Acetic acid compared with *i*-scan imaging for detecting Barrett's esophagus: a randomized, comparative trial

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Background: Traditional surveillance in patients with Barrett's esophagus (BE) has relied on random biopsies. Targeted biopsies that use advanced imaging modalities may significantly improve detection of specialized columnar epithelium (SCE).

Objective: We compared the efficacy of targeted biopsies that used *i*-scan or acetic acid to random biopsies in the detection of SCE.

Design: Patients with visible columnar lined epithelium or known BE were randomized at a 1:1 ratio to undergo acetic acid application or *i*-scan with targeted biopsies.

Setting: Targeted biopsies were performed based on surface architecture according to the Guelrud classification followed by 4-quadrant biopsies.

Patients: A total of 95 patients were randomized.

Intervention: A total of 46 patients underwent acetic acid staining, and 49 underwent *i*-scan imaging. Random biopsies were performed in 86 patients.

Main Outcome Measurements: The primary outcome was the yield of SCE as confirmed by histologic assessment.

Results: The diagnostic yield for SCE was significantly higher with targeted biopsies than with random biopsies in both groups combined (63% vs 24%; $P = .0001$). The yield of targeted biopsies was significantly greater with both *i*-scan (66% vs 21%; $P = .009$) and acetic acid (57% vs 26%; $P = .012$) technologies and did not differ between these groups. The accuracy for predicting SCE was 96% ($k = .92$) for *i*-scan and 86% ($k = .70$) for acetic acid analysis.

Limitations: No dysplastic lesions were found.

Conclusion: The *i*-scan or acetic acid–guided biopsies have a significantly higher diagnostic yield for identifying SCE, with significantly fewer biopsies, as compared with a protocol of random biopsies. Acetic acid and *i*-scan showed comparable results diagnosing SCE in our study. (Clinical trial registration number: NCT01442506.) (Gastrointest Endosc 2014;79:46-54.)

Abbreviations: BE, Barrett's esophagus; CLE, columnar-lined lower esophagus or columnar-lined epithelium; NBI, narrow-band imaging; SCE, specialized columnar epithelium.

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Barrett's esophagus (BE) is defined as the presence of metaplastic specialized columnar epithelium (SCE)[1] in the distal esophagus. SCE is defined on a histologic basis by the presence of goblet cells, thereby signifying intestinal metaplasia as opposed to gastric metaplasia.[2] Patients with BE are at increased risk of developing esophageal adenocarcinoma, and endoscopic surveillance is recommended in these patients.[3,4] Columnar-lined epithelium (CLE) within the esophagus generally can be recognized endoscopically, but SCE can be diagnosed only histologically.[1,4]

The distribution of SCE within CLE is often patchy and multifocal. Therefore, 4-quadrant random biopsies are recommended at 1-to-2 cm intervals throughout the length of identified CLE.[4] However, random biopsies can be associated with sampling error and require additional procedure time.[4]

Acetic acid chromoendoscopy can differentiate various mucosal surface patterns according to the Guelrud classification, thereby allowing distinction of SCE from other types of metaplasia.[5] However, this technique has several limitations, including inadequate surface coating with acetic acid, additional equipment costs, and increased procedure time. Recent reports have indicated that narrow-band imaging (NBI) combined with high-definition endoscopy (HDE) may lead to SCE detection capabilities similar to those of acetic acid chromoendoscopy, with decreased procedure time.[6-9]

A technology alternative (virtual chromoendoscopy) to NBI is *i*-scan imaging (Pentax, Japan). This technology uses digital image processors with different software algorithms, along with real time image mapping technology, embedded in a high definition processor.[10] By pressing a button on the hand piece of the endoscope, *i*-scan technology is activated and can provide detailed images of surface and vessel architecture (Fig. 1). No studies to-date have evaluated the role of *i*-scan in surveillance for BE.

The aim of the present study was to compare the diagnostic yield of *i*-scan and acetic acid–guided biopsies to random biopsies and to compare the relative efficacies of these two imaging modalities in the detection of SCE within CLE.

Take-home message

- Patients with Barrett's esophagus containing specialized columnar epithelium (SCE) are at increased risk of cancer, and surveillance is recommended.
- Random biopsies every 1 to 2 cm within columnar-lined lower esophagus are recommended to identify SCE; however, random biopsies harbor the risk of overlooking SCE. Based on the results of our prospective, randomized, controlled trial, *i*-scan–guided imaging is superior to random biopsies and is of similar value as acetic acid imaging.

