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A High-Resolution Microendoscope Improves Esophageal Cancer Screening and Surveillance: Implications for Underserved Global Settings Based on an International Randomized Controlled Trial

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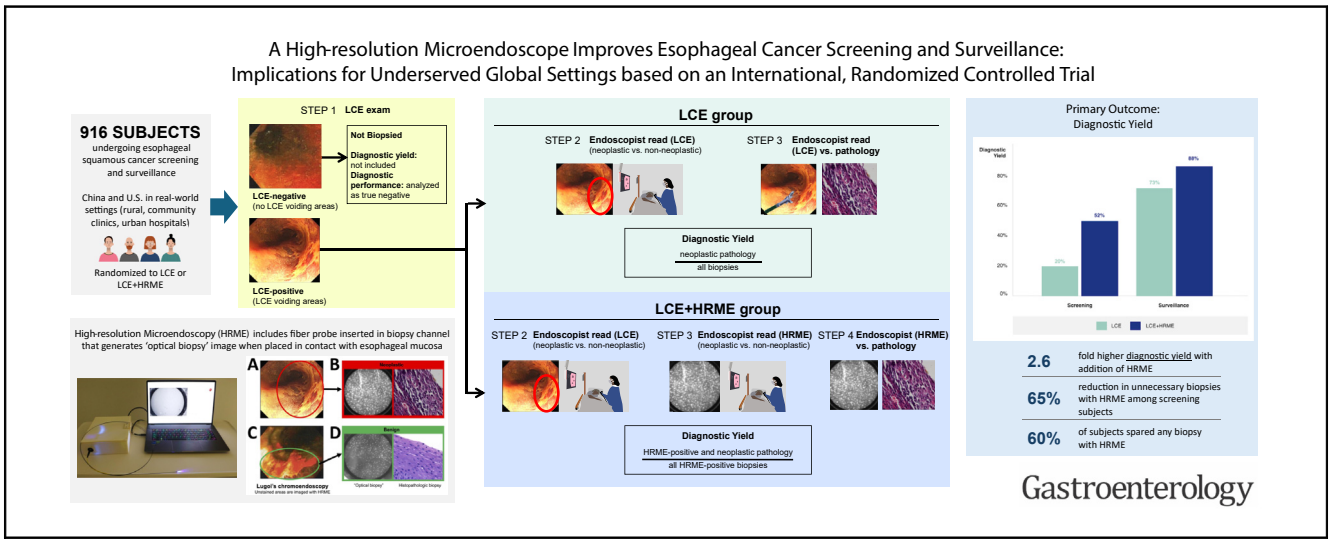

BACKGROUND & AIMS: Lugol's chromoendoscopy (LCE)–based detection of esophageal squamous cell neoplasia (ESCN) is limited by low specificity. High-resolution microendoscopy (HRME) was shown to improve specificity and reduce unnecessary biopsies when used by academic endoscopists. In this international randomized controlled trial, we determined the clinical impact, efficiency, and performance of HRME in true global health contexts with a range of providers. **METHODS:** Individuals undergoing screening or surveillance for ESCN by expert and novice endoscopists were enrolled in China and the United States from diverse clinical settings. Participants were randomized to LCE (standard of care) or LCE + HRME (experimental). The primary outcomes were the efficiency and clinical impact of LCE vs LCE + HRME using gold-standard consensus pathology. **RESULTS:** Among 916 consented participants, 859 (93.8%) were recruited in China and 36 (3.9%) in the United States; 21 (2.3%) were excluded due to incomplete procedure or data. In the screening arm, 217 participants were randomized to LCE and 204 to LCE + HRME; in the surveillance arm, 236 were randomized to LCE and 238 to LCE + HRME. HRME increased efficiency in screening: diagnostic yield (neoplastic/total biopsies) improved from 20.0% (95% confidence interval [CI], 12.7–29.2) to 51.7% (95% CI, 32.5–70.6) with 65.2% (95% CI, 54.6–74.9) of biopsies potentially saved and 59.7% (95% CI, 47.5–71.1) of participants potentially spared any biopsy. Six participants (0.7%) had neoplasia missed by the endoscopist on HRME (false negatives); of these, 3 were moderate or high-grade dysplasia missed by novices. **CONCLUSIONS:** A low-cost microendoscope improves the efficiency and clinical impact of ESCN screening and surveillance when combined with LCE. HRME may spare unnecessary biopsies, leading to cost savings in underserved global settings

where the disease is prevalent. (ClinicalTrials.gov, Number NCT02029937)

Keywords: High-Resolution Microendoscopy; Esophageal Squamous Cell Neoplasia; Esophageal Cancer; Artificial Intelligence; Computer-Assisted Diagnosis.

Esophageal cancer is the sixth leading cause of cancer-related death worldwide.[1] Of the 2 subtypes, esophageal squamous cell neoplasia (ESCN) is the predominant subtype, accounting for 85% of all esophageal cancer cases globally.[2] In high-prevalence areas (northern China, central Asia, Iran, southern/eastern Africa), known as cancer belts, the incidence of ESCN can exceed 100 per 100,000 persons.[3] Early detection of ESCN is accomplished through endoscopic screening and surveillance in high-risk populations using Lugol's chromoendoscopy (LCE).[4,5] Although LCE has high sensitivity (96%–100%),[6,7] it is limited by its low specificity (37%–63%),[8–10] resulting in unnecessary, costly biopsies. In many underserved regions, biopsy-related costs (consumables, interpretation) are often borne out of pocket by the patient.[11–15] In low-resource, global settings with high ESCN burden and significant infrastructure, clinical, and financial limitations, there is a great need for technologies that can reduce unnecessary biopsies, provide an immediate diagnosis, and facilitate point-of-care therapy.

The high-resolution microendoscope (HRME) is a low-cost (<$2,500), portable, battery-powered device composed of a fiber-bundle probe inserted into the accessory channel of a standard endoscope (Figure 1). When used with a topical fluorescent contrast agent (ie, 0.01% proflavine), it provides cellular and subcellular images of the esophageal mucosa.[16–19] These high-resolution images (4.5-μm spatial resolution) can be interpreted by trained endoscopists to provide a real-time assessment of the epithelium, thus differentiating benign from neoplastic mucosa (Figure 2). We previously evaluated HRME in ESCN diagnosis in a single-arm pilot study of 147 high-risk individuals enrolled from 4 academic hospitals in the United States and China. The addition of HRME to LCE resulted in improved accuracy (90% vs 57%) and specificity (88% vs 48%), without significantly compromising sensitivity, when compared to LCE alone.[7] Furthermore, 60% of unnecessary biopsies could have been spared with HRME when used by endoscopists with microendoscopic expertise and/or formal training and competency in HRME.[7] Indeed, in a cost modeling study, an HRME-based approach was shown to be more cost-effective than the standard of care (SOC) in both high-risk and average-risk settings.[20]

The purpose of this international, multicenter clinical trial was to expand upon the previous single-arm pilot study and evaluate this technology in real-world settings with highly diverse providers and clinical care environments. We aimed to determine the efficiency, clinical impact, and diagnostic performance of LCE + HRME in a true global health context involving a range of settings (rural, community-based screening sites; rotating clinics; urban hospitals; etc.) and a range of providers (advanced endoscopists, trainees, nurse endoscopists).

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Screening and surveillance for esophageal squamous cell neoplasia (ESCN) is currently performed using Lugol's chromoendoscopy (LCE), which has low specificity for neoplasia detection, resulting in unnecessary biopsies and cost.

NEW FINDINGS

In this international, multicenter randomized controlled trial, a low-cost high-resolution microendoscope (HRME) improved diagnostic yield, potentially spared unnecessary biopsies, and enhanced diagnostic performance of LCE-based evaluation for ESCN in a true global health context (low- and high-resource areas) when used by experts.

LIMITATIONS

Although the microendoscopic probe allows high-resolution visualization of the cellular and subcellular architecture and real-time neoplasia assessment, it must be used in conjunction with a wide-field, red-flag technology (LCE), given the small size of the probe (1 mm). Due to pandemic limitations, we were not able to meet our proposed sample size but were still able to meet our primary outcome (increase in diagnostic yield).

