormal Pap test, a positive HPV test or were being followed for previous dysplasia. Women were ineligible for the study if they were pregnant, undergoing menses or treatment for cervical cancer. Enrollment and data collection occurred from 2004 to 2008 and were consecutive, unless a woman declined to participate. Two year follow-up visits occurred according to the current guidelines for up to two years after enrollment and were completed in 2010. Each of the seven participating centers obtained IRB approval and used a standard consent form to enroll subjects.

Statistical methods

Minimum sample sizes were computed to ensure 80% power at an alpha level of less than 0.05. McNemar's test (two-sided) was used to compare the sensitivity of MHS to that of the current management guidelines that consist of Pap result, HPV and colposcopically-directed biopsy. In order to assess the number of CIN2+ lesions not identified by current management guidelines at the time of enrollment, up to two years of follow-up data was collected from a cohort of 804 subjects that returned to the clinic based on current management guidelines for follow-up. Because the follow-up data provided a better estimate of true negative as well as true positive cases, it allowed for more accurate comparisons of sensitivity, specificity and predictive values between different detection modalities or combinations of those modalities [22–25]. The combination of a QA consensus histopathology diagnosis and up to two year follow-up data allowed the calculation of the sensitivity of the current management guidelines for detecting moderate and high grade dysplasia.

As the ALTS demonstrated, one way to assess the effectiveness of the current management guidelines and reduce verification bias is to determine the number of interval or cumulative cases of CIN2+ identified through follow-up. The sensitivity of the current management guidelines can then be estimated by the equation:

$$(\text{Site Pathology CIN2+})/(\text{QA Consensus CIN2+}) + (\text{Interval CIN2+})$$

where Site Pathology CIN2+ is the number of CIN2+ cases diagnosed by the site pathologist at the time of study enrollment, QA consensus CIN2+ is the number of CIN2+ cases diagnosed by QA consensus histopathology and Interval CIN2+ is the number of CIN2+ cases found during the two year follow-up that were not diagnosed with CIN2+ at the time of the study. The sensitivity of the current management guidelines can be directly compared with that of MHS, using McNemar's test, if the sensitivity of MHS is calculated as:

$$(\text{MHS True Positives})/(\text{QA Consensus CIN2+}) + (\text{Interval CIN2+}).$$

Rather than calculate the specificity of the current management guidelines directly, it is more appropriate to determine referral rates and compare them with MHS, similar to ALTS [22–25]. Therefore, specificity of MHS represents an estimate of the percentage of women with a normal cervix, or CIN1, that could have avoided biopsy.

Results

There were 1607 women that fulfilled the inclusion criteria and were enrolled in the study. Demographic data for the study