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Recurrent intestinal metaplasia after radiofrequency ablation for Barrett's esophagus: endoscopic findings and anatomic location

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Abstract

Background—Radiofrequency ablation (RFA) is a safe and effective treatment for Barrett's esophagus (BE) that results in high rates of complete eradication of intestinal metaplasia (CEIM). However, recurrence is common after CEIM and surveillance endoscopy is recommended. Neither the anatomic location nor the endoscopic appearance of these recurrences is well described.

Objective—The objectives of this study are to describe the location of histologic specimens positive for recurrence after CEIM and the testing performance of endoscopic findings for the histopathologic detection of recurrence.

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Design—Retrospective cohort.

Setting—Single referral center.

Patients—198 BE patients with at least 2 surveillance endoscopies after CEIM.

Interventions—RFA, endoscopic mucosal resection (EMR), surveillance endoscopy.

Main outcome measurements—The anatomic location and histologic grade of recurrence.

Results—In a mean 3.0 years of follow-up, 32 (16.2%; 95% CI, 11.0%–22.0%) patients recurred, 5 (2.5%; 95% CI, 0.3%–4.7%) of which progressed beyond their worst pre-treatment histology. Recurrence was most common at or near the gastroesophageal junction (GEJ). Recurrence greater than 1 cm proximal to the GE junction was always accompanied by endoscopic findings, and random biopsies in these areas detected no additional cases. The sensitivity of any esophageal sign under high-definition white-light or narrow-band imaging for recurrence was 59.4% [42.4%, 76.4%] and the specificity was 80.6% [77.2%, 84.0%].

Limitations—Single-center study

Conclusions—Recurrent IM is often not visible to the endoscopist and is most common near the GEJ. Random biopsies >1 cm above the GEJ had no yield for recurrence. In addition to biopsy of prior EMR sites and of suspicious lesions, random biopsies oversampling the GEJ are recommended.

Introduction

Radiofrequency ablation (RFA) is a safe and effective treatment for Barrett's esophagus (BE) that results in high rates of complete eradication of intestinal metaplasia (CEIM.)[1] Though rates of progression after CEIM are low, recurrence happens commonly, and endoscopic surveillance is indicated to identify and treat recurrent or progressive neoplasia.[2] Clinical evidence to guide best practices for endoscopic surveillance is lacking and expert opinion varies considerably on this matter.[3,4] Data regarding the appearance and location of recurrences of BE after RFA are necessary to optimize surveillance practices. Additionally, the cost effectiveness of ablative therapies for BE largely depends on the duration and intensity of surveillance, and optimizing the utility of these examinations may allow for cost savings.[5]

The currently recommended biopsy technique in surveillance is systematic four-quadrant biopsies at each centimeter of the prior BE segment.[6] In long segments of BE, such a regimen requires a large number of biopsies with the attendant costs, as well as the potential for post-endoscopy pain and/or bleeding. Clinical evidence to guide biopsy practices in endoscopic surveillance is scant. Recent studies have examined the location of dysplastic nodules within treatment-naïve segments of BE, but data describing the location of recurrent BE after radiofrequency ablation are scant.[7–9] Additionally, the endoscopic phenotype of recurrent BE is not well-described, and inference from the few studies that report the appearance of recurrence is limited by small samples of patients, populations with predominantly non-dysplastic BE before treatment, and/or the lack of description of endoscopic findings in patients under surveillance that do not experience recurrence.[10–12]

Without data reporting endoscopic findings in patients that do not recur, it is difficult to empirically judge the diagnostic value of endoscopic findings.

The objectives of this study are to describe the location of biopsies and EMR specimens positive for recurrence after CEIM. We also described the sensitivity and specificity of various endoscopic findings during post-RFA endoscopic surveillance for the histopathologic detection of recurrence.