CLINICAL RESEARCH RELEVANCE

The addition of HRME improved diagnostic yield 2.6-fold in ESCN screening and spared unnecessary biopsies in 60% of participants. HRME helped experts improve their specificity in neoplasia detection among high-risk surveillance participants. Although HRME alone did not improve the specificity of novices, future computer-assisted diagnostic algorithms could potentially overcome limited user expertise in low-resource settings.

BASIC RESEARCH RELEVANCE

HRME images could form the basis for a machine learning–based image analysis program. If successful, this might allow for reliable onsite diagnostics without the need for local expertise.

Methods

Study Design and Population

We conducted a prospective, multicenter, randomized controlled trial of individuals undergoing screening or surveillance endoscopy for ESCN from December 2014 to October 2019. We recruited from the Ben Taub Hospital and Baylor–St.

*** Authors share co-first authorship; § Authors share co-senior authorship.**

Abbreviations used in this paper: **AI, artificial intelligence; CI, confidence interval; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; ESCN, esophageal squamous cell neoplasia; HGD, high-grade dysplasia; HRME, high-resolution microendoscopy; IRB, institutional review board; LCE, Lugol's chromoendoscopy; NBI, narrow-band imaging; NPV, negative predictive value; PPV, positive predictive value; SD, standard deviation; SOC, standard of care; WLE, white-light endoscopy.**

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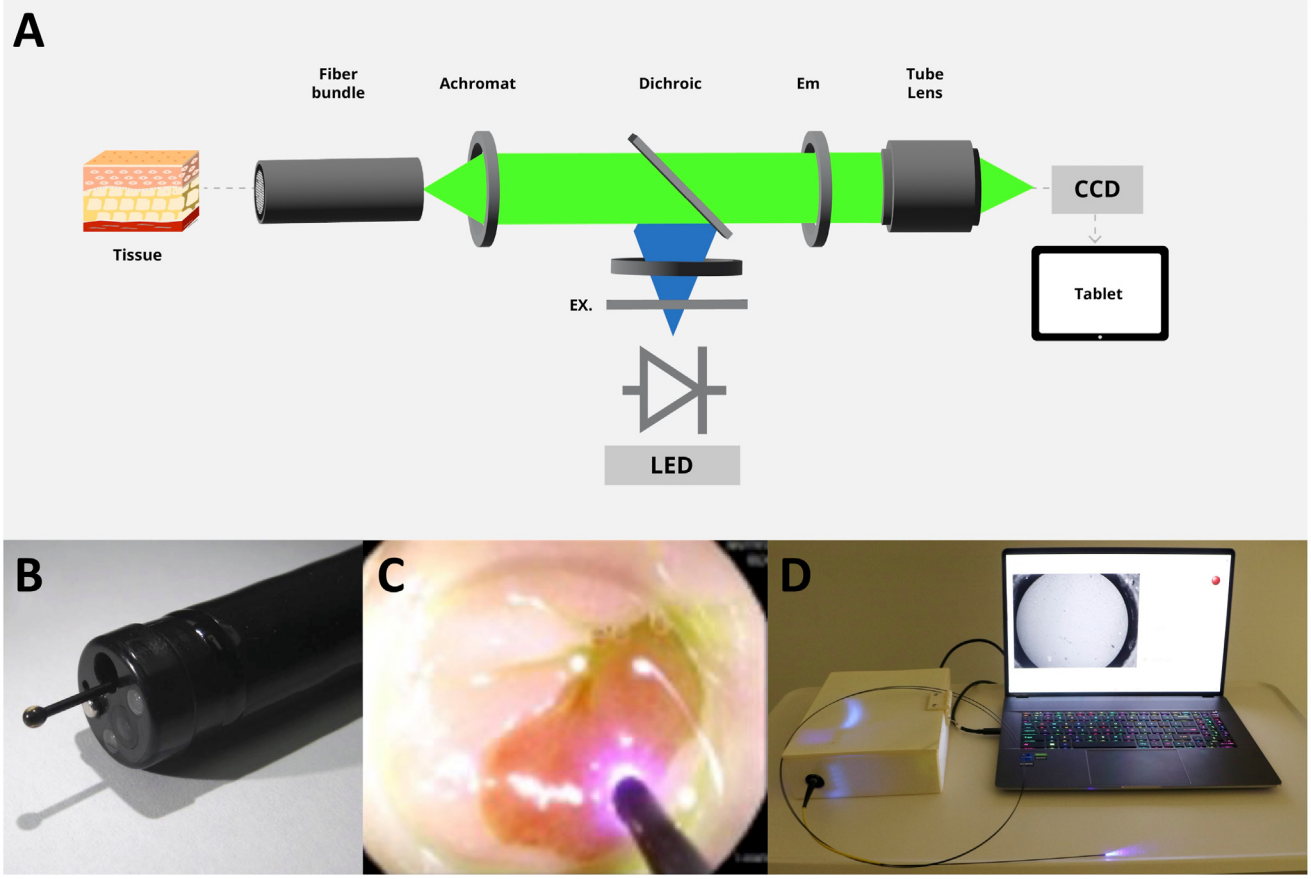

Figure 1. (*A*) Schematic the HRME device. (*B*) The design consists of a coherent fiber bundle that is placed in contact with the tissue to acquire high-resolution images when used with a topical fluorescent agent. (*C*) The flexible fiber probe is 1 mm in diameter and inserted through the biopsy channel. (*D*) Image of the HRME device.

Luke's Medical Center in Houston, Texas, United States (1 public and 1 private hospital), in addition to The Cancer Institute, Chinese Academy of Medical Science in Beijing, China; the First Hospital of Jilin University in Jilin, China; and several rural screening clinics in Feicheng, Shandong Province, and Yanting, Sichuan Province, China (Supplementary Figure 1). Participants were randomized to SOC upper endoscopy with LCE or SOC upper endoscopy with LCE plus HRME imaging using a permuted block randomization stratified by indication (screening or surveillance) and by study site. Randomization allocation was concealed in a sealed envelope and then revealed by a coordinator and relayed to the endoscopist before the start of the procedure. Participants recruited to the screening arm had a history of oropharyngeal squamous cancer (United States) or were from areas of high ESCN prevalence in China, where rotating endoscopy clinics were set up for periods of time. Participants recruited in the surveillance arm had a history of known dysplasia (low-grade dysplasia or higher) or were referred from external community screening clinics for possible early neoplasia (high-grade dysplasia [HGD], ESCN) warranting possible treatment. Inclusion criteria included age $\geq$18 years and willingness to provide informed consent and complete a telephone follow-up within 7 days of the endoscopy. Exclusion criteria included known cancer, nodule, or any lesion of $\geq$2 cm (in these cases, there would be no role or benefit to diagnostic optical imaging and/or endoscopic therapy); allergy to Lugol's iodine or proflavine contrast stains; or existing contraindication to upper endoscopy with biopsy (eg, significant cardiopulmonary disease, coagulopathy, pregnancy). All individuals provided written informed consent, and the study was approved by the institutional review boards (IRBs) at Baylor College of Medicine; Rice University; The Cancer Institute, Chinese Academy of Medical Science; and First Hospital of Jilin University. This clinical trial was registered using ClinicalTrials.gov identifier NCT02029937. All authors had access to the study data and reviewed and approved the final manuscript.