METHODS

Patients and study design

This was a randomized, comparative, balanced superiority trial comparing targeted biopsies after acetic acid staining or virtual chromoendoscopy with *i*-scan to random biopsies. This study was designed to compare the efficacy of *i*-scan imaging to acetic acid chromoendoscopy in the detection of SCE within CLE. Patient enrollment occurred between June 2009 and April 2010 at the Interdisciplinary Endoscopic Unit of the Johannes Gutenberg University of Mainz.

Consecutive patients with CLE ($\geq$1 cm) or with known nondysplastic BE were screened for study eligibility. Patient inclusion and exclusion criteria are presented in Table 1. All patients had to provide written informed consent to be eligible to participate in the study. Eligible patients were randomized at a 1:1 ratio to undergo either acetic acid chromoendoscopy (10-15 mL; 1.5%) or *i*-scan imaging for SCE detection (Fig. 1). Patients with circumferential CLE also underwent random 4-quadrant biopsies at 2-cm intervals. All procedures were performed with high-definition endoscopes (90i series; Pentax).

All eligible patients received daily proton-pump inhibitor therapy for $\geq$14 days before endoscopy to minimize inflammatory changes within the distal esophagus. All endoscopies were performed by 3 endoscopists (R.K., A.H., M.G.) who were highly familiar with acetic acid chromoendoscopy and *i*-scan imaging in BE surveillance (each endoscopist had performed more than 200 procedures with each imaging modality).

Endoscopic imaging by using *i*-scan

First, complete high-definition EGD (90i series gastroscopes; Pentax) was performed. Subsequently, *i*-scan 1 (settings: brightness 0; AVE; blue = 0; red = 0; enhancement low; SE = +5; contrast enhancement = off; tone enhancement = 0) surface enhancement mode by using white light was switched on, and the endoscope was slowly withdrawn from the upper stomach to the maximum extent of CLE or known BE. BE was judged according to the Prague classification.[11] Finally, the distal part of the esophagus was reinspected by using *i*-scan 2/3 (settings: brightness +1; AVE; blue = 0; red = 0; enhancement low; SE = +4/+5; CE = off/+2; TE = c) tone enhancement mode by using digital image processing, and the surface architecture was judged according to the Guelrud classification (Fig. 2) (type I-II: predicting gastric epithelium; type III-IV: predicting Barrett's epithelium[8]). Electronic magnification was allowed to further highlight surface architecture (Fig. 3). Targeted biopsy specimens were taken during both *i*-scan 1 and *i*-scan 2/3 settings (see the following).

