Low-cost, high-resolution imaging for detecting cervical precancer in medically-underserved areas of Texas

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HIGHLIGHTS

• High-resolution microendoscopy provides real time evaluation to detect high-grade cervical precancer without a biopsy.
• High-resolution microendoscopy significantly decreased the number of false positives compared with traditional colposcopy.
• High-resolution microendoscopy image quality remained consistent across different clinical settings in urban and rural Texas.

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ABSTRACT

Objective. Cervical cancer rates in the United States have declined since the 1940’s, however, cervical cancer incidence remains elevated in medically-underserved areas, especially in the Rio Grande Valley (RGV) along the Texas-Mexico border. High-resolution microendoscopy (HRME) is a low-cost, in vivo imaging technique that can identify high-grade precancerous cervical lesions (CIN2+) at the point-of-care. The goal of this study was to evaluate the performance of HRME in medically-underserved areas in Texas, comparing results to a tertiary academic medical center.

Methods. HRME was evaluated in five different outpatient clinical settings, two in Houston and three in the RGV, with medical providers of varying skill and training. Colposcopy, followed by HRME imaging, was performed on eligible women. The sensitivity and specificity of traditional colposcopy and colposcopy followed by HRME to detect CIN2+ were compared and HRME image quality was evaluated.

Results. 174 women [227 cervical sites] were included in the final analysis, with 12% [11% of cervical sites] diagnosed with CIN2+ on histopathology. On a per-site basis, a colposcopic impression of low-grade precancer or greater had a sensitivity of 84% and a specificity of 45% to detect CIN2+. While there was no significant difference in sensitivity (76%, p = 0.62), the specificity when using HRME was significantly higher than that of traditional colposcopy (56%, p = 0.01). There was no significant difference in HRME image quality between clinical sites (p = 0.77) or medical providers (p = 0.33).

Conclusions. HRME imaging increased the specificity for detecting CIN2+ when compared to traditional colposcopy, HRME image quality remained consistent across different clinical settings.

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1. Introduction

Cervical cancer remains a significant global health problem, especially in medically-underserved areas (MUAs) of the world [1]. Most cases of cervical cancer and related deaths occur in low- and middle-income countries where access to cervical cancer screening and prevention is limited. In contrast, the incidence and mortality of cervical cancer in the United States (U.S.) and other high-income countries have significantly decreased due to the implementation of cervical cancer screening with cytology and/or human papillomavirus (HPV) testing as a standard part of routine women’s health care [2]. However, cervical
cancer incidence is higher among medically-underserved women living in poverty in the U.S. [3–5].

The incidence and mortality of cervical cancer in Texas along the Texas-Mexico border are among the highest in the United States, with rates of 12.3 per 100,000 and 4.1 per 100,000 respectively; in contrast, the overall incidence and mortality of cervical cancer in the U.S. are 8 per 100,000 and 2 per 100,000 respectively [6,7]. The Rio Grande Valley of Texas (RGV) is a region along the Texas-Mexico border that is made up of some of the poorest counties in the state of Texas: Hidalgo, Cameron, Willacy, and Starr counties [8]. Over 20% of people under the age of 65 years living in the RGV have no health insurance, severely limiting their access to health care, including services for cervical cancer prevention [4,9]. Another factor contributing to limited health care access is the lack of trained medical providers who are able to provide follow-up diagnostic and treatment services for women who have a positive screening test (abnormal cytology and/or positive HPV test) [10].

The standard of care in the U.S. for a woman with a positive cervical screening test is to undergo colposcopy, a procedure in which acetic acid is placed on the cervix and a medical provider examines the cervix with a colposcope (a magnifying instrument) to identify any potential precancerous lesions [11]. Abnormal lesions identified by the provider as potential precancer are biopsied and submitted for pathologic evaluation, the results of which take days or weeks to return depending on the type and availability of pathology services required. Any diagnosis of high-grade precancer is followed-up with ablative or excisional treatment to remove the dysplastic cells and prevent the development of cancer.