HRME

HRME has previously been described for imaging in ESCN, Barrett's esophagus, and colorectal polyps.[7,17,21,22] Briefly, HRME consists of a light source, 1-mm flexible fiberoptic probe, microscope objective lens, and a charge-coupled device camera. The portable fiberoptic probe is inserted into the endoscope channel and provides magnified (1100×) cellular and subcellular imaging of esophageal tissue when used with a topical fluorescent agent (ie, 0.01% proflavine). A high-power LED produces excitation light centered at 455 nm (20-nm full-width half maximum), which passes through a bandpass filter (40-nm full-width half maximum), is reflected at a 475-nm dichroic mirror, and passes through a 10×/0.25 numerical aperture infinity-corrected objective lens to illuminate the proximal end

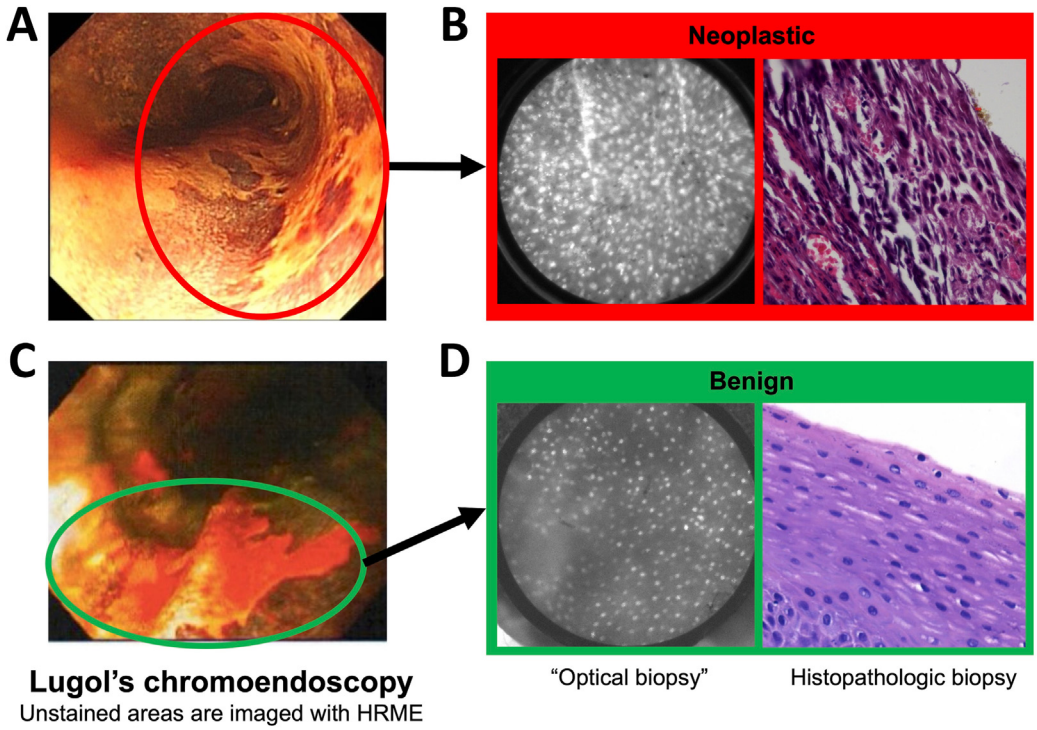

Figure 2. (*A*) Neoplastic as well as (*C*) benign areas can appear unstained on Lugol's iodine chromoendoscopy. These areas are imaged with HRME, which generates "optical biopsy" images that correspond closely with the subcellular imaging on pathology. (*B*) Neoplastic images have larger, crowded, pleomorphic nuclei along with architectural disorganization. (*D*) Nonneoplastic images have small, bright, and evenly spaced nuclei.

of the fiber bundle. The distal end of the fiber bundle is placed in gentle contact with the tissue surface. The fluorescent emission from the imaged site is transmitted through the dichroic mirror and emission filter and then imaged onto a charge-coupled device camera by a tube lens. The HRME images are transferred to a tablet computer for real-time display at 12 frames/second. The fiberoptic probe provides a 720-μm diameter field of view and 4.5-μm spatial resolution.

Endoscopist Training in HRME

A total of 15 endoscopists (6 expert and 9 novice microendoscopists) performed the study endoscopy on all study participants. Expert microendoscopists had performed a minimum of 25 HRME procedures in the past and had participated in prior HRME studies in the United States or China in academic centers. Novice microendoscopists were entirely new to HRME and included trainees, general gastroenterologists, non-gastroenterologist physicians, and nurse endoscopists (China) who had never used HRME in the past but were involved in general screening efforts. Our goal was to evaluate the technology in the hands of actual users in real-world, community-based settings where endoscopic ESCN screening is typically performed rather than academic centers alone. Nonetheless, all endoscopists were trained on HRME use and interpretation using a training presentation that included HRME still images and videos describing the visual differences between ESCN, dysplasia, esophagitis, and normal squamous epithelium. The fluorescent contrast stain (proflavine) is nuclear specific, and endoscopists were specifically trained to focus on nuclear and cytoplasmic features of neoplasia, including nuclear enlargement, crowding (increased nuclear/cytoplasm ratio), pleomorphism as well as architectural features (disorganization), and overlying keratin. After the training set, all endoscopists were shown a test set of 40 videos of HRME. All endoscopists were required to have an accuracy of $\geq$80% in the test videos before trial participation.

Standard-of-Care (LCE) Procedure

All participants underwent standard, high-definition white-light endoscopy (WLE) (Olympus GIF 180/190 endoscopes) without any digital chromoendoscopy or narrow-band imaging (NBI) followed by LCE with spraying of 1% Lugol's iodine dye stain (12 g iodine + 24 g potassium iodine in 1000 mL water diluted in a 1:3 ratio with saline, resulting in 1% iodine[23]) to the entire esophagus (red-flag imaging). LCE voiding areas ranged in size from 2 to 20 mm (typically, LCE voiding areas of $<$2 mm in size are not considered abnormal and are not biopsied). Per the SOC, LCE voiding (abnormal) areas were biopsied. Those with no findings on LCE (ie, LCE "normal"), with no voiding areas to image or biopsy, were considered true negatives (consistent with the SOC for LCE screening). Presence of esophagitis, ulcers, or masses on WLE were recorded but did not change the protocol.

Experimental (LCE + HRME) Procedure

In the LCE + HRME group, LCE voiding areas were targeted for imaging with HRME before biopsy. For HRME imaging, 3–9 mL (average, 6.1 mL) of topical proflavine hemisulfate 0.01% (weight/volume) was sprayed. Proflavine is a fluorescent

contrast agent that stains cell nuclei and was used as an investigational new drug (no. 102,217) under the U.S. Food and Drug Administration. It should be noted that residual Lugol's iodine does not interfere with HRME imaging due to the bright fluorescence of proflavine. After proflavine administration, the HRME probe was gently inserted through the biopsy channel of the endoscope and placed in contact with the LCE voiding area (<30 seconds). As an example, a typical 5- to 7-mm LCE voiding area would result in 5–7 images. The HRME images were displayed on a tablet computer and captured using a foot pedal, which froze and saved the images to a tablet computer. The endoscopist was asked their impression (neoplastic, nonneoplastic) after LCE and then again after HRME for each imaged site along with their clinical "plan of action" (biopsy; no biopsy; treat: resect with endoscopic mucosal resection [EMR], endoscopic submucosal dissection [ESD], and/or ablate). The HRME-imaged site was documented and either biopsied or resected (EMR or ESD) to ensure there was corresponding histopathology for all imaged sites. Per IRB requirements, if the LCE finding was abnormal, biopsy specimens were obtained (regardless of the HRME read) to adhere to the current SOC, which requires histopathologic evaluation of all LCE voiding (abnormal) areas. In the cases of EMR or ESD where multiple areas were imaged, the whole EMR/ESD specimen served as the final biopsy pathology specimen for all imaged sites.

Pathology

All biopsy specimens were sectioned and stained using H&E and interpreted by local pathologists. In addition, slides of all biopsied sites were interpreted by 2 expert study pathologists (D.G.R., S.M.D.), blinded to the randomization allocation and endoscopic findings, who provided a consensus read, which served as the gold standard for comparing LCE to LCE + HRME. All pathology was interpreted using a binary classification: neoplastic (ie, ESCN, HGD) or nonneoplastic (ie, low-grade dysplasia, esophagitis, normal).

