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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

Table 1
Selected demographics all sites — Race and age.

Race	Age 16–20	Age 21–30	Age >30	Total
American Indian	1	2	0	3
Asian	2	9	5	16
Black	188	389	305	882
Pacific islander	0	4	0	4
White	99	279	324	702
Total	290	683	634	1607

Table 2
Number and prevalence of final QA histopathology as a function of the reason for referral for colposcopy. Cases with no or indeterminate histopathology excluded (n = 74).

Reason for referral	Normal	CIN 1	CIN 2+	Total	Prevalence CIN 1 (%)	Prevalence CIN 2+ (%)
Negative pap (other)[a]	23	12	2	37	32.4	5.4
ASC/HPV+[b]	326	271	71	668	40.6	10.6
LSIL	245	332	132	709	46.8	18.6
HSIL	8	26	85	119	21.8	71.4
Total	602	641	290	1533	41.8	18.9

[a] Includes subjects referred for colposcopy based on 2001 ASCCP guidelines (27) or other reasons, including HIV+, abnormal colposcopy, abnormal bleeding or warts.
[b] Includes subjects referred for colposcopy based on 2006 ASCCP guidelines (28) including ASC-US, ASC-H, HPV+, AGC and/or follow-up for recent previous dysplasia.

population are presented in Table 1. Consistent with HPV testing having become a more common criterion among referrals for the evaluation of minimally abnormal Pap cytology, we found that all Pap referral groups in the study harbored significant evidence of HPV infection, and that HPV was the major reason why women with negative, benign or ASC-US Pap cytology were referred to colposcopy and, thus, were enrolled in our study. In order to justify pooling of data across referral groups, the prevalence of CIN1 and CIN2+ for all women with a defined histopathology outcome was examined, excluding women with no or discordant histopathology results. As may be observed in Table 2, the prevalence of CIN1 and CIN2+ was relatively uniform for all referral groups except women referred with HSIL. For example, for all referral groups except HSIL, the prevalence of CIN1 was between 30% and 50%, while the prevalence of CIN2+ was below 20%. Thus, the risk for dysplasia was relatively uniform among the groups without an antecedent HSIL cytology, so these groups were pooled for estimating sensitivity and specificity. In contrast, women referred on the basis of HSIL cytology had a much lower prevalence of CIN1 (21.8%) and a much higher prevalence of CIN2+ (71.4%).

In addition to the 74 women enrolled that did not have a definitive histopathological outcome, 86 subjects were excluded from the efficacy analysis because they were either prospectively identified training subjects (n = 50), or they did not have an evaluable referral cytology (n = 1). An additional 35 subjects were excluded because of device malfunction (n = 25) or user error/protocol violation (n = 10). This resulted in 1447 subjects available for efficacy analysis.

The sensitivity of MHS for CIN2+ was 91.3% (252/276), the specificity for normal or benign histology was 38.9% (222/570) and the specificity for CIN1 histology was 30.3% (182/601). Pooling normal/benign cases with CIN1 cases resulted in a specificity of 34.5% (404/1171). Positive predictive value was 24.7% and negative predictive value was 94.4%. Table 3 shows these results with 95% confidence intervals, both with and without inclusion of women with HSIL referral cytology. Analyzing data without adolescent women (ages 16–20), who under current guidelines are no longer included as part of the screened population, did not reduce performance of MHS (see Table 3). For women aged 21 to 30, sensitivity for CIN2+ was 91.9% (114/124) and specificity for normal women was 33.9% (76/224). For women aged 31 and older, sensitivity for CIN2+ was 92.3% (96/104) and specificity for normal women was 45.8% (119/260).

Two types of follow-up analyses were performed in order to estimate sensitivity of CIN2+ disease that was missed by the current management guidelines. The first follow-up analysis (QA histopathology review) investigated the number of cases of CIN2+ disease diagnosed by the site pathologist as normal or CIN1 pathology, but later diagnosed as CIN2+ by the two expert blinded QA pathologists. This occurred for 38 subjects and MHS identified 33 of these (86.8%) as positive for CIN2+. The second follow-up analysis included 804 subjects that returned for follow-up visits for up to two-years following initial enrollment. These women were managed by each site's PI, based on ASCCP guidelines. Of these 804 subjects, biopsies were performed and histology results obtained for 243 subjects. If follow-up histology indicated that a subject had a more severe disease classification than the diagnosis made at the time of study enrollment, then the subject's final histology result was re-classified to that disease category (i.e., either CIN1 or CIN2+). A subject's final histopathology result was never reclassified to a less severe disease state based on findings from the two year follow-up period. In 29 cases, subjects initially diagnosed to be negative for CIN2+ were found to actually harbor CIN2+ lesions. In 27 of these 29 cases (93.1%), MHS was positive for CIN2+.