The ability to identify precancerous lesions during colposcopy is a skill that requires training and practice, and providers with this expertise are not always available in MUAs [12]. In vivo microscopy has the potential to assist medical providers in the accurate detection of precancerous lesions at the point-of-care. We developed a high-resolution microendoscope (HRME), a low-cost fiber-optic device that images cervical epithelial cell nuclei in real time, providing morphologic information associated with high-grade dysplasia [13–15]. The HRME system is equipped with real time image analysis software to provide decision-making support at the point-of-care. Recent studies conducted in Brazil at a central hospital and mobile clinic found the HRME to have similar sensitivity and specificity to detect high-grade cervical precancer and cancer as traditional colposcopy performed by an experienced colposcopist [16]. In this study, we aimed to evaluate the feasibility and clinical performance of the HRME in five clinical settings in Texas: an outpatient clinic at a tertiary academic cancer center in Houston, TX, an outpatient clinic at a large county hospital in Houston, TX, two federally-qualified health care clinics in the RGV, and one mobile clinic in the RGV. Furthermore, the study was conducted with medical providers of different skills and training to investigate the potential for HRME to support the detection of cervical high-grade precancer in a variety of clinical settings in the U.S.

2. Materials and methods

2.1. Study design

We conducted a single-arm prospective study to evaluate the use of colposcopy followed by HRME imaging in MUAs in Texas to diagnose high-grade cervical precancerous lesions. The study conducted in Houston, TX (Clinical Trial ID: NCT02420665) was approved by the institutional review boards at The University of Texas MD Anderson Cancer Center (MD Anderson) (IRB# 2014-0368) and Rice University (IRB# 2017-385). The study conducted in the RGV (Clinical Trial ID: NCT02714439) was approved by the institutional review boards of The University of Texas Medical Branch at Galveston (UTMB) (IRB# 14-0302), Rice University (IRB# 2017-436), MD Anderson (IRB# 2015-0477), and The University of Texas Health Science Center at Houston School of Public Health (UTHealth) (IRB# HSC-SPH-16-0569).

2.1.1. Clinical settings

The study was conducted at five clinical sites in Houston and the RGV of Texas: MD Anderson outpatient colposcopy clinic (Houston), Lyndon B. Johnson County Hospital (LBJ) outpatient clinic (Houston), the UTMB Dysplasia and Cancer Stop Clinic located in McAllen, TX (RGV), Su Clinica Brownsville in Brownsville, TX (RGV), and the UTHealth Mobile Health Clinic (RGV). All of the clinical sites primarily serve uninsured and underinsured populations, with the exception of the clinic at MD Anderson.

MD Anderson is a tertiary care hospital specializing in cancer care and prevention. LBJ is a public county hospital that primarily serves uninsured or underinsured patients in the Houston area. The LBJ Hospital colposcopy clinic is staffed by physicians and nurse practitioners from MD Anderson. For this study, patients seen at either the MD Anderson or LBJ colposcopy clinics were examined by a gynecologic oncologist or general gynecologist from MD Anderson.

The UTMB Dysplasia Cancer Stop Clinic and Su Clinica Brownsville are both federally-qualified health care clinics in the RGV. For the study, colposcopy examinations at the UTMB clinic were conducted by a general gynecologist from Galveston who travels to the clinic in the RGV once per month, while colposcopy examinations at Su Clinica were conducted by a local general gynecologist and nurse practitioner who typically provide colposcopy services at that site. The UTHealth Mobile Health Clinic is a mobile clinic supported by UTHealth that rotates between different sites in the RGV region on a monthly basis to provide health care to those without health insurance. Screening with cytology/HPV testing and colposcopy are provided by one physician assistant who staffs the mobile clinic.

2.1.2. Patient enrollment

Patients were eligible to participate in the study if they were visiting the clinic for a colposcopy examination due to an abnormal Pap test, positive HPV test, and/or had a history of cervical dysplasia and met the following criteria: 1) had an intact cervix (patients who had undergone a previous LEEP, cone, and/or cryotherapy were eligible); 2) were not pregnant or breastfeeding; 3) were at least 21 years of age; 4) had no known allergy to profylavine, acriflavin, or iodine; and 5) were willing and able to provide written informed consent. Women of childbearing potential were required to have a negative pregnancy test within the past 14 days in order to be eligible.

2.1.3. High-resolution microendoscopy

The HRME is an in vivo imaging device that allows medical providers to further interrogate cervical lesions noted during a clinical exam (Fig. 1). The HRME consists of a portable, low-cost fluorescence

Fig. 1. Photo of the HRME. Photo of the high-resolution microendoscope (HRME).
molecular image and analyzed the data to identify the growth patterns of various cell types. The results showed that the new technique could accurately predict the progression of the disease in individual patients.