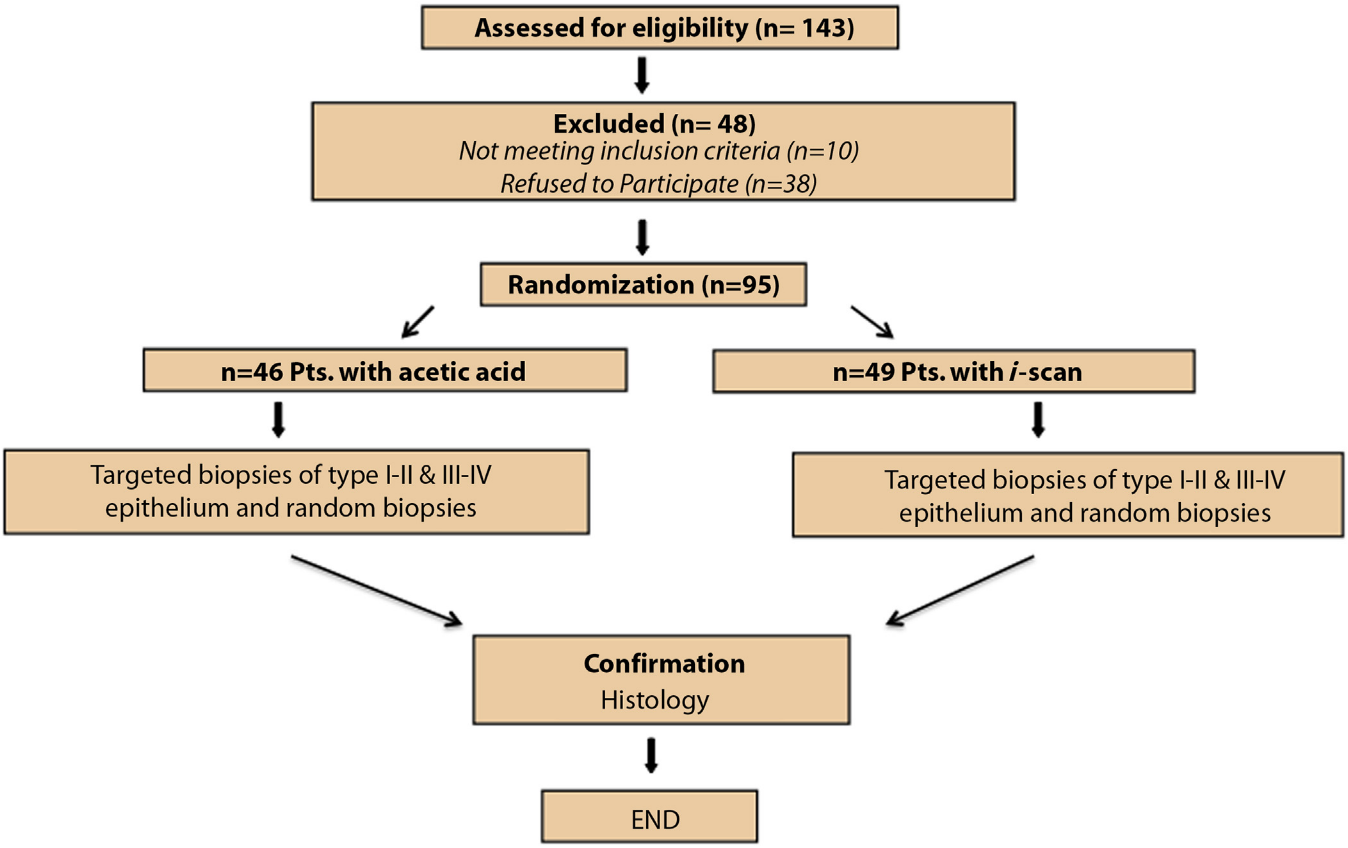

Figure 1. Flow diagram of the progress through the phases of the actual randomized trial; (n = patients) according to the CONSORT statement.[25]

Endoscopic imaging by using acetic acid

The first complete high-definition EGD was performed by using the same processor and endoscopes as in the *i*-scan group. However, *i*-scan imaging (*i*-scan 1 or *i*-scan 2) was not allowed.

Acetic acid (pH 2, 5; pKa 4, 8) at a final concentration of 1.5% (5-25 mL) was sprayed via a catheter (PW-205 L; Olympus Optical Co, Hamburg, Germany) onto the mucosa of the distal esophagus as previously described.[12] The endoscope was slowly withdrawn as in the *i*-scan group, and the mucosal surfaces were judged in the same way.

Biopsy protocol

Biopsy specimens of suspicious areas were first taken in a targeted fashion toward two distinct surface patterns, based on the Guelrud classification (I/II vs III/IV), in each arm of the study. Subsequently, random, 4-quadrant biopsy specimens were taken at 1-to-2 cm intervals along the length of the CLE, if these changes extended circumferentially (random biopsies could not be performed if only short tongue-like changes were visible).

Outcome parameters

The primary outcome was the percentage of biopsy specimens with SCE among all patients that contained at least one biopsy specimen with SCE. Targeted biopsies (surface structure III/IV) in each group were compared with random biopsies.

Secondary outcomes were the correlation between surface architecture (I/II vs III/IV) and the histologic presence of SCE (per patient analysis) and the number of patients with SCE, which were missed with either targeted or random biopsies.

Another secondary outcome was the comparison between *i*-scan imaging and acetic acid–guided endoscopy (number of biopsy specimens with SCE/number of all biopsy specimens).

Sample size calculation

We postulated that *i*-scan and acetic acid chromoendoscopy would have a comparable diagnostic yield for identifying SCE. Random quadrant biopsies detect SCE in an average of 20% of all taken biopsy specimens (as analyzed in our own BE cohort at the University of Mainz).[12] We hypothesized that targeted biopsies will increase the diagnostic yield to 50%. We set the alpha value to 0.05 and the power to 80%, which translated into a sample size of at least 58 biopsies for each biopsy protocol.

Given that not all patients with CLE will have SCE, we doubled the number of biopsies to 116 biopsies per group. Assuming that an average of 3 biopsies will be performed in the targeted group, 39 patients were needed in each arm.

