Timeline and Location of Recurrence Following Successful Ablation in Barrett's Esophagus: An International Multicenter Study

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Abstract

Objectives: Surveillance intervals protocols after complete remission of intestinal metaplasia (CRIM) post radiofrequency ablation (RFA) in Barrett's esophagus (BE) are currently empiric and not based on substantial evidence. We aimed to assess the timeline, location, and patterns of recurrence following CRIM to inform these guidelines.

Design: Data on patients undergoing RFA for BE were obtained from prospectively maintained databases of five (three United States and 2 United Kingdom) tertiary referral centers. RFA was performed till CRIM was confirmed on two consecutive endoscopies.

Results: 594 patients achieved CRIM as of May 1st 2017. 151 subjects developed recurrent BE over a median (IQR) follow up of 2.8 (1.4-4.4) years. There was 19% recurrence risk of any BE within 2 years and an additional 49% risk over the next 8.6 years. The recurrence hazard rate of any BE, dysplastic BE, and high grade dysplasia/cancer remained constant over the duration of follow-up (p=0.74, p=0.94, and p=0.88; respectively). 74% of BE recurrences developed at the gastroesophageal junction (GEJ) (24.1% were dysplastic) and 26% in the tubular esophagus. The yield of esophageal random biopsies from the tubular esophagus, in the absence of visible lesions, was 1% (BE) and 0.2% (any dysplasia recurrence).

Conclusions: BE recurrence risk following CRIM remained constant over time, suggesting that lengthening of follow up intervals, at least in the first five years after CRIM, may not be advisable. Sampling the GEJ is critical to detecting recurrence. The requirement for random biopsies of the neo-squamous epithelium in the absence of visible lesions may need to be re-evaluated.

What is already known about this subject?

- Recurrence rates of intestinal metaplasia and dysplasia following successful ablation for Barrett's esophagus are well established.
- Recent data suggests that rates of recurrence are highest in the initial year after remission and may decline thereafter suggesting widening of surveillance intervals after the initial year.
- Data on the timeline and endoscopic patterns of recurrence are scarce.

What are the new findings?

- Recurrence rates of intestinal metaplasia and dysplasia appear to increase progressively with time with no plateauing, in this multicenter international cohort study,
- Yield of neo-squamous epithelium biopsies from the tubular esophagus in the absence of visible recurrences is very low (< 1.0%).
- Most recurrences occur at the gastroesophageal junction (GOJ) or in the distal 5 cm of the esophagus

How might it impact on clinical practice in the foreseeable future?

- Widening of surveillance intervals to detect recurrence after BE ablation may be premature in the absence of additional data.
- Practice guidelines recommending Seattle protocol biopsies in the entire neo-squamous epithelium in the absence of visible recurrences may need to be reevaluated.

Introduction

Barrett's esophagus (BE) is a condition that develops when the normal squamous epithelium is replaced by columnar mucosa with specialized intestinal metaplasia (IM). This process confers an increased risk of progression to esophageal adenocarcinoma (EAC) with an estimated incidence rate of approximately 0.33 per patient year.[1] This risk increases significantly when either low grade dysplasia (LGD) or high grade dysplasia (HGD) develop in the setting of BE.[2] Radiofrequency ablation (RFA) after endoscopic resection of visible lesions has been shown to significantly reduce the risk of cancer progression in patients with both LGD and HGD and has therefore become the standard of care in those patients.[2] RFA is deemed to be successful once complete remission of intestinal metaplasia (CRIM) is achieved both endoscopically and histologically. However, recurrence of both IM and dysplasia occurs, with an estimated annual incidence rate of 9.5% for any recurrence and 2% for dysplastic recurrences.[3, 4] For these reasons, guidelines recommend regular surveillance every 3 months for the first year following CRIM, then every 6 months for the second year and then yearly afterwards.[2]

Data from a recent systematic review suggest that recurrence rate may be significantly higher in the first year compared to subsequent years, raising the question, whether surveillance intervals should be extended to every 2 or 3 years instead of yearly after CRIM.[5] However, this difference was not noted in the subgroup of studies defining CRIM more stringently as two negative endoscopies (n=3).[6-8] The finding of columnar mucosa or IM on histology after one negative endoscopy may represent incompletely treated or missed prevalent disease rather than true recurrence and may therefore overestimate the recurrence rate.[5] None of the latter studies evaluated the variation in the incidence of

recurrence over time across all grades of dysplasia. Moreover, other studies have thus far been limited by either small sample size (of CRIM patients with small number of dysplastic recurrences) [6, 9, 10] or the inclusion of large number of patients treated with no dysplasia whose recurrence patterns may not be reflective of those with dysplasia.[11] Hence, there is currently no conclusive evidence to demonstrate that the recurrence rate following CRIM remains constant over time (new cases developing every year) in order to justify currently recommended yearly surveillance or whether the rate plateaus after some time (no new cases developing) which may therefore justify widening surveillance intervals.