Methods

We conducted a retrospective cohort study of patients who underwent RFA for BE at University of North Carolina (UNC) Hospitals from March 16, 2006 to June 30, 2014. Patients who received RFA were identified by review of the electronic endoscopic database (Provation MD, Wolters Kluwer, Minneapolis, MN) to determine if they met the study's criteria for inclusion. Patients who underwent prior treatment with other ablative modalities were excluded. Using a priori definitions and standardized data collection tools, we systematically collected demographic information and details of patients' medical and social histories from clinic notes, procedure notes, and pathology reports. Endoscopic findings, histopathology data, and treatments were recorded from all visits starting with the first endoscopic procedure associated with RFA treatment.

Baseline pathologic diagnoses were either performed or confirmed by an expert gastrointestinal pathologist at UNC. All findings of dysplasia were confirmed by a second pathologist. Patients underwent careful examination under high-definition white light and narrow band imaging during initial evaluation, treatment, and surveillance. Patients were treated with RFA according to the AIM Dysplasia protocol; endoscopic mucosal resection (EMR) was performed for raised lesions noted either before the performance of RFA or at any time after the first RFA treatment session.[1,13] RFA was carried through the tubular esophagus, and into the gastric cardia for 1–2 cm. All patients were prescribed twice-daily PPI during the treatment period and throughout endoscopic surveillance. Endoscopic findings were recorded from initial evaluation, treatment, and surveillance endoscopies. The initial BE segment before treatment was recorded according to Prague M and C length, with additional description of island size and location.[14] Recorded endoscopic findings included nodularity, irregular Z-line, tongues of columnar-appearing mucosa, islands of columnar-appearing mucosa, and erosions or ulcers. Endoscopic findings were recorded using standardized templates by endoscopist(s) with experience in ablative therapy for BE using the above definitions.

The location of lesions in the tubular esophagus or cardia was defined by the distance of the visible lesion from the top of the gastric folds (TGF) and the distance from the incisors. The location of biopsies positive for recurrence was also recorded as distance from TGF and the incisors. All locations were rounded to the nearest cm.

Patients were considered to enter into surveillance once they had achieved CEIM, which was defined as a non-treatment endoscopy with no endoscopic signs of BE or pathologic findings of intestinal metaplasia or BE-associated dysplasia despite four quadrant biopsies at

one cm intervals throughout the maximum prior extent of BE, as well as in 4 quadrants in the cardia, using large capacity forceps. Patients were considered at risk for recurrence if they had at least 2 surveillance endoscopies. Recurrence was defined as histologic evidence of intestinal metaplasia or dysplasia in the tubular esophagus in the second or later surveillance endoscopies. The finding of IM distal to TGF was not considered recurrence. Progression was defined as recurrence with more severe histology than the worst pre-treatment histology.

Descriptive statistics of baseline characteristics included patients who were at risk for recurrence as defined above. Descriptive statistics were reported as mean, standard deviation, and range for continuous variables and as column percent for categorical variables. All statistical analyses were performed using SAS software (SAS version 9.4, SAS Institute Inc., Cary, NC).

For recurrences, the location, grade, and presence or absence of visible esophageal signs were reported using bar graphs. Missing locations were excluded from bar graphs, but their number and histology were used for the remainder of the analysis. We examined the rate of recurrence using right-censoring at the last visit by the product-limit method, limited to five years. A histogram was constructed for the standardized location of recurrence by distance from TGF as a fraction of initial Prague M length. For example: a recurrence at TGF would be 0, a recurrence at the same point as the initial Prague M would be 1, and a recurrence at 2 centimeters proximal to TGF in a prior Barrett's segment of 8 centimeters would be 0.25. This methodology allowed us to standardize BE segments, in order to assess the region within the BE segment in which the recurrence was present. This distribution was tested against a uniform distribution using Kolmogorov-Smirnov's D statistic. We used general linear models of the time of recurrence after CEIM to examine trends in the histologic grade and location of recurrence. For this analysis, the standardized location of recurrence was treated as a continuous variable and the histology of recurrence was treated as an ordinal variable. We also analyzed the visibility of recurrence by histology and location using logistic regression.