The cumulative number of incremental cases of CIN2+, identified by pathology review and including the two-year follow-up data, represent the number of cases where following the current management guidelines failed to diagnose CIN2+ resulting in a delay in treatment. There were 67 such cases missed and MHS detected 60 (89.6%) of these, as shown in Table 4.

In order to better assess the overall impact of the follow-up data and the effectiveness of MHS in detecting CIN2+ missed by the current management guidelines, a separate analysis was performed on 742 (of 804) evaluable subjects for whom both histopathology review and 2-year follow-up data were available. The results for the follow-up subjects only are summarized in Table 5.

Table 3
Sensitivity, specificity and predictive values (PPV and NPV) of MHS by age group with and without HSIL cytology (n = 1447).

All sites and devices	Sensitivity CIN2+ (%) (95% CI)	Specificity Normal (%) (95% CI)	Specificity CIN1 (%) (95% CI)	PPV (%)	NPV (%)
All Pap categories (n = 1447)	91.3 (252/276) (87.3–94.3)	38.9 (222/570) (34.9–43.1)	30.3 (182/601) (26.6–34.1)	24.7 (252/1019) (22.1–27.5)	94.4 (404/428) (91.8–96.4)
Ages 16–20 (n = 255)	87.5 (42/48) (74.8–95.3)	31.4 (27/86) (21.8–42.3)	27.3 (33/121) (19.6–36.1)	22.2 (42/189) (16.5–28.8)	90.9 (60/66) (81.3–96.6)
Ages 21–30 (n = 625)	91.9 (114/124) (85.7–96.1)	33.9 (76/224) (27.8–40.5)	29.6 (82/277) (24.3–.35.4)	24.9 (114/457) (21.0–29.2)	94.0 (158/168) (89.3–97.1)
Ages 31-older (n = 567)	92.3 (96/104) (85.4–96.6)	45.8 (119/260) (39.6–52.0)	33.0 (67/203) (26.6–39.9)	25.7 (96/373) (21.4–30.5)	95.9 (186/194) (92.0–98.2)
All women except HSIL referral Paps (n = 1330)	87.4 (167/191) (81.9–91.8)	39.5 (222/562) (35.4–43.7)	31.5 (182/577) (27.7–35.5)	18.5 (167/902) (16.0–21.2)	94.4 (404/428) (91.8–96.4)

Table 4
Histopathology review and two year follow-up combined: Subjects reclassified as CIN2+ based on histopathology review and two year follow-up (n = 1447).

Clinical site	Number of incremental subjects with CIN2+	Number detected by MHS	Sensitivity MHS (%)
Histopathology review	38	33	86.8
2 year follow-up	29	27	93.1
Total	67	60	89.6

Of the 38 subjects where histopathology review indicated CIN2+ was not diagnosed by the site pathologist, 21 of these subjects also had up to two-year follow-up results. Combining these with the 29 cases missed by the current management guidelines (those identified with CIN2+ during the two year follow-up) resulted in a total of 50 cases of missed CIN2+, 44 of which (88.0%) were detected by MHS at the time of study enrollment. Six of these cases were initially diagnosed as CIN2+ by the site pathologist and later diagnosed as either CIN1 or normal by both QA pathologists. Eliminating these six cases from the data presented in Table 6 left a total of 44 cases of CIN2+ missed by the current management guidelines, of which 38 (86.4%) were correctly identified as CIN2+ by MHS.

For the 804 subjects with both histopathology review and two year clinical follow-up data available, there were 742 evaluable cases; 132 were diagnosed with CIN2+, including those reclassified due to pathology review. Management according to the current guidelines detected CIN2+ in 88 of these cases for a sensitivity of 66.7%, while MHS detected 120 for a sensitivity of 90.9%, as shown in Table 6. The 88 CIN2+ cases include six cases originally diagnosed as CIN2+ by the site pathologists and later diagnosed as normal or CIN1 by both QA pathologists. The 36.4% increase in sensitivity shown by MHS over the current management guidelines is statistically significant, using McNemar's Test ($p < 0.0001$). Excluding HSIL cytology, the current management guidelines detected 48 of 81 CIN2+ (59.3%) cases, while MHS detected 69 of 81 CIN2+ (85.2%) cases, an improvement of 43.8% ($p < 0.0001$). Specificity of MHS for women in the follow-up cohort with normal histology was 40.4% (113/280) and for women with CIN1, it was 35.5% (117/330).

Discussion

The ability of MHS to detect CIN2+ in this pivotal study was similar to that previously reported for smaller populations tested with earlier prototypes of the device [6,7,16,17]. Sensitivity of MHS was 91.3% (252/276) for women with CIN2+ lesions and 93% (93/100) for women with CIN3+, while specificity for women with normal or benign histology was 38.9% and specificity for women with CIN1 histology was 30.3%. Pooling the normal/benign cases with CIN1 cases resulted in a specificity of 34.5%, a positive predictive value of 24.7% and a negative predictive value of 94.4%. There were no adverse events and subjects tolerated evaluation with MHS well.

