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# Low-Cost High-Resolution Microendoscopy for the Detection of Esophageal Squamous Cell Neoplasia: An International Trial

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**BACKGROUND & AIMS:** Esophageal squamous cell neoplasia has a high mortality rate as a result of late detection. In high-risk regions such as China, screening is performed by Lugol's chromoendoscopy (LCE). LCE has low specificity, resulting in unnecessary tissue biopsy with a subsequent increase in procedure cost and risk. The purpose of this study was to evaluate the accuracy of a novel, low-cost, high-resolution microendoscope (HRME) as an adjunct to LCE. **METHODS:** In this prospective trial, 147 consecutive high-risk patients were enrolled from 2 US and 2 Chinese tertiary centers. Three expert and 4 novice endoscopists performed white-light endoscopy followed by LCE and HRME. All optical images were compared with the gold standard of histopathology. **RESULTS:** By using a per-biopsy analysis, the sensitivity of LCE vs LCE + HRME was 96% vs 91% ($P = .0832$), specificity was 48% vs 88% ($P < .001$), positive predictive value was 22% vs 45% ($P < .0001$), negative predictive value was 98% vs 98% ($P = .3551$), and overall accuracy was 57% vs 90% ($P < .001$), respectively. By using a per-patient analysis, the sensitivity of LCE vs LCE + HRME was 100% vs 95% ($P = .16$), specificity was 29% vs 79% ($P < .001$), positive predictive value was 32% vs 60%, 100% vs 98%, and accuracy was 47% vs 83% ($P < .001$). With the use of HRME, 136 biopsies (60%; 95% confidence interval, 53%–66%) could have been spared, and 55 patients (48%; 95% confidence interval, 38%–57%) could have been spared any biopsy. **CONCLUSIONS:** In this trial, HRME improved the accuracy of LCE for esophageal squamous cell neoplasia screening and surveillance. HRME may be a cost-effective optical biopsy adjunct to LCE, potentially reducing unnecessary biopsies and facilitating real-time decision making in globally underserved regions. ClinicalTrials.gov, NCT 01384708.

*Keywords:* Esophageal Neoplasm; Endoscopy; Early Detection of Cancer.

Esophageal squamous cell neoplasia (ESCN) is the sixth leading cause of cancer death worldwide, with only 1 in 5 patients surviving more than 3 years because of diagnosis at an advanced stage.[1–3] In the developing world, ESCN is more common than adenocarcinoma, with a particularly high prevalence in northern China, Central Asia, and Iran.[4] In northern China, age-standardized incidence rates exceed 100 per 100,000 per year, compared with the United States, which has approximately 1.4 per 100,000.[4,5] This geographic variation likely stems from a multitude of factors including low socioeconomic status, diet, nutritional deficiencies, and thermal injury.[3] In high-risk regions, endoscopic screening has been implemented, albeit inconsistently, and with limited success. The reasons for these shortcomings are multifactorial and include lack of funding, infrastructure, and trained personnel.[6] Given these constraints, a low-cost, portable, and accurate method of diagnosing ESCN would be invaluable in improving early detection in resource-limited settings.

An early diagnosis of ESCN offers a significant opportunity to improve outcomes. When detected at an early stage (severe dysplasia or intramucosal carcinoma), endoscopic treatment can be performed by endoscopic mucosal resection or radiofrequency ablation with dramatically improved morbidity and survival rates of greater than 90%.[7–10] Unfortunately, intramucosal neoplasia can appear as small erosions, flat mucosal lesions, or normal mucosa, making it difficult to visualize on routine high-definition white-light endoscopy (HD-WLE), even for advanced

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*Abbreviations used in this paper:* CI, confidence interval; CICAMS, Cancer Institute and Hospital, the Chinese Academy of Medical Sciences; CLE, confocal laser endomicroscopy; ESCN, esophageal squamous cell neoplasia; HD-WLE, high-definition, white-light endoscopy; HRME, high-resolution microendoscopy; LCE, Lugol's chromoendoscopy; NBI, narrow band imaging; NPV, negative predictive value; PPV, positive predictive value.


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endoscopists.[11] Currently, endoscopic screening and surveillance is performed in high-risk patients using Lugol's chromoendoscopy (LCE).[12–14] Although LCE increases the sensitivity of HD-WLE to greater than 95%, specificity remains poor (<65%) because inflammation and benign mucosal changes mimic neoplasia, resulting in unnecessary biopsies (LCE positive, pathology negative) and increased cost.[13,15,16] Repeat procedures are always necessary after LCE if treatment is warranted, therefore increasing time and cost, as well as possible patient loss to follow-up evaluation.