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria
Adult ($\geq$18 y)
Columnar lined lower esophagus $\geq$ 1 cm
Known Barrett's esophagus
Exclusion criteria
Pregnancy or breast feeding
Allergy against acetic acid
Inability to obtain informed consent
Impaired coagulation parameters
Prothrombin time >50% of control
Partial thromboplastin time >50 sec
Thrombocyte count, 50,000/mm^3
Visible blood in the upper GI tract
Esophageal varices (any size)
Visible esophagitis (any degree)
Surgery of the upper GI tract
Known esophageal cancer or dysplasia
Known cancer

Statistical analysis

Bivariate comparisons of categorical variables and outcomes between the 2 comparator arms were conducted by using the chi-square test or the Fisher exact test. Bivariate comparisons of normally and non-normally distributed interval variables and outcomes between the 2 comparator arms were conducted by using the *t* test and Wilcoxon rank sum test, respectively. Comparison of the yield of targeted versus non-targeted biopsies within each comparator arm as well as in the combined analysis was conducted by using the McNemar test. The level of agreement with histologic impression for both *i*-scan and acetic acid biopsies was assessed through correlation analysis based on the Cohen kappa coefficient. Absolute and relative frequencies were calculated for all outcomes. The sensitivity, specificity, and positive and negative predictive values of the acetic acid and *i*-scan patterns for the detection of SCE also were calculated.

The acceptable 2-sided type I error rate was set at 5% for all comparisons. Statistical analysis was performed by using the statistical software package SAS (release 6.08; SAS Institute Inc, Cary, NC).

Ethics and registration

The study was approved by the local ethics committee of Rheinland-Pfalz, Germany (837.237.09 [6743]) and registered at clinicaltrials.gov (NCT01442506). All patients provided written informed consent to participate in the study.

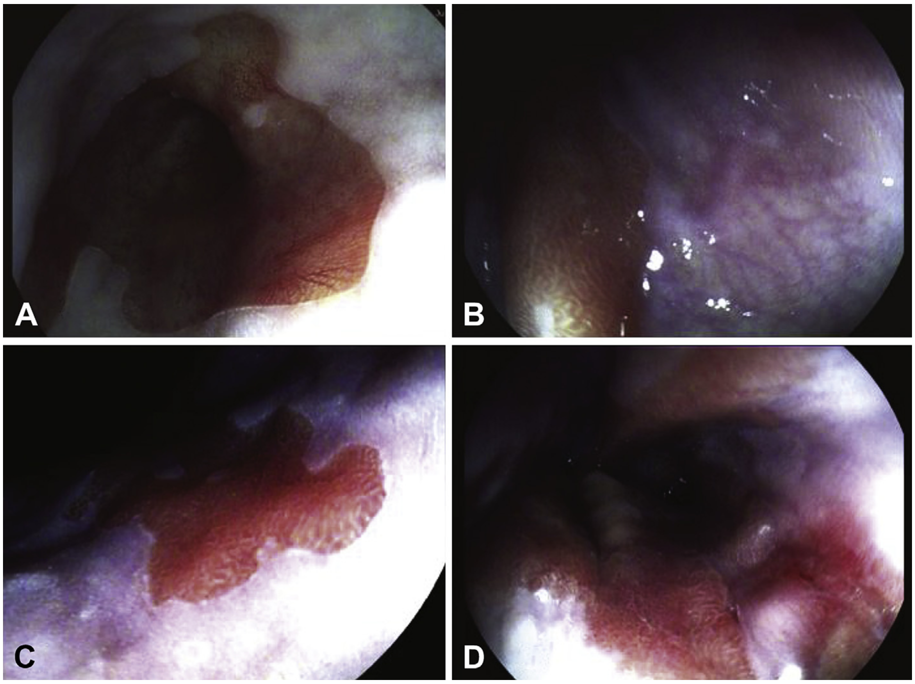

Figure 2. Guelrud classification under virtual chromoendoscopy (*i*-scan). Virtual chromoendoscopy by using *i*-scan showing **A,** Guelrud I, **B,** Guelrud II and Guelrud III, and **C,** Guelrud IV classifications.