While the study protocols and primary objectives of the MHS study reported here and the ALTS trial differed in some ways, both studies used follow-up data to assess whether a new modality, MHS in our study and high risk HPV testing in ALTS, could potentially improve management of women referred for colposcopy and biopsy based on the current management guidelines. In both ALTS and this study, HPV Hybrid Capture 2 (HC-2) data were collected, and the vast majority (over 90%) of women in this study were either positive for high risk HPV subtypes or were cytologically and/or histologically diagnosed with dysplasia, for which high risk HPV infection is nearly ubiquitous. Still, not all women in the study were found to be positive for high risk HPV subtypes and, by way of comparison, there were 57 subjects for which both HPV and MHS results were available. Sensitivity of MHS for CIN2+ was 91.2% compared with 84.2% for HPV, a difference that was not statistically significant. For the subset of women with two year clinical follow-up resulting in a diagnosis of CIN2+, MHS detected 27/29 CIN2+ (93.1%) and HPV HC-2 detected 20/29 CIN2+ (69.0%), with three of the HPV results not available due to insufficient quantity for analysis.

Table 5
MHS results for subjects with CIN2+ diagnosis delayed by the standard of care, evaluable follow-up subjects only (n = 742).

Classification	Number of subjects with CIN2+	Number detected by MHS	Sensitivity MHS (%)
Reclassified as CIN2+ based on QA review histopathology	21	17	81.0
Reclassified as CIN2+ based on up to 2 year follow-up histopathology	29	27	93.1
Total	50	44	88.0

Table 6
Sensitivity for standard of care and MHS for 804 subjects with both histopathology review and up to two year follow-up data.

Follow-up procedure	Standard of care[a] (%)	MHS (%)
Histopathology review	79.6 (82/103)	90.3 (93/103)
2 year follow-up	20.7 (6/29)	93.1 (27/29)
Total	66.7 (88/132)	90.9 (120/132)

[a] Includes Pap test cytology, HPV and colposcopy.

In summary, the primary findings from the follow-up group analyses were:

- Sensitivity for detection of CIN2+ with the current management guidelines was 66.7% (88/132), which was similar to the sensitivity of the current management guidelines reported by ALTS, which was 65% for CIN3.
- MHS detected 90.9% of CIN2+ in the cohort of women with follow-up data, which was 36.4% more CIN2+ than identified by the current management guidelines ($p < 0.0001$).
- MHS detected 88.0% (44/50) of the cumulative cases of CIN2+ missed by managing according to the current guidelines.

There were 24 false negative CIN2+ cases attributable to MHS, but only five of the false negatives were clearly diagnosed as CIN3 lesions, while the rest were borderline CIN1/2, CIN2 or borderline CIN2/3 lesions. Most tests for cervical disease, such as Pap cytology and HPV are less sensitive for CIN2 than CIN3 [26,27]. Because so few high grade lesions were missed, the negative predictive value for CIN3 of MHS was 99%. In addition, eight of the 24 false negative CIN2+ (33.3%) also were missed by tests used under current guidelines, so that a false negative MHS in those cases would not have delayed diagnosis or treatment.

In the group of women with follow-up data available, specificity of MHS was approximately 40% for women with normal cervices and slightly lower for women with CIN1. Since essentially all women in the study were referred for colposcopy and biopsy, this specificity represents the percentage of women that could have avoided colposcopy and biopsy of cervices that were normal or had CIN1.

A positive MHS test will require the clinician to assess the patient carefully for significant CIN2+. While colposcopy is often the first choice of many clinicians, the clinician will have the option to reevaluate over time with proven biologic markers, resample either with colposcopically directed biopsy or perform endocervical curettage. While prescribing the correct choice of follow-up is beyond the scope of this manuscript, a positive MHS adds clinical value to the assessment if ones goal is to find clinically relevant cervical lesions.

MHS is a noninvasive test that reports an immediate, objective result (e.g., high or low likelihood of CIN2+). Exit interviews suggest that women will be receptive to this new form of cervical evaluation [28]. While quantitative cost effectiveness assessments are beyond the scope of this study, one could estimate that given the relatively low costs of the device and procedure (expected to be under $60 per test including the amortized cost of the device and single use disposable), the adoption of this technology is justified as an economic alternative to the current standard of care under which more than 80% of colposcopies and biopsies are performed on women who do not harbor CIN2+ disease. If the results of this pivotal study were extended to all women in the US referred for colposcopy annually, approximately 170,000 women each year would be diagnosed with CIN2+ earlier than they would being managed according to the current guidelines. This would result in lower treatment costs, possibly lower morbidity and, potentially, improved outcomes. MHS might also identify 1.2 million women annually that could avoid the expense, morbidity and anxiety of undergoing colposcopy and biopsies when they don't need it, potentially saving the health care system billions of dollars.

Conflict of interest statement

None of the authors have declared a conflict of interest, with the exception of Dr. Sternfeld who purchased stock in the company that manufactures the MHS device.

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