Statistical Analysis

Comparisons of demographic and clinical characteristics between participants randomized to LCE or LCE + HRME groups were evaluated using Fisher's exact tests for categorical variables and *t* tests for continuous variables. The primary outcomes of this randomized controlled trial were efficiency (diagnostic yield, biopsy efficiency) and clinical impact (change in treatment plan, procedures potentially saved) of HRME. Secondary outcome was diagnostic performance in both ESCN screening and surveillance.

Primary outcome: efficiency. Efficiency was evaluated using diagnostic yield and biopsy efficiency. The calculation for diagnostic yield was taken from prior optical technology studies.[24] Diagnostic yield in the LCE (control) group was defined as the number of biopsy samples with neoplastic pathology (HGD or cancer) divided by the total number of biopsy specimens obtained, which reflects clinical practice. In the LCE + HRME (experimental) group, we were obligated by our IRB to adhere to the current SOC and biopsy all LCE voiding (abnormal) areas. This, however, does not reflect the impact of the HRME. To accurately reflect the number of neoplastic biopsy specimens obtained with use of the HRME, the diagnostic yield was calculated as the number of HRME neoplastic biopsy specimens with neoplastic pathology (HGD or cancer) divided by total the HRME neoplastic biopsy specimens (ie, biopsy specimens read as HRME neoplastic with an ensuing decision to biopsy or treat by the endoscopist). Again, this was done to quantify the effect of the HRME while accounting for the SOC, IRB requirements, and trial outcomes, which required tissue from all imaged sites. Proportions were calculated along with 95% confidence intervals (CIs) and compared between groups by the chi-square test. Ninety-nine patients had multiple (2–5) biopsies totaling 226 biopsies; to account for patients with multiple biopsies, a generalized mixed-models approach was used to account for within-patient correlation and compare the 2 groups.

Biopsy efficiency was classified as biopsies potentially saved with added classification by HRME (those that were classified as positive by LCE but were correctly classified as negative by HRME). That is, these are areas that would have been targeted for biopsy with LCE alone but were correctly read as negative by the HRME and (in theory) not biopsied. Individuals potentially spared any biopsy were defined as individuals who had all biopsy sites correctly changed from LCE-positive to HRME-negative, with all sites having nonneoplastic pathology.

Primary outcome: clinical impact. We evaluated the clinical impact of adding HRME to LCE by examining the change in clinical plan (biopsy vs no biopsy vs treat) based on the LCE read and the HRME read among individuals randomized to LCE + HRME. Procedures potentially saved were defined as a treatment plan correctly changed from "biopsy" to "resect/treat" with the addition of HRME, thus avoiding additional endoscopies. Additional time added by HRME was calculated as the mean HRME time after SOC endoscopy in the LCE + HRME group. Additionally, we reported mean endoscopy time in the LCE and LCE + HRME groups.

Secondary outcome: diagnostic performance. We calculated diagnostic performance, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy along with 95% CI, of the LCE and LCE + HRME groups. All LCE voiding areas underwent biopsy per SOC in both the LCE and LCE + HRME groups, and consensus read of biopsy pathology was used as the gold standard. Diagnostic performance was based on the endoscopist's interpretation of LCE or HRME as neoplastic or nonneoplastic at the time of endoscopy compared to gold standard pathology (Figure 3). Patients (n = 273) with normal LCE endoscopy findings (no LCE voiding areas and, therefore, no biopsies) were included as true negatives in the analysis, consistent with the current SOC and our prior paper (LCE sensitivity of 100% for neoplasia detection[7]). For the per-biopsy analysis, there was an assumption of 1 negative biopsy finding per LCE-negative patient. Lesions detected by LCE (LCE-positive) but missed by the endoscopist on HRME (HRME-negative) with resulting neoplastic pathology were counted as false negatives. We additionally stratified diagnostic performance based on endoscopist experience (ie, expert or novice) when available.

Participants with missing data were excluded from the analysis. Proportions were calculated along with exact 95% binomial CI and compared between the groups by the chi-square test or Fisher's exact test. Analyses were performed using SAS 9.4 (SAS Institute Inc) and R 4.3.1 (R Core Team). A *P* value of <.05 was considered statistically significant.

Sample size. Our initial goal was to recruit 1300 participants with 650 in each of the screening and surveillance arms. Efficiency measured by diagnostic yield was a primary outcome

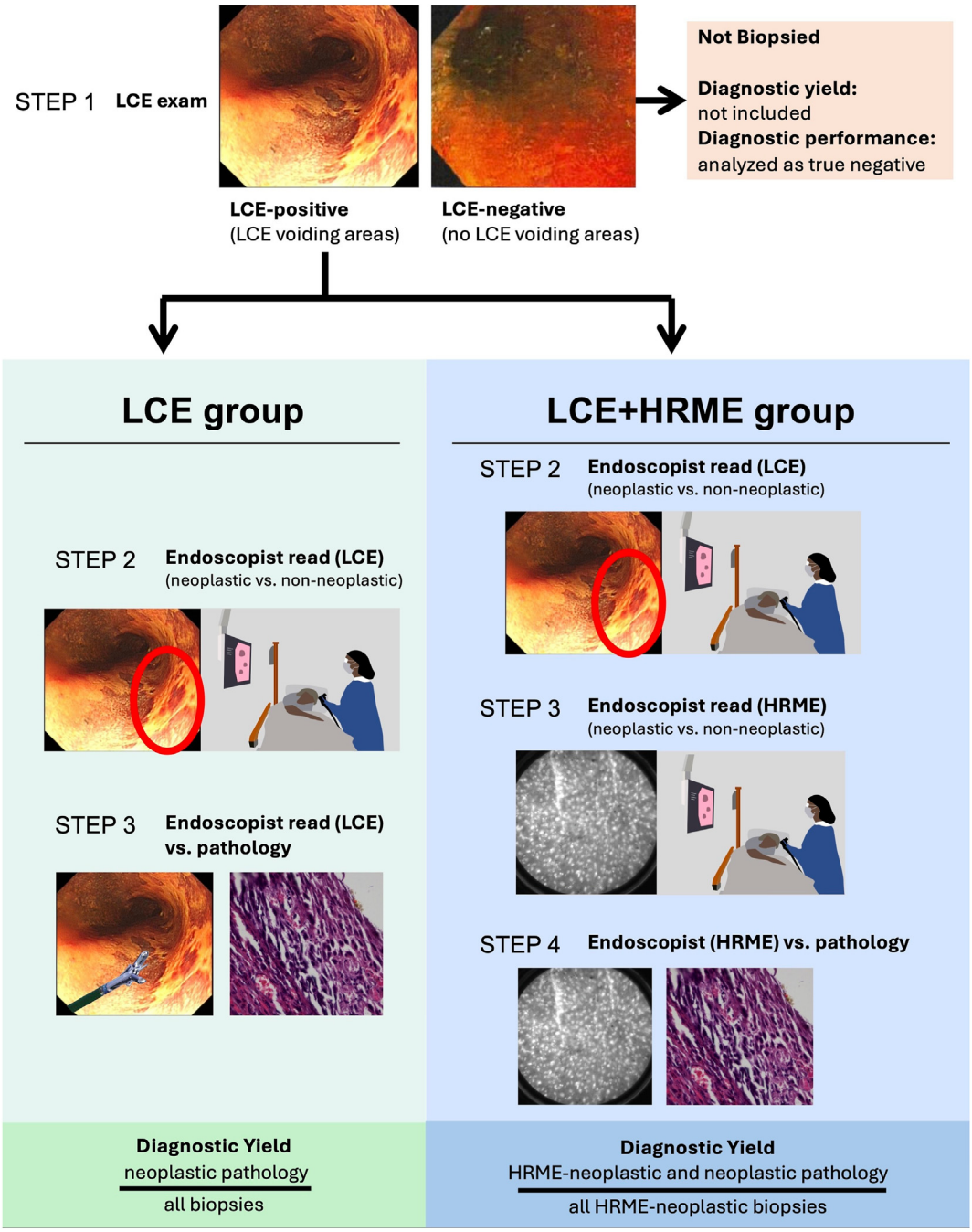

Figure 3. Procedure for participants randomized to LCE or LCE + HRME. The endoscopist interpreted the LCE voiding area as neoplastic or nonneoplastic in the LCE group. The endoscopist interpreted the LCE voiding area as neoplastic or nonneoplastic first on LCE examination and then using HRME in the LCE + HRME group. LCE voiding areas were biopsied to uphold the SOC.

of the study. In the screening group, we expected that one third of participants would be LCE-positive (n = 200, assuming an 8% drop-off). Based on our experiences,[7] estimating the diagnostic yield to be 50% with HRME and at most 25% in the LCE group, 650 participants would provide the study with 94% power to detect a 25% increase (50% vs 25%) in efficiency with LCE + HRME compared to LCE alone. More participants in the surveillance group could be deemed as LCE positive; thus, the power to detect the efficiency difference between LCE and LCE + HRME would be higher in the surveillance arm. Because of prolonged COVID lockdowns in China, the study was forced to terminate at 916 participants.