Diagnostic testing characteristics of endoscopic findings for any recurrence and dysplastic recurrence were reported as the likelihood ratio (LR), sensitivity, specificity, positive predictive value, and negative predictive value for recurrence. Odds ratios were estimated using the Mantel-Haenszel method and testing characteristics were calculated as binomial proportions. Both were assigned asymptotic 95% confidence limits.

Results

The analytic cohort consisted 198 patients who were predominantly male, Caucasian, and older (Table 1). This cohort was predominately dysplastic BE, with only 7 patients (4%) having non-dysplastic BE. At the pre-treatment clinic visit, active GERD symptoms were common (45%), as were tobacco (12%) and alcohol (45%) use. Much of the cohort used aspirin (42%) and/or other NSAIDs (16%) at baseline evaluation. A total of 563 surveillance endoscopies were performed in these 198 patients (2.8/pt; 95% CI, 2.6–3.1). In total 32 (16.2%; 95% CI, 11.0%–22.0%) patients recurred, 5 (2.5%; 95% CI, 0.3%–4.7%) of which

progressed beyond their highest treatment histology. The rate of recurrence was 3.5 [3.3, 3.7] per 100 person-years. There were 3 patients who recurred twice, yielding a total of 35 recurrences. Two patients recurred with intestinal metaplasia and were found to have low grade dysplasia on subsequent endoscopies before second CEIM was achieved, one in an EMR specimen and the other on targeted biopsy of apparent columnar epithelium. Of these recurrences 21 (60%) were associated with endoscopic findings and 14 (40%) were not. Endoscopic findings of nodularity, irregular Z-line, tongues, islands, or erosions were found on 103 (19%) of the 531 surveillance endoscopies in which a first recurrence was possible. In three cases, the precise location of the recurrence could not be determined, due to jar labeling spanning multiple centimeter levels in the esophagus. The mean time to first recurrence was 1.8 years and the mean time of follow-up was 3.0 years.

Most recurrences were at or near the gastroesophageal junction, though there were some recurrences as far as 4cm proximal to TGF (Figure 1a).

Standardizing recurrences, such that a recurrence at TGF is 0 and at the prior proximal-most extent of disease is 1, gave a similar finding (Figure 1b). The distribution was not uniform ($p < 0.01$). Although some recurrences at or near TGF were not visible to the endoscopist, all recurrences more than 1cm proximal to TGF were associated with visible findings. Both of the 2 cases of invasive esophageal cancer recurrence were accompanied by endoscopic signs, but one case of intramucosal esophageal adenocarcinoma at TGF was not visible. Of the 14 recurrences not associated with endoscopic findings, 11 (79%) were found at TGF and 1 (7%) was found 1 cm proximal to TGF. The remaining 2 (14%), which were microscopic areas of non-dysplastic histology, were found within the distal third of the esophagus, however, as noted above, the precise location could not be determined due to comingling of samples within biopsy jars. One recurrence associated with visible endoscopic findings was also treated as a missing location because multiple suspicious areas were comingled within the biopsy jar. The general linear models demonstrated no significant trends in the histology ($p = 0.15$) or location ($\beta = 0.80$, $p = 0.51$) of recurrences with respect to time from CEIM.

The presence of visible endoscopic findings compared to a normal-appearing esophagus was associated with increased odds of recurrence on histopathology (Table 2). The presence of any endoscopic sign in the esophagus was associated with more than a five-fold increase in odds of recurrence in the esophagus (OR = 6.07; 95% CI, 2.75–11.23). The sensitivity of any esophageal sign for recurrence was 59.4% [42.4%, 76.4%] and the specificity was 80.6% [77.2%, 84.0%]. Although most dysplastic recurrences were associated with endoscopic findings, both recurrent high grade dysplasia (HGD) and intramucosal adenocarcinoma (IMC) were detected only by random biopsy at the GE junction (figure 2).