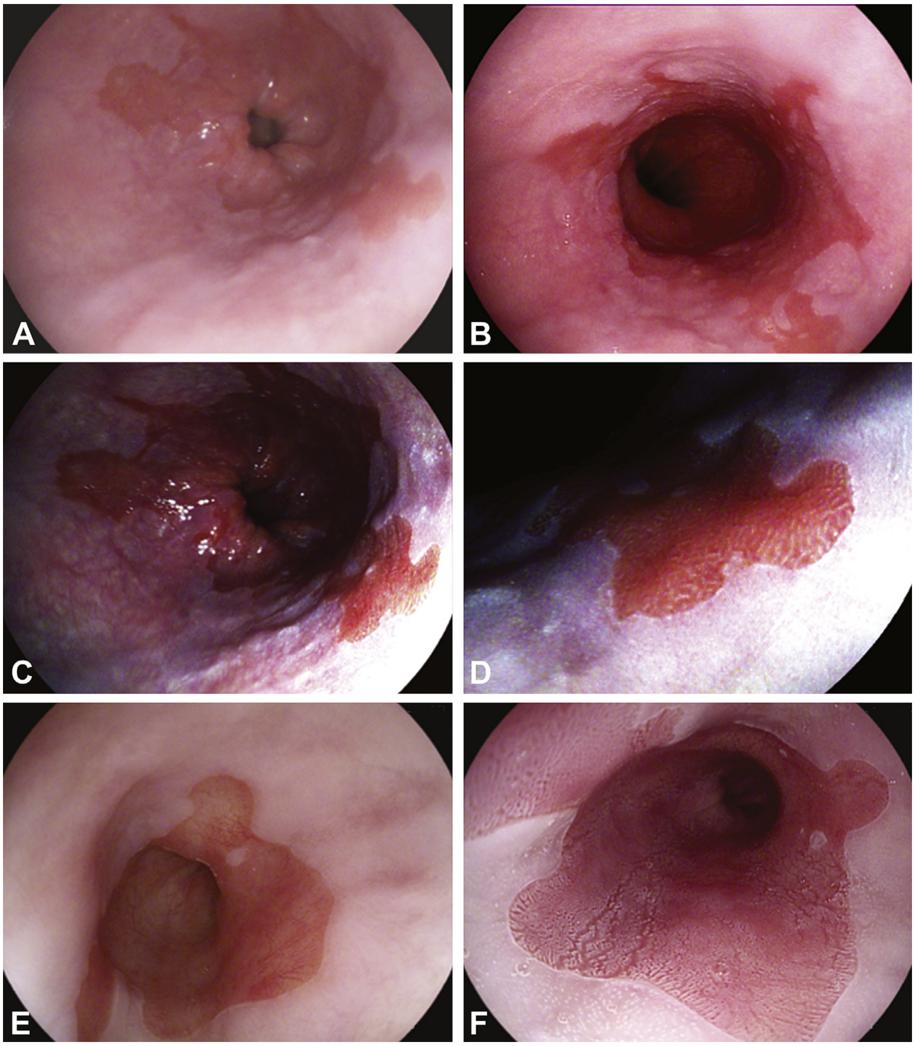

Figure 3. A, The *i*-scan and acetic acid–guided imaging of columnar lined lower esophagus. **B,** Conventional high-definition white-light imaging. **C,** The *i*-scan imaging by using surface enhancement and **D,** tone enhancement. **E,** Barrett's esophagus displayed before and **F,** after acetic acid application.

RESULTS

Of 143 patients with CLE or known nondysplastic BE who met the study inclusion criteria, 48 patients refused to participate, leaving 95 patients for randomization (63 men; mean age 58.2 years).

A total of 46 patients were investigated by using acetic acid–guided imaging, and 49 patients received virtual chromoendoscopy by using *i*-scan imaging. There were no differences in baseline characteristics between the 2 groups (Table 2). Four-quadrant, random biopsies were performed in 86 patients, because 9 patients showed only a tongue-like appearance of CLE.

Final histology identified 50 patients (50/95; 53%) with BE. None of the biopsy specimens showed dysplastic changes. No adverse events were observed in this study.

TABLE 2. Patient characteristics

	The *i*-scan	Acetic acid
No. patients	49	46
Male	36	27
Age, y	57.9	58.5
Known Barrett's esophagus	67.3%	58.5%
Columnar-lined epithelium	32.7%	41.5%
Prague M	2.16 cm	2.3 cm
Prague C	2.35 cm	2.37 cm

Primary outcome analysis—diagnostic yield

Targeted biopsy specimens of Guelrud type III to IV areas (predicting SCE) showed a significantly higher proportion of biopsy specimens (72/117 biopsies; 62%) containing SCE as compared with 4-quadrant random biopsies (75/317 biopsies; 24%) (paired Wilcoxon test; $P < 10^{-4}$). This difference also was significant if the biopsy

TABLE 3. Outcome measurements of the different biopsy protocols

	Acetic acid	The *i*-scan	Total
No.	46	49	95
Patients with SCE			
Patients with SCE identified with targeted biopsies, no. (%)	23/46 (57)	27/49 (55)	50/95 (53)
Patients with SCE identified with random biopsies, no. (%)	15/40 (38)	20/46 (43)	35/86 (41)
Primary outcome—diagnostic yield*			
% Biopsies containing SCE—targeted biopsies, no. (%)	33/58† (57)	39/59‡ (66)	72/117§ (63)
% Biopsies containing SCE—random biopsies, no. (%)	42/162 (26)	33/155 (21)	75/317 (24)
Secondary outcome—missed patients with SCE			
Missed patients with Barrett's esophagus (targeted biopsies), no. (%)	4/46 (9)	4/49 (8)	8/95 (8)
Missed patients with Barrett's esophagus (random biopsies), no. (%)	6/40 (15)	7/46 (15)	13/86 (15)