Results

Participant Characteristics

A total of 916 eligible participants were recruited and randomized (432 in screening arm, 484 in surveillance arm) from December 2014 to October 2019. A total of 21

participants were excluded after randomization due to incompletion of the full study protocol, including 3 participants with incomplete endoscopy due to desaturation or stricture, 12 participants with missing or unreadable pathology, and 6 participants who were enrolled but not scoped due to administrative issues in endoscopy (cancelled due to anesthesia, insurance verification, schedule changes). Of 895 participants included in the analysis, 887 (99.1%) received moderate sedation or monitored anesthesia care. Among these 895 participants, 76 (8.5%) had visible lesions (ulcer, mass) on WLE, which were all LCE voiding, and 175 (19.6%) had esophagitis on WLE. Among screening participants, 263 participants(62.5%) had negative findings on LCE (no LCE voiding lesions and therefore no biopsies); among surveillance participants, 10 participants (2.1%) had negative findings on LCE. The final number of participants analyzed in the screening arm was 217 randomized to LCE (with 232 sites) and 204 randomized to LCE + HRME (with 225 sites) and in the surveillance arm was 236 randomized to LCE (with 297 sites) and 238 randomized to LCE + HRME (with 268 sites) (Figure 4). All participants were analyzed in the group to which they were allocated.

Of 895 participants who completed the study, the mean age was 58.6 years (standard deviation [SD], 9.1 years), and 640 (71.5%) were men. A total of 36 participants (4%) were recruited from the United States, and 859 participants (96%) were recruited from China, which included 12% from rural areas. Overall, 1.5% of participants were White, 1.1% were Black, and 96.4% were Asian; 2.9% of participants reported Hispanic or Latino ethnicity. In the screening and surveillance arms, 7.9% of participants reported having a history of head and neck cancer, and 24.9% reported having a history of esophageal cancer in the surveillance arm. Overall, 27.9% of participants were current smokers, and 22.9% were past smokers. There were no differences in distributions of age, sex, race, ethnicity, study site, family history of esophageal cancer, smoking, and alcohol use between those randomized to LCE or LCE + HRME in both screening and surveillance arms (Table 1).

Primary Outcome: Efficiency—Diagnostic Yield and Biopsy Efficiency

In the screening arm, 20 of the 100 biopsy specimens had neoplastic pathology, making the diagnostic yield 20.0% (20 of 100; 95% CI, 12.7–29.2) in the LCE group. In the LCE + HRME group, 15 of the 29 LCE-positive/HRME-positive sites had neoplastic pathology, making the diagnostic yield 51.7% (15 of 29; 95% CI, 32.5–70.6; $P < .001$ compared to LCE alone), a 2.6-fold increase (Figure 5). In the surveillance arm, the diagnostic yield increased from 73.5% (216 of 294; 95% CI, 68.0–78.4) with LCE to 88.2% (217 of 246; 95% CI, 83.5–92.0) with the addition of HRME ($P < .0001$). The significantly increased diagnostic yield with the addition of HRME in the screening and the surveillance arms was also observed using the generalized mixed models when accounting for within-patient correlation ($P = .0025$ and $P = .0003$, respectively).

In the screening arm, of 92 LCE-positive biopsy specimens, 60 (65.2% [60 of 92]; 95% CI, 54.6–74.9) were HRME-negative with nonneoplastic pathology representing biopsies that potentially would have been saved with HRME. Additionally, 43 participants (59.7% [43 of 72]; 95% CI, 47.5–71.1) would have been potentially spared any biopsy with the addition of HRME. In the surveillance arm, of 261 biopsies, 10 biopsies (3.8% [10 of 261]; 95% CI, 1.9–6.9) would have been potentially spared (HRME-negative, nonneoplastic pathology), and 8 participants (3.5% [8 of 231]; 95% CI, 1.5–6.7) would have been potentially spared any biopsy with the addition of HRME.

Primary Outcome: Clinical Impact—Change in Treatment Plan and Procedures Potentially Saved

In the LCE + HRME group, 13 of 72 screening participants (18.1%; 95% CI, 10.0–28.9) and 3 of 231 surveillance participants (1.3%; 95% CI, 0.3–3.7) had a direct change in clinical plan based on HRME findings (biopsy vs no biopsy vs resect/ablate). The lack of a change in plan in the surveillance arm was related to the overwhelming preponderance of existing neoplasia (>98%) in the surveillance arm—nearly everyone in surveillance underwent either biopsy or resection. One participant in the surveillance arm had the correct change in plan from biopsy to resect, thus avoiding a second procedure.

Overall, the addition of HRME added a mean of 2.9 minutes (SD, 2.5 minutes) to the endoscopy. In the screening arm, the mean endoscopy time in the LCE group was 13.9 minutes (SD, 15.5 minutes) compared to 19.0 minutes (SD, 53.7 minutes) in the LCE + HRME group. In the surveillance arm, there was not a difference in the mean endoscopy time between the LCE group (33.8 minutes; SD, 70.3 minutes) and LCE + HRME group (34.5 minutes; SD, 49.9 minutes). Importantly, no adverse events occurred due to the proflavine fluorescent agent or the HRME procedure.

Secondary Outcome: Diagnostic Performance

Although there was an overall trend toward improved sensitivity in the screening arm with HRME, the greatest benefit of HRME was in high-risk participants undergoing surveillance. The addition of HRME improved accuracy from 80% (239 of 297; 95% CI, 75–85) to 87% (234 of 269; 95% CI, 83–91) and PPV from 80% (210 of 262; 95% CI, 75–85) to 88% (217 of 246; 95% CI, 84–92). Among high-risk surveillance participants, the high sensitivity of LCE (97% [210 of 216]; 95% CI, 94–99) was preserved with the addition of HRME (98% [217 of 222]; 95% CI, 95–99) (Table 2 and Supplementary Table 1).

Furthermore, among high-risk surveillance participants, expert microendoscopists increased their specificity from 36% (29 of 81; 95% CI, 25–47) to 100% (5 of 5; 95% CI, 48–100) with HRME, but novices did not improve their specificity with HRME (36% [29 of 81; 95% CI, 25–47] to 17% [6 of 35; 95% CI, 7–34]). Experts also improved their PPV (reduced false positives) with HRME from 80% (210 of 262; 95% CI, 75–85) to 100% (26 of 26; 95% CI, 87–100),