Guidelines recommend that during surveillance after CRIM, random biopsies should be obtained from the gastroesophageal junction (GEJ) and the neo-squamous epithelium at 1-2 cm intervals to cover the extent of the previous BE segment.[2] Longitudinal data on the yield of this approach, particularly, in the absence of endoscopically visible recurrence are limited. Such data will be valuable in determining the cost effectiveness of this practice and in informing future guidelines. Similarly, the location of recurrence in the tubular esophagus needs to be better defined in order to justify surveillance biopsies over the entire length of the previous BE segment.

Given these knowledge gaps, we aimed to assess the timeline, location, and patterns of recurrence following CRIM in a large multicenter, and international cohort with the goal of informing future guidelines for endoscopic surveillance after CRIM. We also used a conservative definition of CRIM as two consecutive negative endoscopies with biopsies (from the esophagus and GEJ) for the reasons detailed above.

Materials and Methods

Study design

This was a cohort study of patients undergoing RFA for BE in five tertiary referral centers with expertise in the management of this condition. Three centers were located in the United States (Mayo Clinic Rochester, Mayo Clinic Arizona, and Mayo Clinic Florida) and 2 in the United Kingdom (Nottingham and Cambridge University Hospitals). The study was approved by the Institutional Review Boards of the respective centers. Data were obtained from prospectively maintained databases at each of the participating centers. We included patients who are 18 years or older with endoscopically (at least 1 cm of columnar mucosa in the tubular esophagus) and histologically (presence of IM) confirmed BE with or without dysplasia, who underwent RFA. Patients with advanced cancer stage (T2 or higher), pregnancy, or esophageal varices were excluded from the study. RFA procedures were performed between November 2003 and July 2016. All patients included in this study achieved CRIM between March 2004 and May 2017 and had at least one follow up endoscopy to check for recurrence. The study was conducted and reported according to the STROBE guidelines[12].

Participants and Interventions

Patients underwent RFA by expert endoscopists following endoscopic assessment using high definition white light endoscopy and narrow band imaging with or without endoscopic resection of any visible lesions. Both circumferential and focal RFA was used to treat the BE segments as well as the GEJ. Energy settings followed manufacturer recommendations and RFA was performed every 3 months till CRIM was achieved. CRIM was defined as two consecutive endoscopies at least 3 months apart confirming the absence of IM on biopsies from both the GEJ (top of the gastric folds within 1 cm of the

neo-squamo-columnar junction) and tubular esophagus. In addition to RFA, patients could receive argon plasma coagulation or multipolar coagulation, as rescue (adjuvant) techniques for minimal residual BE islands.

Post CRIM surveillance protocol

Once CRIM was achieved, subsequent surveillance was performed at 3, 6, 9, and 12 months thereafter. All patients underwent high definition white light endoscopy and narrow band imaging with random biopsy specimens obtained from the GEJ and every 1-2 centimeters in 4 quadrants to cover the area of the previous BE segment as a minimum requirement. Samples from each level were labelled and stored in separate bottles. In addition, targeted biopsies were taken from any visible lesions (both columnar and/or neo-squamous). Recurrence was defined as the histologic presence of IM with or without dysplasia on biopsy specimens taken from either the tubular esophagus or the GEJ or both after CRIM was achieved. The location, visibility, and the dysplasia status of all recurrences were documented. A separate sensitivity analysis was performed for recurrence incidence rate after excluding non-dysplastic BE (NDBE) recurrences at the GEJ given concern that this may represent residual IM or IM of the cardia rather than true BE recurrence.[13]

Histology

Baseline histology was recorded for all patients upon entry into the study and classified as: non-dysplastic BE (NDBE); indefinite for dysplasia (ID); LGD; HGD; and cancer. Biopsy specimens at each center were examined by an expert gastrointestinal pathologist. The worst grade of dysplasia detected on tissue sampling at baseline (pre-RFA) and at post-CRIM surveillance (post-RFA) was assigned to that patient.

Statistical Analysis

The Kaplan-Meier method was used to estimate the cumulative incidence of recurrence after CRIM. Tests of a constant recurrence hazard rate were performed with likelihood ratio tests comparing exponential vs. Weibull distributions for time to recurrence. Cox proportional hazards models were used to measure associations of a priori-set baseline variables with recurrence. Multivariable Cox models were used to estimate adjusted effects of each variable on recurrence, with Firth estimation in cases with low recurrence totals. A separate sensitivity analysis was performed for recurrence incidence rate after excluding NDBE recurrences at the GEJ given concern in some studies that this may represent residual IM or IM of the cardia rather than true BE recurrence.[13]

Results

Baseline Characteristics

594 patients achieved CRIM as of May 1st 2017 and were included in the analysis (Table 1). Figure 1 shows patient flowchart. Mean (standard deviation (+/-SD)) age was 67 (+/-10) years and 86% were males. Median (interquartile range (IQR)) BE segment length was 4 (2-6) cm. 90% of patients were treated for dysplasia or carcinoma.