Discussion

This retrospective surveillance cohort at a single center describes the endoscopic findings and location associated with recurrence of metaplastic and dysplastic mucosa after RFA for BE. We found that recurrence tended to occur most around the GE junction. Although recurrences further proximal to TGF did occur, all of these were associated with visible

esophageal findings. Our findings suggest that, as opposed to uniformly spaced random surveillance biopsies, random biopsies specifically directed to the area at and around the GE junction have the highest yield. By contrast, recurrences occurring more than a cm proximal to the GEJ were visible to the endoscopist, making these areas unfruitful for random surveillance biopsies. Our data, therefore, suggest that random biopsies throughout the length of the previous BE is wasted effort; in the absence of endoscopic findings, only the GE junction and distal-most centimeter of the esophagus have any yield for occult recurrent disease. Although the marginal increase in harm from additional biopsies higher in the esophagus is likely small, these biopsies accrue costs, both in the time necessary to acquire them, and the resources used to process and evaluate them. Our data suggest that this additional cost and any incremental risk could be avoided, as these biopsies do not provide a clinically significant benefit in discovering recurrent disease.

Prior research by Sharma et al. on the effects of random four quadrant biopsies has demonstrated that their yield is not significantly different from targeted biopsies alone.[15] However, these observations relate to the treatment-naïve esophagus whereas ours reflect post-treatment surveillance. Our findings are nonetheless similar with the exception of the area near the GEJ, where random biopsies sometimes yielded IM, dysplasia, and intramucosal cancer that was missed by targeted biopsies. A later manuscript from the same authors reported insensitivity of narrow band imaging at the squamocolumnar junction immediately after ablation; our findings suggest that this observation can be generalized to all times in surveillance after CEIM.[16]

We did not observe a linear pattern in the location or histology of recurrences over time. Although we cannot directly infer the mechanisms of recurrence from a study such as this, if recurrence was occurring by distinct mechanisms early after CEIM versus late after CEIM, we might expect these 2 mechanisms to manifest in different patterns of recurrence with respect to location and histology. Regardless of the mechanism, until meaningful clinical differences are found between early and late recurrences, it seems arbitrary to address recurrence after only one CEIM endoscopy differently from recurrence after more than one CEIM endoscopy in clinical studies.

An important motivation for biopsy of proximal areas of prior BE is the possibility of subsquamous IM or dysplasia beneath a layer of squamous mucosa. The incidence of subsquamous metaplasia after RFA is unclear, as studies of its prevalence are limited by random sampling and biopsy depth, which may not be adequate to detect subsquamous IM.[17,18] Even if the true prevalence of subsquamous IM is higher, it is clear that the yield for this lesion from random biopsies is low. The malignant potential of such lesions also appears to be low, as subsquamous cancer after successful ablation is extremely rare.[1,19,20]

If our results can be generalized and replicated, random surveillance biopsies in a four-quadrant one-centimeter regimen could give way to a “z-line oversampling regimen,” with an increase in random biopsies at and immediately proximal to the z-line and fewer, if any, random biopsies in the more proximal esophagus. One such regimen could consist of 8 evenly spaced biopsies around the z-line, as well as four-quadrant biopsies at one cm proximal to the z-line and 2 cm proximal to the z-line. Biopsies proximal to 2 cm above the

top of the gastric folds would only be taken if a visible abnormality was noted. Because previous EMR sites are generally easily identified due to scarring, it seems prudent to target these sites of previous nodular neoplasia for histopathologic evaluation during surveillance endoscopies as well, particularly if they previously harbored higher-grade neoplasia. Although we have not prospectively tested such an approach, these data suggest that this biopsy protocol would have missed none of the recurrences noted in this study, and would have resulted in a savings in total numbers of biopsies of >50%.

In our study, any abnormal endoscopic findings during surveillance endoscopies significantly increased the rates of detection of recurrent BE on concurrent histopathologic samples. Their testing performance, however, was lackluster. Sensitivity of any endoscopic findings (59.3% [40.6%, 76.4%]) for recurrence was not sufficient to obviate the need for surveillance biopsies in the endoscopically normal-appearing Z line. The immediate implication of this finding is that presently, random biopsies at and just above the Z line are still required. In the longer term, this finding underscores the need for advanced mucosal imaging and/or sampling technologies, which have the potential to increase the yield of surveillance endoscopy and further decrease our reliance on random biopsies.[21–23]

The strengths of this study are several. Because endoscopists described findings from surveillance endoscopies in standardized terms, we were able to ascertain reliable endoscopic findings. All pathology readings in our surveillance cohort were performed by a single, experienced, specialized pathology service. The person-time at risk in our cohort and the number of surveillance endoscopies is large enough to analyze features of recurrence with relative precision.

