Preliminary Assessment of Cervical Spectroscopy for Primary Screening of Moderate and High Grade Cervical Dysplasia

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Objective: The implementation of organized Pap test screening programs has been successful in reducing both the incidence and mortality due to cervical cancer. However, the Papanicalou (Pap) test has several characteristics that make it less than the ideal screening test, including a high false negative rate, referral of a large number of women without disease to colposcopy and biopsy, delay in reporting and the requirement for a laboratory infrastructure and trained cytotechnicians. In many parts of the world where cervical cancer is common, the infrastructure does not exist for the implementation of laboratory based screening tests such as Pap or HPV. In order to overcome these limitations, there is a need to develop and evaluate cost effective new technologies with operating characteristics that are fundamentally conducive to accepted screening objectives. One such potential technology is multimodal hyperspectroscopy (MHS), an in vivo test which does not require a tissue sample for laboratory analysis, is easy to perform, provides an immediate and objective result and more recently has been engineered to meet the low cost required by screening programs. The objective of the current study is to examine the potential for MHS as a primary screening test.

Table 1. Age Distribution for 296 Patients

Age Category (Years)	Number	Percent (%)
Median	27	
Range	16 - 70	
16 - 20	47	15.9
21 - 30	124	41.9
31 - OVER	125	42.2

Image 1—LuViva MHS Device

Methods: In this seven-center pivotal study, 1,607 women at risk for cervical neoplasia were tested using MHS (LuViva® Advanced Cervical Scan, Guided Therapeutics, Inc. Norcross, GA), including 1,457 with abnormal Papanicolaou Pap cytology, one with no referral Pap result and 149 with normal or benign cytology, but were at risk for other reasons including positive Human Papilloma Virus (HPV) results, previous dysplasia and/or recurrent benign findings. A subset of the data from the pivotal trial (Table 1) was analyzed to simulate a screening population and evaluate MHS (Image 1) as a primary screening modality. In order to estimate the screening performance of MHS, the sensitivity was calculated for subjects with known precancerous lesions (i.e., CIN3+identified by at least 2 of 3 QA histopathologists with no diagnoses of CIN1 or Normal) and the specificity for women verified as free of any dysplasia on the basis of negative Pap, negative for high risk HPV and with histopathology. Data analyses included receiver operating characteristic (ROC) curves along with estimates of sensitivity, specificity and predictive values.

Table 2. Reason for Referral with Histology Outcomes for 296 subjects

Histology	REFERRAL PAP CATEGORIES							
	Negative or Benign*	ASC-US	AGC	AGUS	ASC-H	LSIL	HSIL/ Cancer	TOTAL
Normal	14	51	0	0	0	0	0	65
CIN2	2	26	0	0	6	79	26	139
CIN3+	0	16	1	0	5	27	43	92
* Referred on the basis of Positive HPV, previous dysplasia or other risk factors								296

Results: Data from 91 subjects with CIN3+ lesions, 140 with CIN2 lesions and, to simulate a population of normal women, 65 subjects free of dysplasia as verified by referral cytology, negative colposcopy, negative HPV and normal histopathology (Table 2) were analyzed. For primary screening, a higher specificity is desired over a higher sensitivity in order to reduce the burden of over-referrals to more expensive and invasive procedures, such as biopsy. Using a prospective algorithm originally developed to assess MHS as a post-screening triage test, MHS demonstrated sensitivity of approximately 50% for CIN2 and CIN3+ with a corresponding specificity of 84%. All false positive cases had referral cytology of ASC-US and there were no false positives among the cases with negative cytology but referred to colposcopy for other reasons (positive HPV, followed for previous dysplasia). An improved algorithm that used a reduced set of spectroscopic variables produced a cross-validated sensitivity of approximately 60% and a corresponding specificity of 88% (Table 3). This compares favorably with the performance of the Pap test, which has lower sensitivity (20-35%) but minimally higher specificity (90-95%), according to meta-analysis of published studies[1](Figure 1), (Table 4).

Table 3. Effectiveness of MHS compared to Pap

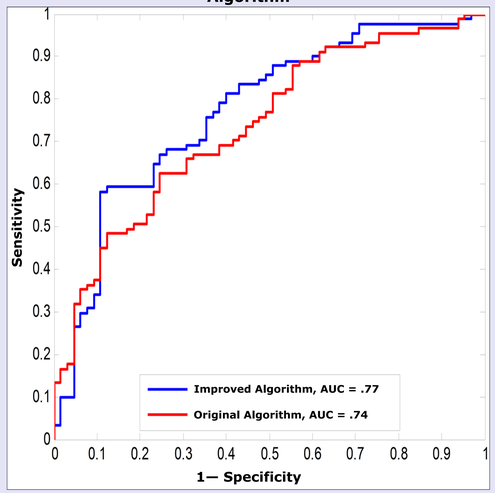
Value (%)	Sensitivity	Specificity
MHS	50 - 60	84 - 88
Pap[1]	20 - 35	90 - 95

Table 4. Specificity of MHS in simulated screening analysis

Normal Women Subgroup	Number Correct/Tested	Specificity @ 60% Sensitivity
Referral Pap Normal	14/14	100%
Referral Pap ASC-US	44/51	86.3%

"MHS can provide an immediate objective result at the point of care, so that management can occur without delay and loss to follow up."

Figure 1. ROC curves for Prospective and Improved Algorithm



Conclusions: MHS, while originally evaluated as a triage to colposcopy, shows potential for a screening application, particularly in territories with no established screening program currently in place. MHS can provide an immediate objective result at the point of care, so that management can occur without delay and loss to follow up. MHS is also cost effective with no associated laboratory cost and is easily transportable. MHS has been successfully tested on over 3,000 women with no adverse events. The preliminary results reported here justify further investigation into MHS as a primary screening modality. To better evaluate MHS for primary screening, a larger scale clinical trial is planned integrating a larger sample size of normal cervices.

References

1 Fahey, Michael T., Irwig, Les and Macaskill, Petra. "Meta-analysis of Pap Test Accuracy". American Journal of Epidemiology. Vol. 141, No. 7 (1995): 680-689.

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