3. Results

Table 1 summarizes the results of the study. The data showed that the new technique was significantly more accurate in predicting the progression of the disease compared to the traditional methods. The researchers also noted that the new technique was more cost-effective and easier to implement in clinical settings.

4. Conclusion

In conclusion, the new technique offers significant advantages over traditional methods in predicting the progression of the disease. Further research is needed to validate these findings in a larger patient population. However, the results suggest that this new technique has the potential to revolutionize the way we approach the treatment of this disease.
Table 1
Summary of clinical data for enrolled patients included in the final analysis.

<table>
<thead>
<tr>
<th>Clinical sites</th>
<th>Houston, TX</th>
<th>Rio Grande Valley, TX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The University of Texas MD Anderson Cancer Center</td>
<td>UTMB Dysplasia and Cancer Stop Clinic</td>
</tr>
<tr>
<td></td>
<td>Lyndon B. Johnson Hospital</td>
<td>Su Clinica Brownville</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UHealth Mobile Health Clinic</td>
</tr>
<tr>
<td>Medical providers (no. providers)</td>
<td>Gynecologic oncologist (1) General gynecologist (1)</td>
<td>Gynecologic oncologist (1) General gynecologist (1) Physician assistant (1)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Final pathology diagnosis per patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/ benign</td>
<td>11 (61%)</td>
<td>49 (70%)</td>
</tr>
<tr>
<td>CIN1</td>
<td>6 (33%)</td>
<td>11 (15%)</td>
</tr>
<tr>
<td>CIN2/3</td>
<td>1 (6%)</td>
<td>11 (15%)</td>
</tr>
<tr>
<td>AIS</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number of cervical sites</td>
<td>19</td>
<td>85</td>
</tr>
<tr>
<td>Final pathology diagnosis per site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. sites (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/ benign</td>
<td>12 (63%)</td>
<td>59 (70%)</td>
</tr>
<tr>
<td>CIN1</td>
<td>6 (32%)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td>CIN2/3</td>
<td>1 (5%)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td>AIS</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number of HRME + sites by final pathology diagnosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤CIN2</td>
<td>6 (33%)</td>
<td>35 (49%)</td>
</tr>
<tr>
<td>CIN2+</td>
<td>1 (100%)</td>
<td>12 (52%)</td>
</tr>
</tbody>
</table>

Bold numbers represent the overall number of patients/cervical sites.

4. Discussion

In the U.S., women who have a positive cervical cancer screening test are referred for colposcopic evaluation. Medical providers, especially those in MUAs, do not always have access to the training required to perform colposcopy due to limited time, funding, or proximity to a training location. HRME imaging provides real time evaluation of the cervix that can be used in addition to colposcopy to support clinicians in detecting high-grade precancerous lesions at the point-of-care.

Moreover, the inclusion of HRME imaging with colposcopy can reduce the number of unnecessary biopsies, decreasing clinical costs and patient discomfort. The primary finding of our study is that quality HRME imaging of the cervix is possible in a variety of clinical settings, ranging from a high-resource cancer specialty clinic in Houston staffed by a gynecologic oncologist, to a mobile clinic located in one of the most underserved regions of Texas staffed by a physician assistant.

There were no significant differences in HRME image quality between clinical sites or medical providers. This is most relevant for MUAs of the U.S. where expert clinicians might not always be available and the automatic and real time feedback of HRME imaging could offer assistance with cervical precancer detection.

In this study, the per-site specificity of colposcopy followed by HRME imaging was significantly higher than traditional colposcopy when using a colposcopic impression threshold of low-grade precancer or worse for detecting CIN2+. As part of standard of care, colposcopists take biopsies of any precancerous lesions found on exam to confirm any diagnosis of CIN2+ [21]. In this study, taking biopsies based on HRME would have resulted in 21% fewer unnecessary biopsies being taken (88 HRME false positive sites vs 111 false positive sites by traditional colposcopy) with no significant difference in the detection of CIN2+. Three patients (6 cervical sites) with CIN2+ were missed using HRME, in comparison to two patients (4 cervical sites) using traditional

Fig. 2. HRME images of four cervical sites. HRME images of four cervical sites from four different patients. A–D) provide the colposcopic impression, the HRME result, and the final histopathology diagnosis along with the corresponding HRME image for each cervical site. A–C) are cases in which both the colposcopy impression and the HRME result corresponded with the final histopathology result, while D) is an example in which the colposcopic impression and HRME result differed and HRME correctly identified that the area did not contain CIN2+.
colposcopy, however the detection for CIN3+ was the same with both HRME and traditional colposcopy missing two patients (4 cervical sites) diagnosed with CIN3.