SCE, Specialized columnar epithelium.
*In patients with proven Barrett's esophagus.
†P = .012.
‡P = .009.
§P = .0001.

protocols were compared within each group (acetic acid: $P = .012$; *i*-scan: $P = .009$) (Table 3). Acetic acid–guided biopsy specimens and *i*-scan–targeted biopsy specimens showed similar diagnostic yields for SCE (57% vs 66%; $P = .075$).

Figure 4A and B shows the relative diagnostic yield for detecting SCE for i-scan imaging and acetic-acid chromoendoscopy, relative to random biopsies, among patients who demonstrated BE on histology.

Secondary outcome—prediction of SCE

Surface analysis within CLE and corresponding histology under acetic acid or *i*-scan-guided biopsy specimens by using the Guelrud classification showed a similar level of agreement (Cohen kappa k = 0.70 and k = 0.92) with final histology (per patient analysis).

Sensitivity and specificity were 96% and 74% for acetic acid, with accuracy of 85% compared with 100% and 90% for *i*-scan and accuracy of 96% (Table 4). Interobserver agreement between endoscopic and histologic prediction of biopsied areas was high for both imaging modalities on a per-patient basis (Cohen kappa $k = 0.70$ and $k = 0.92$).

Secondary outcome—missed patients with BE

Thirteen BE patients (13/86; 15%) were missed as having SCE by using random biopsies, and 8 patients (8/95; 8%) were missed by using *i*-scan[4] or acetic acid–guided biopsies.[4] This difference was not statistically significant.

DISCUSSION

Patients with GERD are at risk to develop esophageal cancer.[13] Patients with BE containing SCE are at increased risk, and surveillance is recommended.[1,3,4] Although a recent study from Denmark revealed a lower cancer risk in patients with nondysplastic BE, the authors approve SCE as a risk factor and suggest a more rational and effective surveillance program.[14] Further, the definition of BE is currently changing, and despite good reasons for a purely endoscopic definition of BE without the need for histologic proof, goblet cells are still mandatory for the diagnosis of BE in Europe and the USA.[15,16] Therefore, random biopsies every 1 to 2 cm within CLE are still recommended to identify SCE.[3,4] Although random biopsies harbor the risk of overlooking SCE, they are still not abandoned outside study settings. Furthermore, it is widely accepted that taking additional time to perform an examination of the esophageal mucosa improves the yield of BE surveillance, although new imaging techniques increase the detection rate of SCE and early neoplastic changes even more.[15,17]

We performed a randomized, comparative trial to evaluate the diagnostic yield identifying SCE by using different biopsy protocols. Acetic acid–guided or *i*-scan–guided biopsy results showed a significant reduction of the number of biopsies to predict SCE, with a higher diagnostic yield for SCE, and fewer patients with SCE were missed compared with results of random biopsies. Furthermore, surface architecture within CLE could readily be identified, and distinct mucosal patterns correlate strongly with the