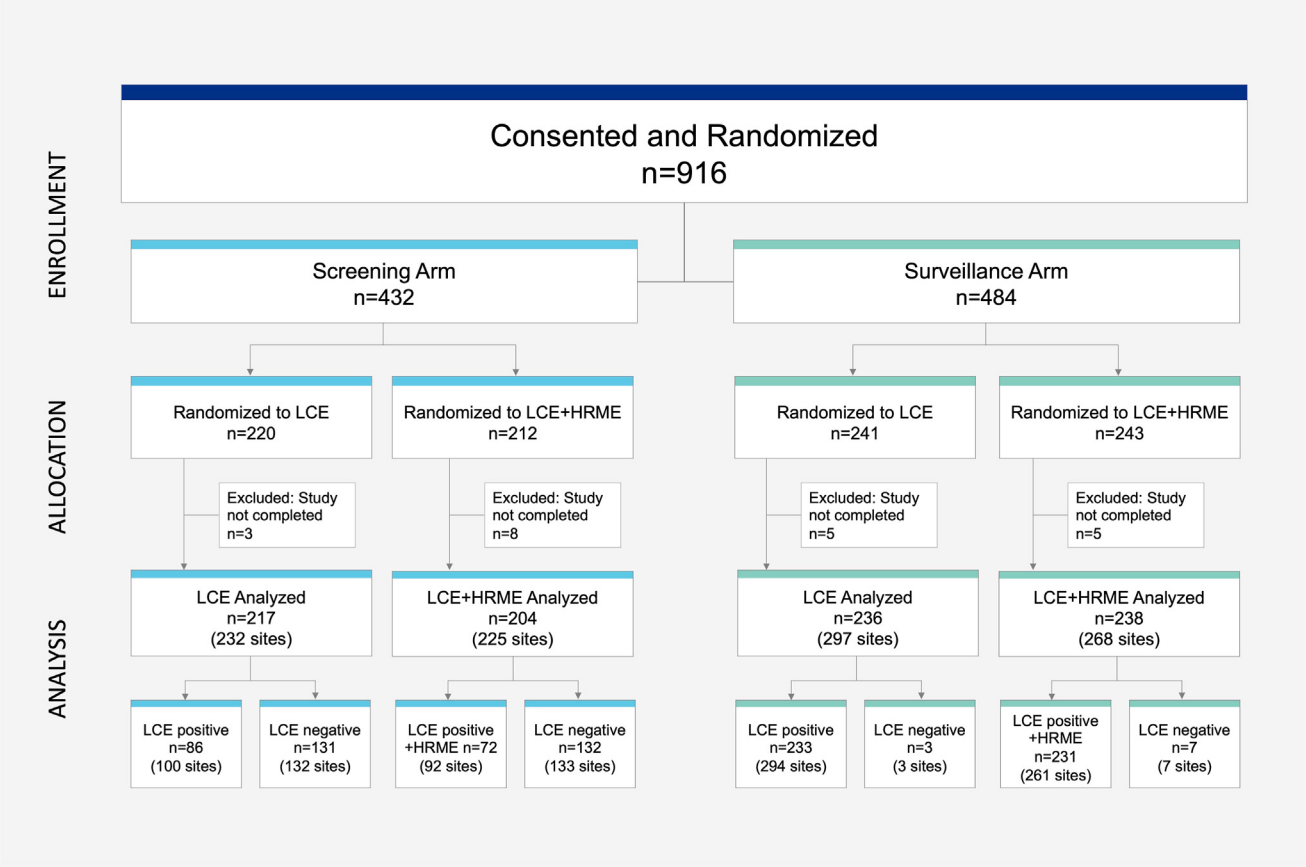

Figure 4. Schematic representation of participants enrolled and randomized to LCE or LCE + HRME stratified by the ESCN screening and surveillance arms.

which was not seen in novices (80% [210 of 262; 95% CI, 75–85] to 87% [191 of 220; 95% CI, 82–91]). With the addition of HRME to LCE, experts increased their overall accuracy from 80% (239 of 297; 95% CI, 75–85) to 94% (31 of 33; 95% CI, 80–99), whereas novices maintained similar accuracy (80% [239 of 297; 95% CI, 75–85] to 86% [197 of 229; 95% CI, 81–90]) (Supplementary Table 2).

False Negatives

Six participants (2 screening, 4 surveillance) had neoplasia missed by the endoscopist on HRME (HRME-negative, neoplastic pathology). Of these participants, 3 were missed by novices, including 2 with moderate-grade dysplasia (borderline neoplasia) (Supplementary Figure 2).

Discussion

In this randomized controlled trial, we evaluated the efficiency, clinical impact, and performance of a low-cost, mobile HRME system for ESCN detection in diverse global health settings (ie, academic hospitals, public hospitals, rural community sites, etc) using the usual (noncurated) range of providers performing cases in those real-world settings. In screening for ESCN, HRME improved diagnostic yield 2.6-fold and would have potentially spared 60% of participants from any biopsy, a potentially considerable cost savings. The addition of HRME improved accuracy in ESCN surveillance from 80% to 87%. Notably, the greatest benefit of HRME was seen among experts, who improved their specificity from 36% to 100% with HRME.

The greatest benefit of HRME in resource-limited settings is in clinical impact, efficiency, and cost savings. The diagnostic yield of biopsies increased 2.6-fold (20.0% to 51.7%) with HRME among participants undergoing screening, and 60% of participants would have been correctly spared any biopsy (LCE-positive correctly changed to HRME-negative). Although the expert endoscopists included in our study had high accuracy in interpreting LCE appearance, the SOC requires LCE-voiding areas of >5 mm to undergo biopsy for pathologic confirmation. Therefore, we calculated diagnostic yield based on the SOC biopsy protocol for LCE evaluation. HRME as an adjunct to LCE can better evaluate the LCE false positive lesions (ie, esophagitis) resulting in reduced biopsies. Pathology costs can exceed the cost of endoscopy in low- and middle-income countries, so a reduction in the costs and risks of unnecessary biopsies with the addition of HRME is not trivial. For example, in a US context, pathology services are reimbursed starting at US$70.[25] For an international context, biopsy costs were estimated at I$28.2 (Chinese currency converted to international dollars), which is almost as costly as the endoscopy itself (I$35.8).[20] A previous study found LCE +

Table 1. Comparison of Participants Randomized to LCE or LCE + HRME and Who Completed the Study in the Screening and Surveillance Arms

	Screening (n = 421)					Surveillance (n = 474)				
	LCE (n = 217)		LCE + HRME (n = 204)		*P* value[a]	LCE (n = 236)		LCE + HRME (n = 238)		*P* value[a]
Age, *y*, mean (SD)	56.2 (8.6)		55.7 (9.8)		.558	61.2 (8.0)		60.6 (8.9)		.469
	n	%	n	%		n	%	n	%	
Sex					.919					1.000
Female	78	35.9	72	35.3		50	21.2	49	20.6	
Male	138	63.6	131	64.2		185	78.4	186	78.2	
Unknown	1	0.5	1	0.5		1	0.4	3	1.3	
Race					.344					—
White	4	1.8	9	4.4		0	0	0	0	
Black	5	2.3	4	2.0		1	0.4	0	0	
Asian	200	92.2	190	93.1		235	99.6	238	100.0	
Unknown	8	3.7	1	0.5		0	0	0	0	
Ethnicity					.111					.448
Hispanic/Latino	14	6.5	6	2.9		4	1.7	2	0.8	
Non-Hispanic	201	92.6	195	95.6		231	97.9	236	99.2	
Unknown	2	0.9	3	1.5		1	0.4	0	0	
Study site					1.000					—
United States	19	8.8	17	8.3		0	0	0	0	
China	198	91.2	187	91.7		236	100.0	238	100.0	
Family history of esophageal cancer					.614					.347
Yes	1	0.5	2	1.0		19	8.1	26	10.9	
No	215	99.0	202	99.0		217	91.9	212	89.1	
Unknown	1	0.5	0	0.0		0	0.0	0	0.0	
Smoking status										
Never	137	63.1	123	60.3	.461	90	38.1	87	36.6	.952
Current	52	24.0	60	29.4		68	28.8	70	29.4	
Past	26	12.0	21	10.3		78	33.1	80	33.6	
Unknown	2	0.9	0	0		0	0	1	0.4	
Alcohol use status										
Never	135	62.2	139	68.1	.348	107	45.3	91	38.2	.270
Current	59	27.2	49	24.0		64	27.1	66	27.7	
Past	23	10.6	15	7.4		65	27.5	79	33.2	
Unknown	0	0	1	0.5		0	0	2	0.8	

[a]The *t* test or Fisher's exact test with unknown or missing data being excluded.