This study also has limitations, which are important in its interpretation and generalizability. Because this is a single center study, its findings might not be generalizable to other centers. The 3 recurrences with missing locations could theoretically bias our findings if they were differentially concentrated in one anatomic area. The recurrences with missing locations were all focal and non-dysplastic, and all were known to originate in the lower third of the esophagus. As such, we think their potential for bias is small. It should also be noted that, although the definition of recurrence as histologic intestinal metaplasia after CEIM is useful, whether such disease represents latent, persistent disease or a true *de novo* process is unclear. It should also be noted that endoscopic landmarks in the esophagus are imperfect for ascertaining the location of the GEJ, especially after ablative therapy. It is possible that some biopsies thought to represent the GEJ actually came from the high cardia.

A large proportion of our patients undergoing RFA had high-grade disease (either HGD or IMC), pre-ablation nodularity, and long segment length, which may increase the rates of recurrence compared to a more general BE population. The sensitivity and specificity of various endoscopic findings for histologic recurrence may differ depending on baseline disease and patient characteristics, but sample size limited both investigation of these effects and/or standardization to reference population.

In conclusion, after successful CEIM, endoscopic findings under high-resolution plain white light and narrow band imaging predict histologic recurrence. However, their testing

characteristics are insufficient to obviate random surveillance biopsies. Suspicious lesions should be targeted for biopsy. Distal location predicts the likelihood of histologic recurrence, which suggests the need for a "z-line oversampling regimen," in which the GEJ is sampled more aggressively, with no or sparse sampling of normal-appearing proximal areas within the prior segment of BE. Endoscopic imaging and sampling technologies hold promise to dramatically change biopsy practices during surveillance after RFA in the future. For now, however, a focused program of random surveillance biopsies at the GE junction and in the distal-most centimeter of the esophagus offers the best yield for the detection of neoplasia.

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Acronyms

Spell-out	
RFA	Radiofrequency ablation
BE	Barrett's esophagus
CEIM	Complete eradication of intestinal metaplasia
EMR	Endoscopic mucosal resection
GEJ	Gastroesophageal junction
UNC	University of North Carolina at Chapel Hill
TGF	Top of gastric folds
IM	Intestinal metaplasia
LR	Likelihood ratio
GERD	Gastroesophageal reflux disease
NSAID	Non-steroidal anti-inflammatory drug
HGD	High grade dysplasia
IMC	Intramucosal adenocarcinoma
BMI	Body mass index
CAE	Columnar-appearing epithelium
LGD	Low grade dysplasia
EAC	(Invasive) esophageal adenocarcinoma
TIM	Top of intestinal metaplasia