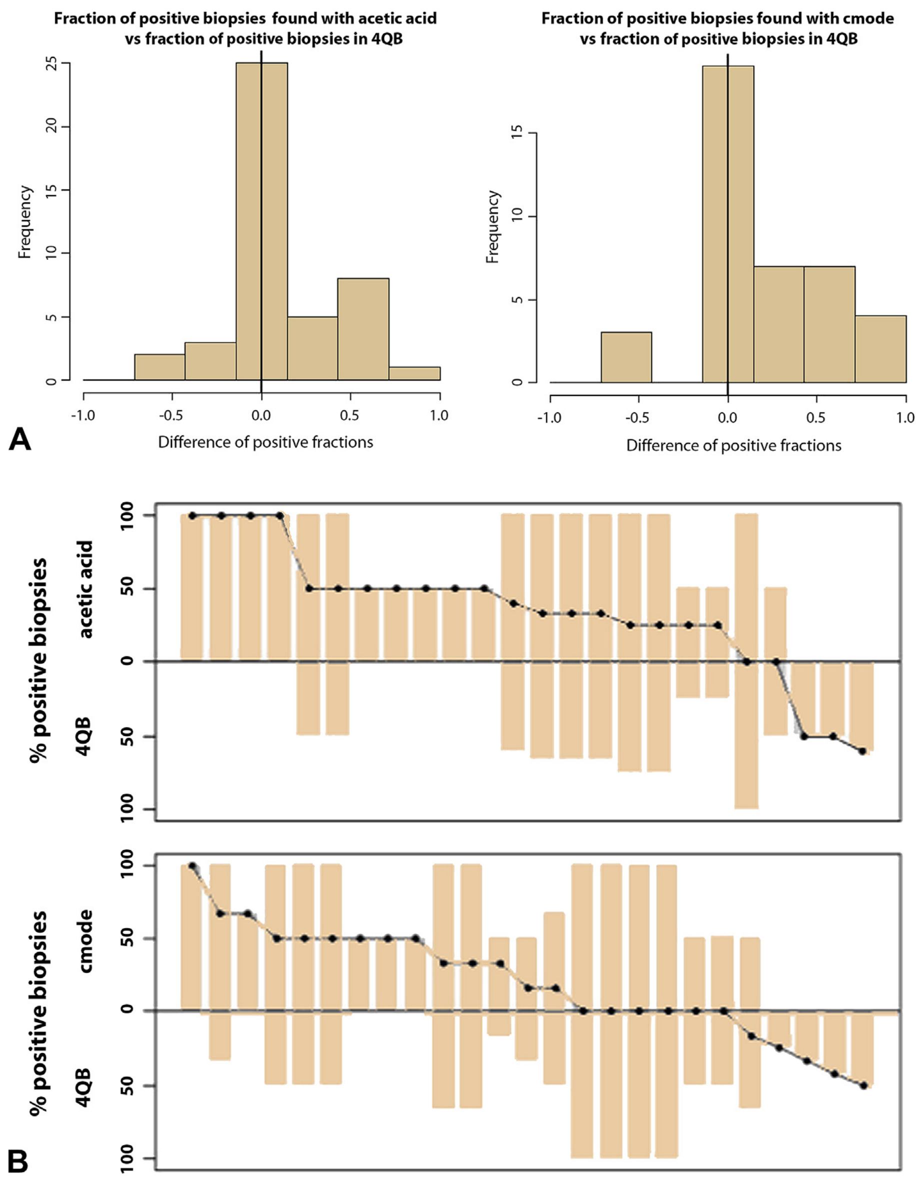

Figure 4. A, Positive predictive values (PPV) for the different biopsy protocols. Methods comparison with respect to their positive predictive values. The PPV measures the fraction of truly positive results (biopsy results confirmed by histology) among all positive results (number of biopsy specimens taken with the respective method) in a patient. For each patient, we report the difference between the more advanced method, either acetic acid (*left*) or *i*-scan (*right*), and the basic method (4-quadrant biopsy). Positive values indicate the superiority of the advanced method, and negative values indicate favorable performance of the basic method. The histogram of the differences shows that the advanced methods (*i*-scan and acetic acid) both have a higher PPV, and this finding is significant (Wilcoxon test, *P* value $<10^{-4}$ for both cases). *PPV,* positive predictive value; *4QB,* 4-quadrant biopsy. **B,** Diagnostic yield of specialized columnar epithelium (SCE) for different biopsy protocols. Fraction of biopsies containing SCE for each patient who was diagnosed with Barrett's esophagus on histology (25 patients total). The light grey bars represent the fraction of SCE-positive biopsy specimens in the reference method, and the dark grey bars represent the fraction of SCE-positive biopsy specimens obtained with the alternate methods (*acetic acid in the upper panel and* i-*scan in the lower panel*). The black dots show the difference in the fraction of SCE-positive biopsies (*alternative method minus reference method*). Values above the x-axis indicate the superiority of the advanced method, whereas values below the x-axis indicate a favorable performance of the reference method. Patients in which no method detected a positive biopsy were omitted from the plot (*Wilcoxon test; P value* $<10^{-4}$ *for both alternate methods relative to reference method*). *SCE,* specialized columnar epithelium; *4QB,* 4-quadrant biopsies.

presence of SCE. Acetic acid or *i*-scan imaging showed comparable results diagnosing SCE.

Thus, it can be recommended to perform targeted biopsies (using *i*-scan or acetic acid) only to initially identify patients with SCE, who require surveillance. However, this study focused on diagnosing SCE only and solely in patients with nondysplastic BE or visible CLE. But random biopsies might still be required for diagnosing BE-associated dysplasia.