HRME to be more cost-effective than no screening or screening with LCE alone in high-risk populations (I$8173 per quality-adjusted life-year).[20]

To our knowledge, this is the first randomized controlled trial (in vivo study) comparing the diagnostic yield, clinical impact, and accuracy of LCE to LCE + HRME for ESCN detection in real-world, diverse global settings. The addition of HRME improved PPV (88% vs 80%) and accuracy (87% vs 80%) among high-risk surveillance populations while maintaining the high sensitivity of LCE. Our previous pilot study, which did not stratify participants based on screening or surveillance status, found that LCE + HRME resulted in sensitivity of 91%, specificity of 88%, PPV of 45%, NPV of 98%, and accuracy of 90% for ESCN detection on per-biopsy analysis.[7] A meta-analysis evaluated NBI (sensitivity, 94%; specificity, 93%), confocal laser endomicroscopy (CLE) (sensitivity, 94%; specificity, 90%), and autofluorescence imaging video endoscopy (sensitivity, 100%; specificity, 83%) in screening for ESCN.[26] However, these studies included technologies exclusively evaluated by experts, whereas our study also reflected real-world HRME use in the hands of novices (trainees, nurse endoscopists).

HRME is designed to be used in globally resource-limited settings as an adjunct to standard red-flag imaging with the goal of increasing diagnostic yield and decreasing unnecessary biopsies, procedures, and costs. In the hands of experts, the addition of HRME increases specificity while maintaining the high sensitivity of LCE. However, we have shown that specificity is severely limited in novices. Novices tended to overcall neoplasia (false positives), particularly in

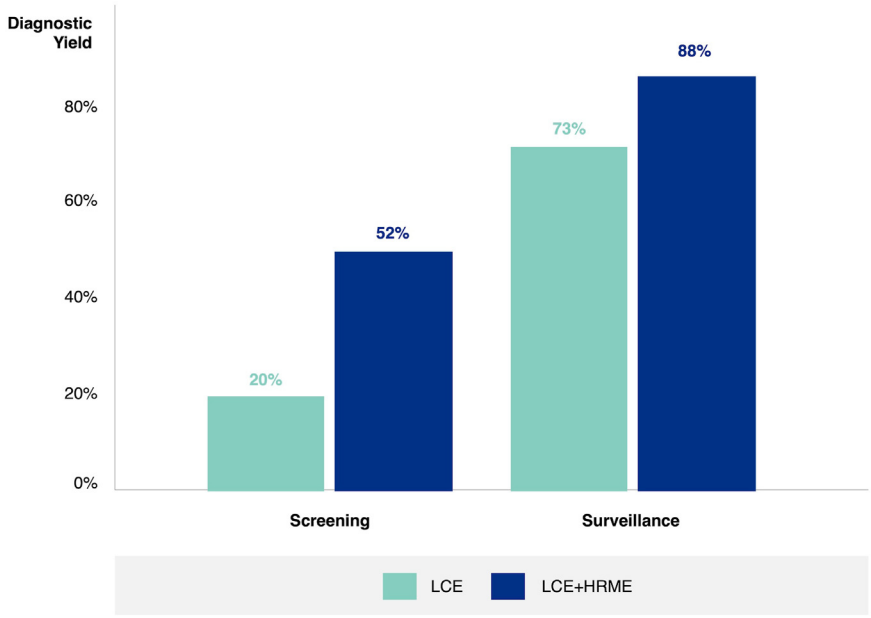

Figure 5. Comparison of diagnostic yield between LCE vs LCE + HRME among screening and surveillance participants.

surveillance populations, after finding LCE voiding lesions. User inexperience and/or bias may potentially be overcome with artificial intelligence (AI)–based tools. Indeed, we have previously shown that novices relying on an AI algorithm for HRME interpretation had a significant improvement in their specificity.[21] Implementation of HRME in global settings will depend on accurate interpretation of these "optical biopsy" images by an expert microendoscopist or, possibly, by an AI-assisted tool. Implementation studies examining the clinical impact of HRME on ESCN screening and surveillance along with real-time evaluation of an AI algorithm on endoscopist interpretation and stakeholder analysis are currently underway in Brazil and the United States.

Table 2. Diagnostic Performance With 95% CIs of HRME in Diagnosing ESCN Compared to LCE Alone

	Per biopsy			
	Screening		Surveillance	
	LCE (n = 232)	LCE + HRME (n = 225)	LCE (n = 297)	LCE + HRME (n = 268)
Sensitivity	0.75 (0.51–0.91)	0.83 (0.59–0.96)	0.97 (0.94–0.99)	0.98 (0.95–0.99)
Specificity	0.93 (0.89–0.96)	0.93 (0.89–0.96)	0.36 (0.25–0.47)	0.37 (0.23–0.52)
PPV	0.52 (0.33–0.71)	0.52 (0.33–0.71)	0.80 (0.75–0.85)	0.88 (0.84–0.92)
NPV	0.98 (0.94–0.99)	0.98 (0.96–1.00)	0.83 (0.66–0.93)	0.77 (0.55–0.92)
Accuracy	0.92 (0.88–0.95)	0.92 (0.88–0.96)	0.80 (0.75–0.85)	0.87 (0.83–0.91)
	Per patient			
	Screening		Surveillance	
	LCE (n = 217)	LCE + HRME (n = 204)	LCE (n = 236)	LCE + HRME (n = 238)
Sensitivity	0.74 (0.49–0.91)	0.88 (0.62–0.98)	0.97 (0.94–0.99)	0.98 (0.95–0.99)
Specificity	0.93 (0.88–0.96)	0.93 (0.88–0.96)	0.33 (0.20–0.50)	0.47 (0.29–0.65)
PPV	0.50 (0.31–0.69)	0.52 (0.32–0.71)	0.87 (0.82–0.91)	0.92 (0.88–0.95)
NPV	0.97 (0.94–0.99)	0.99 (0.96–1.00)	0.74 (0.49–0.91)	0.79 (0.54–0.94)
Accuracy	0.91 (0.87–0.95)	0.93 (0.88–0.96)	0.86 (0.81–0.90)	0.91 (0.87–0.94)

Strengths of the study include the prospective trial design with randomization of participants to LCE or LCE + HRME, stratified by screening or surveillance status. Additionally, pathologic diagnosis was the gold standard for the primary outcomes and was provided by consensus diagnosis between 2 expert pathologists, blinded to the endoscopic and HRME findings. Unlike prior clinical trials that included trained endoscopists, this study took microendoscopy "to the streets" and included the actual providers performing endoscopy in a true global health context: nurses, nongastroenterologists, and trainees. By evaluating real-world use of HRME in ESCN screening and surveillance, we found that novices tended to overcall neoplasia and relied heavily on the LCE findings, resulting in low specificity. In real-world applications of these advanced imaging technologies (ie, HRME, NBI, CLE), user expertise is a large barrier to diagnostic accuracy, but AI algorithms providing computer-assisted diagnosis may be a means to overcome user limitations. Studies that integrate AI algorithms into the HRME device for real-time clinical interpretation are currently underway.

Limitations of HRME are the lack of commercial availability currently and the investigational status of the proflavine fluorescent agent. Because HRME is limited by size of the probe (1 mm), it cannot be used as a stand-alone technology but in conjunction with another red-flag technology (LCE in the case of ESCN). Endoscopists were informed of the randomization when they started the procedure; however, this likely did not introduce bias because endoscopists provided a diagnosis and clinical plan for LCE and again for HRME in those randomized to HRME. Our findings may not be generalizable to other populations because our cohort was enriched with cases of neoplasia in the surveillance arm; therefore endoscopists, particularly novices, were likely to overcall neoplasia, leading to high false positive rates. The results should be viewed with caution given the multiple primary outcomes and lack of type 1 error adjustment for multiple testing. Additionally, we did not evaluate endoscopist confidence when interpreting HRME images. Follow-up studies that incorporate qualitative and quantitative measures of endoscopist confidence, particularly in the context of computer-assisted diagnosis, are currently underway. Finally, due to the pandemic and prolonged COVID lockdowns in China, we were only able to recruit 916 participants (70% of the proposed sample size), which may have lowered statistical power to detect the difference between the groups. However, even with the reduced recruitment, we were able to meet our primary outcome (sample size calculation to detect increase in diagnostic yield of 25%).