Advanced endoscopic imaging solutions have been developed but widespread dissemination has been limited by high cost or limited accuracy. Confocal laser endomicroscopy (CLE) provides 1100× magnified, subcellular views of the esophageal epithelium and can differentiate ESCN from benign esophageal mucosa with high diagnostic accuracy (>95%).[17–19] Current CLE platforms are expensive (>$150,000) and available in only a few tertiary care centers worldwide.[17,18] Narrow-band imaging, an image-enhancement technology, uses narrow-bandwidth filters of different wavelengths to visualize the microvasculature including intrapapillary capillary loop patterns. Despite an accuracy rate as high as 95%, similar to LCE, narrow-band imaging (NBI) is limited by poor specificity.[20–24] In addition, NBI is operator-dependent, with experienced endoscopists outperforming novices (eg, sensitivity of 100% for experienced endoscopists vs 53% for novices in one study on a per-lesion basis).[23]

To address these issues, we developed a novel, low cost (<$3500), portable, battery-operated, high-resolution microendoscope (HRME) that provides subcellular resolution images when used with a topical fluorescent agent.[25–31] When inserted through the endoscope's accessory channel and placed in gentle contact with the mucosa, the 1-mm fiberoptic microendoscope provides clear delineation of cellular features, including nuclear size, crowding, and pleomorphism. Nuclear size can be quantified using image analysis software, assisting the endoscopist to rapidly differentiate benign epithelium from neoplasia in real time (Figure 1).

The aims of this international multicenter trial were to evaluate the accuracy and efficiency of this novel approach in the hands of both expert and novice endoscopists performing ESCN screening and surveillance. Specifically, we compared the performance characteristics of LCE vs LCE + HRME in the hands of both expert and novice microendoscopists, and the number of LCE-positive biopsies saved and patients saved any biopsy with use of HRME. Our goal was to see if HRME could enhance the current gold standard of LCE by increasing specificity and decreasing unnecessary biopsies.

## Materials and Methods

### *Study Design and Patient Selection*

This prospective, single-arm study was approved by the Institutional Review Boards at the Icahn School of Medicine at Mount Sinai (New York, NY; GCO 10-0982/GCO 10-0443); Rice University (Houston, TX); MD Anderson Cancer Center (Houston, TX; 2010-0234); First University Hospital (Changchun, China); and the Cancer Institute and Hospital, the Chinese Academy of Medical Sciences (CICAMS) (Beijing, China). The 2 Chinese sites are both areas of high incidence of ESCN. A total of 147 consecutive patients previously scheduled for upper endoscopy with LCE were enrolled. Screening subjects were from high-risk provinces (northern China) or had a history of

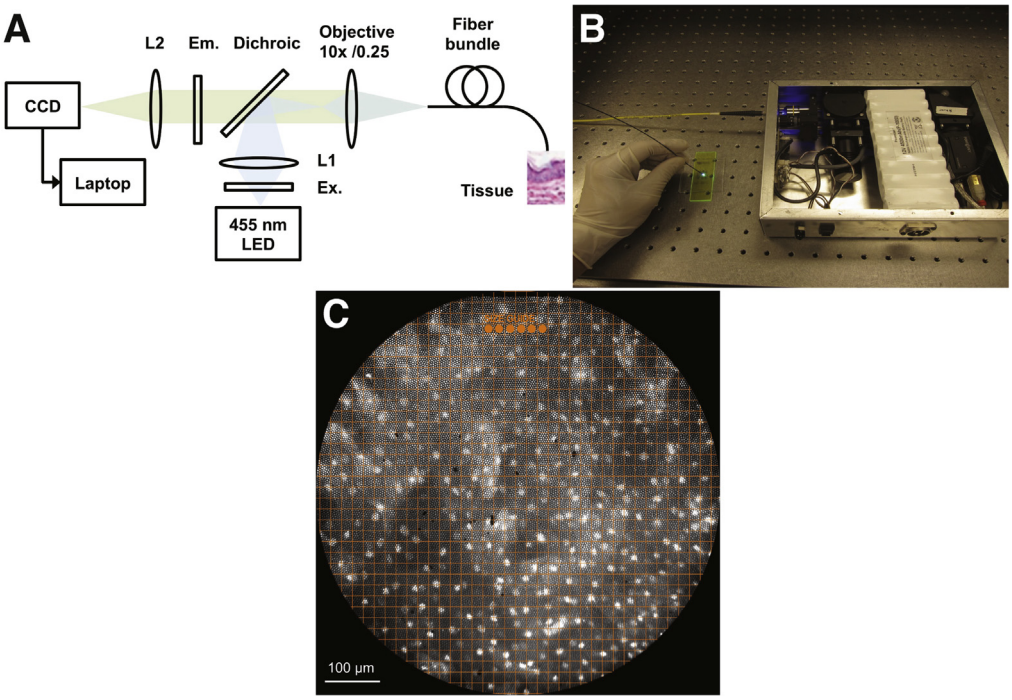


**Figure 1.** (*A*) Device configuration. (*B*) The device is battery-operated and easily fits in a briefcase. (*C*) To facilitate objective, real-time assessment of nuclear size and spacing, a grid with 19.4-$\mu$m spacing was superimposed on the display monitor and 15.1-$\mu$m diameter dots were placed. The image shows normal esophageal mucosa. CCD, charged-couple device; Em, emission; Ex, excitation; LED, light emitting diode.