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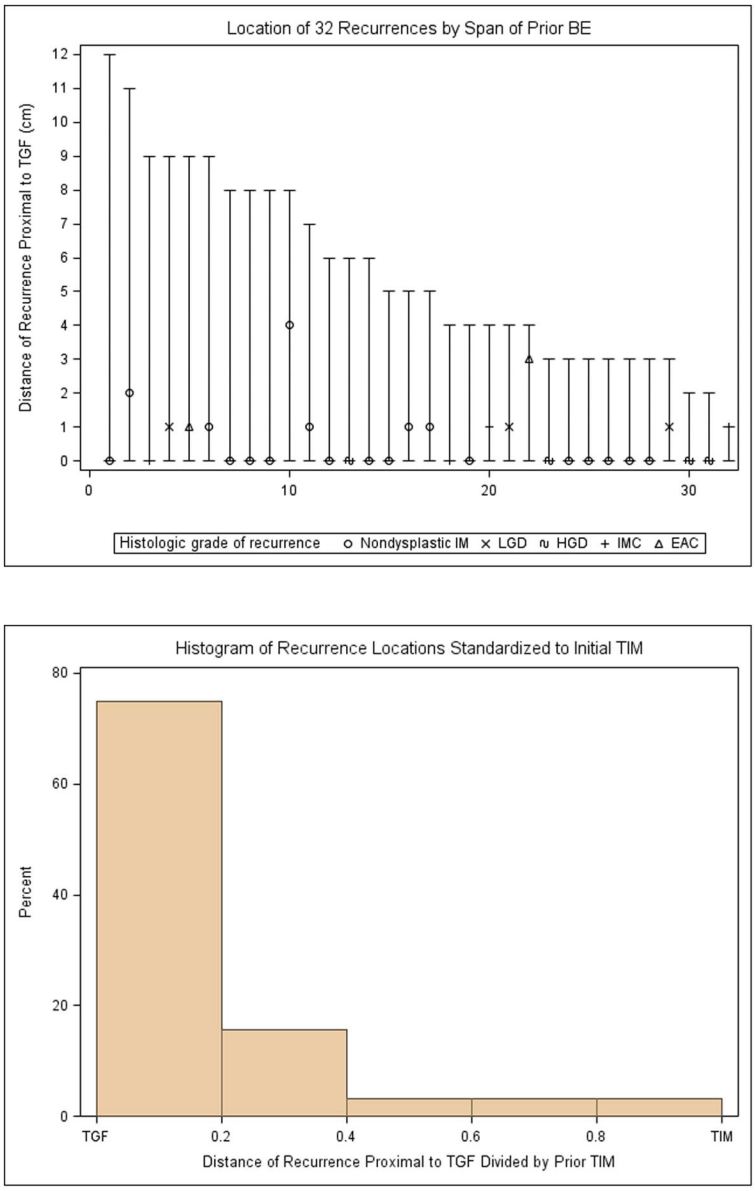

Figure 1.

Figure 1a and 1b Distribution of recurrences by proximal distance from the top of gastric folds in terms of (a) absolute distance and (b) distance as a proportion of initial Barrett's esophagus segment length. BE, Barrett's esophagus; TGF, top of gastric folds; IM, intestinal metaplasia; LGD, low grade dysplasia; HGD, high grade dysplasia; IMC, intramucosal adenocarcinoma; EAC, invasive esophageal adenocarcinoma; TIM, top of intestinal metaplasia.

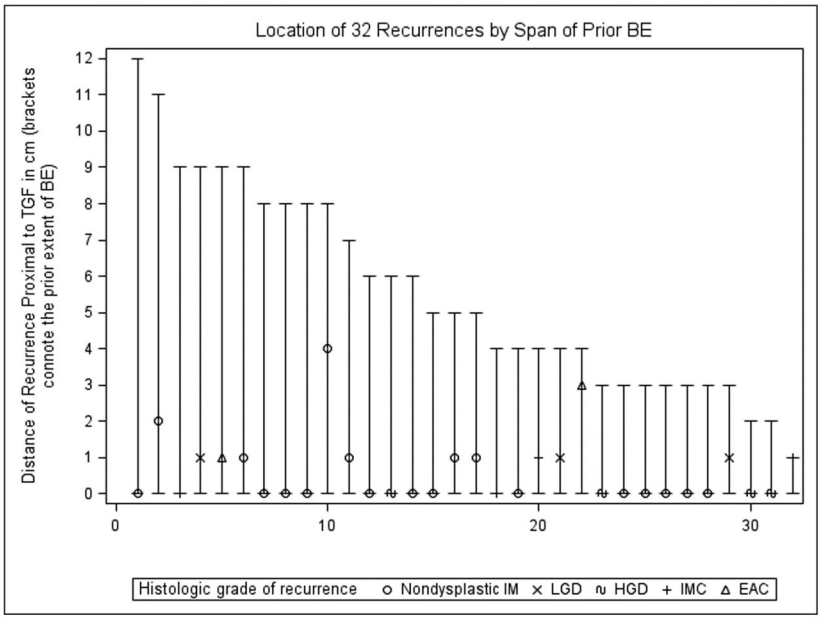

Figure 2.