Chromoendoscopy has been used for decades to enhance mucosal surface detail of patients with BE.[18] Methylene blue failed to show any benefit diagnosing SCE

TABLE 4. Surface analysis of CLE and corresponding histology (per patient analysis)

Cohen kappa: $\kappa = 0.70$ (high agreement)		Histology Negative	Histology Positive	Sum
Acetic acid	Negative	17	1	18
	Positive	6	22	28
	Sum	23	23	46
		Specificity 74%	Sensitivity 96%	

Cohen kappa: $\kappa = 0.92$ (high agreement)		Histology Negative	Histology Positive	Sum
The *i*-scan	Negative	19	0	20
	Positive	2	28	29
	Sum	21	28	49
		Specificity 90%	Sensitivity 100%	

CLE, Columnar-lined epithelium.

or BE-associated dysplasia.[19] Guelrud et al[5] first described acetic-acid enhanced endoscopic imaging in 2001. Acetic acid leads to acetylation via desulfation and denaturation of the proteins, causing a reversible alteration of the proteins' tertiary structure, thereby providing altered optical and 3-dimensional characteristics of the mucosa. Distinct mucosal patterns can be recognized, and biopsies can be targeted to suspicious areas. Patterns I and II predict the absence and III and IV the presence of SCE. We could confirm the strong correlation between tubular or villous pattern and the presence of BE. These findings correlate well with earlier studies, although we used high-definition endoscopes.[8,11,20-22]

Most recently, Longcroft-Wheaton et al[23] proved the increased value of acetic acid–guided imaging for detecting BE-associated dysplasia. Acetic acid chromoendoscopy had a sensitivity of 95.5% and specificity of 80% for the detection of neoplasia ($n = 190$). There was a strong correlation between lesions predicted to be neoplasias by acetic acid and those diagnosed by histologic analysis ($r = 0.98$).

Acetic acid seems to be of great promise for diagnosing SCE and BE-associated neoplasia. We questioned whether acetic acid might be replaced by virtual chromoendoscopy. Virtual chromoendoscopy has the advantage that it can be switched on and off by using a distinct button of the endoscope. NBI narrows the light spectrum and focuses on the blue band, which highlights vessel architecture.

A meta-analysis of Mannath et al[24] (including 446 patients with 2194 lesions) showed impressive results of the diagnostic value of NBI. For the characterization of SCE, the pooled sensitivity, specificity, and accuracy were 95%, 65%, and 88% on a per-lesion analysis. We therefore concluded that virtual chromoendoscopy and acetic acid imaging are of similar efficiency.

However, we used in our study a virtual chromoendoscopy technique, which is denoted *i*-scan. The *i*-scan uses the reflected light from the mucosa, and post-processing algorithms are used to highlight surface (surface enhancement) or tissue and vessel architecture (tone enhancement). Both algorithms were used within the study. Surface enhancement was first used to describe and judge CLE or BE, whereas tone enhancement was used to characterize surface architecture. Acetic acid and *i*-scan showed similar results diagnosing SCE in our study. However, the correlation between surface architecture III and IV predicting SCE was slightly higher with the use of *i*-scan.

The comparable diagnostic yield between chromoendoscopy and *i*-scan is in concordance with a previous study from our group.[12] Here, we used Lugol solution and *i*-scan to identify inflammatory changes (minimal or distinct esophagitis). Both techniques were able to identify inflammatory changes in 19 of 50 patients, which could not be identified by using white-light endoscopy.

It can be concluded, based on the results of our prospective, randomized, comparative trial, that *i*-scan–guided imaging can reduce significantly the number of needed biopsies in comparison to random biopsies for predicting Barrett's epithelium, and the benefit was of similar value as acetic acid imaging. However, one limitation of the study is that there was no increase of absolute diagnosis of SCE, and another limitation of the study is that only nondysplastic BE patients were investigated. The value of *i*-scan to diagnose BE-associated neoplasia is not specified yet. It can be speculated that *i*-scan might have a similar effect as acetic acid, but further studies are needed to clarify this assumption.

The *i*-scan imaging has the advantage, compared with acetic acid staining, that it can be immediately applied, and the virtual staining effect is standardized based on distinct computer algorithms. Also, no further costs (like those of a spraying catheter or intravital dye) are added.

In conclusion, *i*-scan or acetic acid–guided biopsies can reduce significantly the number of needed biopsies to predict SCE, and they have a significantly higher diagnostic yield for identifying SCE within columnar lined lower esophagus compared with random biopsies. Fewer biopsies to identify patients, which require surveillance based on the higher cancer risk in patients with BE containing SCE, means a more efficient procedure with time reduction.

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