In summary, this multicenter, international randomized controlled trial in real-world global health settings showed that the addition of HRME to LCE improved diagnostic yield, decreased unnecessary biopsies, and enhanced clinical impact. Technologies that improve efficiency while decreasing costs are most needed in low-resource global settings with infrastructure and financial limitations and high ESCN rates. Furthermore, HRME improved accuracy among high-risk participants receiving surveillance endoscopy, particularly when used by experts. Although novices were not able to use HRME with high accuracy, we are examining AI algorithms to potentially help overcome this deficiency. Although real-time clinical data need to be obtained (and this is in progress), advanced imaging technologies can improve clinical efficiency and limitations in globally underserved settings to facilitate real-time diagnosis, impact, and cost reduction.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.10.025.

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Conflicts of interest
The authors disclose no conflicts.

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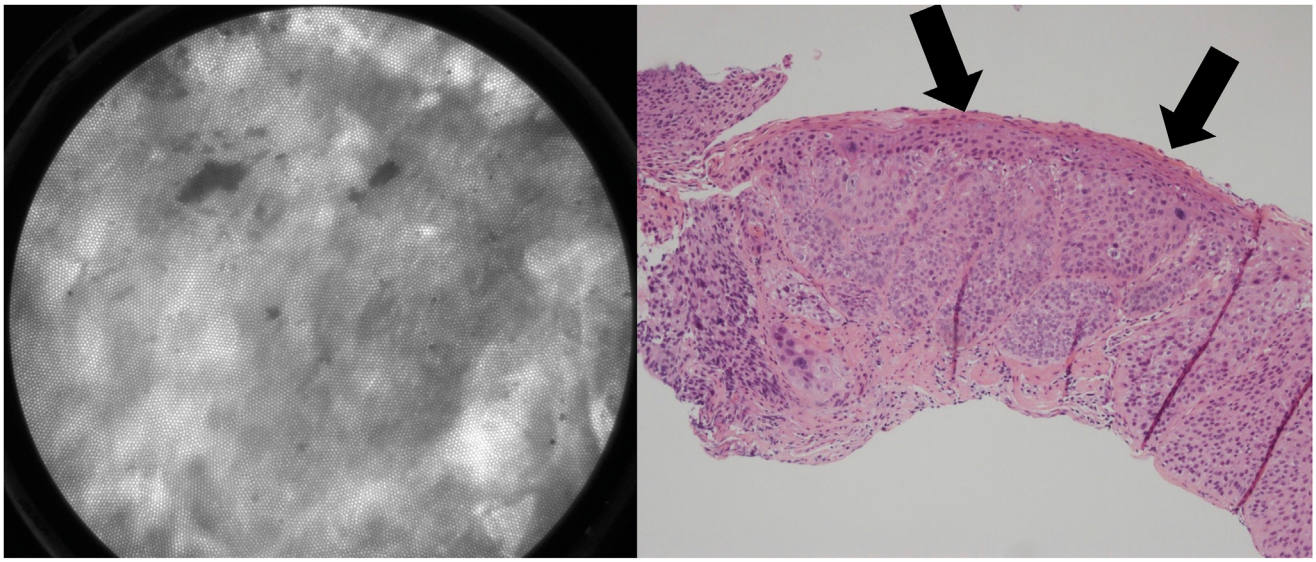
Data Availability
Deidentified data and supporting materials will be made available 3 months after publication to other researchers for a period of 3 years after the publication date upon reasonable request and approval from the corresponding author within limitations of the local institutional review board rules. The study protocol is included as a data supplement available with the online version of this article.

Supplementary Figure 1. Example of a rural community screening clinic in Feicheng, Shandong, China.



Supplementary Figure 2. Example of neoplasia overlooked on a human read of HRME. Human HRME interpretation is made challenging by the parakeratosis (*arrows*) covering the carcinoma in situ, which hides the underlying nuclei on the HRME image.

Supplementary Table 1. A 2 × 2 Table of Diagnostic Performance of HRME in Diagnosing Esophageal Squamous Cell Neoplasia Compared to LCE Alone

Per biopsy								
	Screening				Surveillance			
	LCE (n = 232)		LCE + HRME (n = 225)		LCE (n = 297)		LCE + HRME (n = 268)	
LCE/LCE + HRME	Path(+)	Path(–)	Path(+)	Path(–)	Path(+)	Path(–)	Path(+)	Path(–)
(+)	15	14	15	14	210	52	217	29
(–)	5	198	3	193	6	29	5	17

Per patient								
	Screening				Surveillance			
	LCE (n = 217)		LCE + HRME (n = 204)		LCE (n = 236)		LCE + HRME (n = 238)	
LCE/LCE + HRME	Path(+)	Path(–)	Path(+)	Path(–)	Path(+)	Path(–)	Path(+)	Path(–)
(+)	14	14	14	13	189	28	202	17
(–)	5	184	2	175	5	14	4	15

NOTE. LCE/LCE + HRME (+) indicates neoplastic read by endoscopist, and LCE/LCE + HRME (–) indicates nonneoplastic read by endoscopist on either LCE or LCE + HRME. Path(+) indicates neoplastic pathology, and Path(–) indicates nonneoplastic pathology.

Supplementary Table 2. Diagnostic Performance With 95% CIs of LCE Compared to LCE + HRME Among Experts and Novices

	Per biopsy					
	Screening			Surveillance		
		LCE + HRME			LCE + HRME	
	LCE (n = 232)	Experts (n = 47)	Novices (n = 62)	LCE (n = 297)	Experts (n = 33)	Novices (n = 229)
Sensitivity	0.75 (0.51–0.91)	0.78 (0.40–0.97)	0.89 (0.52–1.00)	0.97 (0.94–0.99)	0.93 (0.76–0.99)	0.98 (0.96–1.00)
Specificity	0.93 (0.89–0.96)	0.87 (0.72–0.96)	0.83 (0.70–0.92)	0.36 (0.25–0.47)	1.00 (0.48–1.00)	0.17 (0.07–0.34)
PPV	0.52 (0.33–0.71)	0.58 (0.28–0.85)	0.47 (0.23–0.72)	0.80 (0.75–0.85)	1.00 (0.87–1.00)	0.87 (0.82–0.91)
NPV	0.98 (0.94–0.99)	0.94 (0.81–0.99)	0.98 (0.88–1.00)	0.83 (0.66–0.93)	0.71 (0.29–0.96)	0.67 (0.30–0.93)
Accuracy	0.92 (0.88–0.95)	0.85 (0.72–0.94)	0.84 (0.72–0.92)	0.80 (0.75–0.85)	0.94 (0.80–0.99)	0.86 (0.81–0.90)
	Per patient					
	Screening			Surveillance		
		LCE + HRME			LCE + HRME	
	LCE (n = 217)	Experts (n = 41)	Novices (n = 48)	LCE (n = 236)	Experts (n = 29)	Novices (n = 203)
Sensitivity	0.74 (0.49–0.91)	0.86 (0.42–1.00)	0.89 (0.52–1.00)	0.97 (0.94–0.99)	0.92 (0.73–0.99)	0.99 (0.96–1.00)
Specificity	0.93 (0.88–0.96)	0.85 (0.69–0.95)	0.79 (0.64–0.91)	0.33 (0.20–0.50)	1.00 (0.48–1.00)	0.19 (0.05–0.42)
PPV	0.50 (0.31–0.69)	0.55 (0.23–0.83)	0.50 (0.25–0.75)	0.87 (0.82–0.91)	1.00 (0.85–1.00)	0.91 (0.87–0.95)
NPV	0.97 (0.94–0.99)	0.97 (0.83–1.00)	0.97 (0.84–1.00)	0.74 (0.49–0.91)	0.71 (0.29–0.96)	0.67 (0.22–0.96)
Accuracy	0.91 (0.87–0.95)	0.85 (0.71–0.94)	0.81 (0.67–0.91)	0.86 (0.81–0.90)	0.93 (0.77–0.99)	0.91 (0.86–0.94)