The HRME uses a 0.8 mm diameter probe to provide flexibility when imaging different parts of the cervix. A widefield imaging/visualization method, such as colposcopy, is needed to guide the placement of the probe so that HRME images are taken of the most suspicious areas of the cervix. However, expert colposcopists are not always available in MUAs, and even when colposcopists are available, colposcopic image interpretation can still be inaccurate [22,23]. A recent study showed that using deep learning approaches to classify cervigrams (a widefield imaging technique used to screen for cervical cancer) could more accurately detect CIN2+ than the original cervigram interpretation provided by an expert physician colposcopist [24]. Following the publication of this study, MobileODT, a company that develops low-cost and portable visual assessment technology, is now exploring how to incorporate automated visual evaluation on their Enhanced Visual Assessment (EVA) system, a mobile smartphone-based colposcope, to provide reliable colposcopy results in MUAs [25]. Pairing automatic visual evaluation of the cervix with the automatic image interpretation of the HRME could make it possible to accurately detect CIN2+ without the need for biopsy.

The ultimate goal of the HRME is to omit biopsies altogether to provide the diagnosis and treatment of high-grade cervical precancer in a single patient visit. This is especially important in MUAs where patient follow-up is low or timely pathology services are unavailable. Future work is now focused on incorporating automatic visual evaluation methods of the cervix when using the HRME to increase the specificity of the HRME and further decrease the number of false positives associated with the current system.

The strengths of this study are the demonstration that HRME imaging can be used by medical providers of different levels of training at various clinical sites, including MUAs in Texas. Additionally, HRME imaging can help significantly decrease the number of false positives

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**Fig. 3.** Graphs comparing the positivity of colposcopy vs HRME. Graphs showing the positivity rate for colposcopy and HRME in comparison to the final histopathology result on a per-patient basis. A) 2 × 2 tables showing the correlation of colposcopy and HRME results for patients diagnosed with <CIN2 (above) and CIN2+ (below). B) Bar graph showing positivity rate for colposcopy and HRME stratified by the final histopathology diagnosis for each patient.

**Fig. 4.** Graph of sensitivity and specificity. Sensitivity and specificity of traditional colposcopy and HRME to detect CIN2+ on a per-patient and per-site basis. Significance was calculated using McNemar’s test. Error bars represent 95% exact binomial confidence intervals.
Currently associated with traditional colposcopy. The main limitation of this study is that there were not as many cases of CN2+ as there were <CN2, resulting in larger confidence intervals when calculating sensitivity in comparison to specificity. Furthermore, not enough patients were recruited at each clinical site to provide a comparison of the sensitivity and specificity of HRME imaging between clinical sites or medical providers. Future work would expand the study to be able to provide such analysis.

HRME imaging offers a visual way to further interrogate abnormal lesions of the cervix during a traditional gynecologic exam that can help support clinicians to detect high-grade precancerous lesions at the point-of-care.

Author contribution

Rodriguez A, Gowen R, Fisher-Hoch S, Schmeler K, and Richards-Kortum R were all co-principal investigators who co-designed the study. Rodriguez A, Gowen R and Schmeler K also were medical providers who conducted the study. Parra S participated in data collection, conducted the analysis of the final results, and wrote and prepared the final manuscript. Cherry K and Schwarz R participated in data collection and analysis. Schmeler K and Richards-Kortum R helped write and prepare the final manuscript. All other authors were medical providers who conducted the study. All authors reviewed and approved the final manuscript before submission.

Declaration of Competing Interest

One author (Richards-Kortum R) is named as an inventor on patent applications for high resolution imaging owned by Rice University and The University of Texas. The authors report no other conflicts of interest.

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