Histologic grade of recurrence by distance from TGF. TGF, top of gastric folds; IM, intestinal metaplasia; LGD, low grade dysplasia; HGD, high grade dysplasia; IMC, intramucosal adenocarcinoma; EAC, esophageal adenocarcinoma.

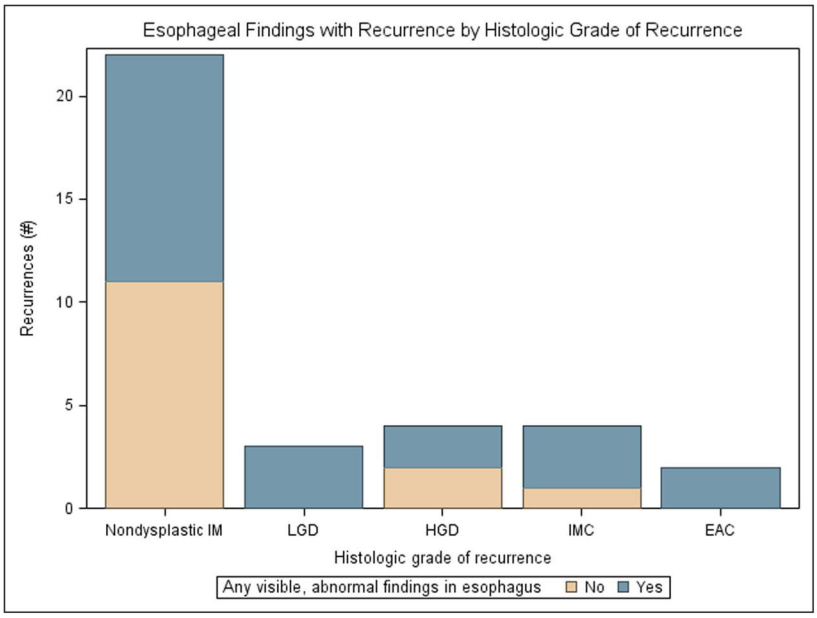

Figure 3.

Visibility of endoscopic signs of recurrent intestinal metaplasia under plain white light and narrow band imaging by histologic grade of recurrence. IM, intestinal metaplasia; LGD, low grade dysplasia; HGD, high grade dysplasia; IMC, intramucosal adenocarcinoma; EAC, invasive esophageal adenocarcinoma.

Table 1

Baseline Clinical and Endoscopic Characteristics of 198 patients at risk for recurrence.

Characteristic	Mean (STD)/Percent (N)
Age (years)	69.8 (10.2)
Sex (% Male)	70.7 (140)
BMI (m/kg^2)	29.9 (5.5)
Race - white (%)	98.4 (184)
- African American	1.6 (3)
Prior Esophagectomy	1.5 (3)
Prior Nissen Fundoplication	5.6 (11)
Use of Aspirin	42.4 (84)
Use of other NSAID	16.2 (32)
Tobacco use - Current	12.2 (24)
- Past	40.1 (79)
Alcohol use - Current	44.9 (105)
- Past	11.1 (26)
Active GERD Symptoms	45.4 (84)
Prague M Length (cm)	4.7 (3.1)
Prague C Length (cm)	1.1 (2.4)
Worst Histology During or before Treatment - Non-dysplastic BE	3.5 (7)
- Low-Grade Dysplasia	28.8 (57)
- High-Grade Dysplasia	53.0 (105)
- Intramucosal Adenocarcinoma	13.6 (27)
- Invasive Esophageal Adenocarcinoma	1.0 (2)

Table 2

Testing Characteristics and Exact Confidence Limits of Endoscopic Findings for Recurrence of IM in the Tubular Esophagus in post-RFA Surveillance Endoscopies after CEIM.

Endoscopic Finding(s)	Likelihood Ratio	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Number of Recurrences with Finding
Any recurrence (n=35)						
Any columnarappearing epithelium (CAE)	3.26 [1.48, 7.19]	31.3 [15.2, 47.3]	87.8 [85.0, 90.6]	13.3 [5.6, 21.0]	95.5 [93.7, 97.3]	10
Tongue of CAE	4.36 [0.87, 21.4]	6.3 [0.0, 14.6]	98.5 [97.5, 99.5]	20.0 [0.0, 44.8]	94.6 [92.7, 96.5]	2
Irregular Z-line	4.14 [1.58,10.89]	18.8 [5.2, 32.3]	94.7 [92.8, 96.6]	17.7 [4.8, 30.5]	95.1 [93.2, 96.9]	2
Island of CAE	1.15 [0.26, 5.07]	6.3 [0.0, 14.6]	94.5 [92.6, 96.5]	6.5 [0.0, 15.1]	94.4 [92.4, 96.3]	5
Erosion/ulcer	2.02 [0.67, 6.09]	12.5 [1.0, 24.0]	93.4 [91.3, 95.5]	10.3 [0.7, 19.8]	94.6 [92.7, 96.4]	4
Nodule	49.00 [9.09, 264.08]	15.6 [3.0, 28.2]	99.6 [99.0, 100.0]	71.4 [38.0, 100.0]	95.1 [93.4, 96.9]	5
Any endoscopic finding	6.07 [2.90, 12.70]	59.4 [42.4, 76.4]	80.6 [77.2, 84.0]	15.6 [9.1, 22.0]	97.1 [95.5, 98.6]	19
Dysplastic recurrence (n=13)						
Any columnarappearing epithelium (CAE)	3.98 [1.27, 12.48]	38.5 [13.9, 68.4]	86.4 [83.4, 89.1]	5.9 [1.9, 13.2]	98.5 [97.0, 99.3]	5
Tongue of CAE	4.39 [0.52, 36.74]	7.7 [0.2, 36.0]	98.1 [96.7, 99.1]	8.3 [0.2, 38.5]	98.0 [96.5, 99.0]	1
Irregular Z-line	2.88 [0.62, 13.5]	15.4 [1.9, 45.5]	94.1 [91.9, 95.8]	5.4 [0.7, 18.2]	98.1 [96.6, 99.0]	2
Island of CAE	1.15 [0.26, 5.07]	6.3 [0.0, 14.6]	94.5 [92.6, 96.5]	6.5 [0.0, 15.1]	94.4 [92.4, 96.3]	2
Erosion/ulcer	0.96 [0.12, 7.57]	7.7 [1.2, 36.0]	92.0 [89.6, 94.1]	2.1 [0.1, 11.1]	97.8 [96.3, 98.9]	1
Nodule	183.75 [30.92, 1091.86]	38.5 [13.9, 68.4]	99.7 [98.8, 100.0]	71.4 [29.0, 96.3]	98.7 [97.4, 99.4]	5
Any endoscopic finding	19.46 [4.26, 88.9]	84.6 [54.6, 98.1]	78.8 [74.0, 81.3]	7.8 [4.0, 13.5]	99.6 [98.5, 100.0]	11

Table 3

Baseline Histologic Grade and Histologic Grade of Recurrences in the Tubular Esophagus in post-RFA Surveillance Endoscopies after CEIM.

	Worst Histologic Grade at Baseline				
Worst Histologic Grade of Recurrence	**NDBE**	**Low-grade dysplasia**	**High-grade dysplasia**	**Intramucosal adenocarcinoma**	**Total**
Non-dysplastic IM	1	11	9	1	22
Low grade dysplasia	0	2	1	0	3
High grade dysplasia	0	0	4	0	4
Intramucosal adenocarcinoma	0	1	3	0	4
Invasive Esophageal Adenocarcinoma	0	0	1	1	2
Total	1	14	18	2	35

NDBE, nondysplastic Barrett's esophagus; IM, intestinal metaplasia;