Table 1: Baseline characteristics of included patients (n=594). Data presented as number (%); mean (+/- standard deviation); or median (interquartile range).

Variable	Value
Age, years	67 (+/-10)
Male sex	509 (86%)
Body mass index	30.0 (+/-4.9)

Length of Barrett's, cm (Prague M) - Patients with long segment BE (≥3 cm)	4 (2-6) 385 (65.0%)
Hiatal hernia presence - Length of hiatal hernia, cm	492 (82.8%) 3 (2-5)
Pre-RFA baseline histology: - Non-dysplastic BE - Indefinite for dysplasia - Low grade dysplasia - High grade dysplasia - Cancer	 62 (10.4%) 21 (3.5%) 121 (20.4%) 292 (49.2%) 98 (16.5%)
Pre-RFA endoscopic resection - Lesion histology: • Non-dysplastic BE • Indefinite for dysplasia • Low grade dysplasia • High grade dysplasia • Cancer i. Stage T1a; T1b; uncertain	326 (54.9%) 48 (14.7%) 1 (0.3%) 53 (16.3%) 142 (43.6%) 82 (25.1%) 78 (95.1%); 3 (3.7%), 1 (1.2%)
Index RFA device used - Circumferential - Focal	 302 (51.3%) 287 (48.7%)

Number RFA sessions needed to CRIM	2 (1-3)
- 1-4	554 (93.3%)
- 5-8	40 (6.7%)

BE, Barrett's esophagus; RFA, radiofrequency ablation; CRIM, complete remission of intestinal metaplasia

151 subjects developed recurrent BE (Table 2) over a median (IQR) follow up of 2.8 (1.4-4.4) years.

Table 2: Baseline characteristics of recurrent cases (n=151). Data presented as number (%).

Recurrence parameter	**Value**
Location	
- Gastroesophageal junction:	112 (74.2%)
- Tubular esophagus:	39 (25.8%)
Histology: overall, tubular esophagus, GEJ	
- Non-dysplastic BE	104 (68.9%), 21 (13.9%), 83 (55%)
- Indefinite for dysplasia	3 (2.0%), 1 (0.7%), 2 (1.3%)
- Low grade dysplasia	18 (11.9%), 8(5.3%), 10 (6.6%)
- High grade dysplasia	12 (7.9%), 4 (2.6%), 8 (5.3%)
- Cancer	14 (9.3%), 5 (3.3%), 9 (6.0%)

• Stage T1a • Stage T1b • Stage T2	8 (5.3%), 2 (1.3%), 6 (4.0%) 4 (2.6%), 2 (1.3%), 2 (1.3%) 2 (1.3%), 1 (0.65%), 1 (0.65%)
Recurrence treated†	108 (71.5%)
Recurrence treatment modality: - Endoscopic resection - Ablation - Endoscopic resection + ablation - Endoscopic resection + chemo-radiation - Radiation only	 10 (9.3%) 83 (76.9%) 13 (12.0%) 1 (0.9%) 1 (0.9%)
Recurrence treatment outcome - CRIM achieved - Ongoing endoscopic therapy - Lost to follow up - Esophagectomy +/- chemo-radiation - Radiation therapy only	 73 (67.6%) 25 (23.1%) 4 (3.7%) 4 (3.7%) 2 (1.9%)

†Recurrence not treated in 43 (28.5%) patients (n=27 awaiting treatment at the time of analysis; n=7 lost to follow up; n= 1 deceased/lung cancer; n=3 no intestinal metaplasia on follow up; n=5 surveillance only). GEJ, gastroesophageal junction; BE, Barrett's esophagus; CRIM, complete remission of intestinal metaplasia.

Recurrence incidence and timeline

The annual incidence rates of any recurrence, dysplastic recurrence, and HGD/cancer recurrence for the entire cohort are shown in Table 3.

Table 3: Annual incidence rates of recurrence.

Patient group	**any recurrence**	**Dysplastic recurrence**	**HGD/cancer recurrence**
All recurrences in entire study cohort (n=594)	9.6%	2.8%	1.6%
Excluding NDBE recurrence at GEJ (n=594)	4.3%	2.8%	1.6%
Stratified by baseline histology pre-RFA			
- NDBE/ID subgroup (n=83)	5.2%	0.7%	0.7%
- LGD subgroup (n=121)	5.9%	0.9%	0.9%
- HGD/cancer subgroup (n=390)	12.4%	4.3%	2.3%

HGD, high grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; GEJ, gastroesophageal junction; RFA, radiofrequency ablation; ID, indefinite for dysplasia; LGD, low grade dysplasia; HGD, high grade dysplasia.

The recurrence hazard rate remained constant over the follow-up duration (p=0.74) with 19% risk within 2 years and an additional 49% risk over the next 8.6 years. The recurrence hazard rate of dysplasia and HGD/Cancer while lower, also remained constant (p=0.94 and p=0.88, respectively) over the duration of follow up (Figure 1). When NDBE recurrences at the GEJ were excluded, the recurrence hazard rate of any BE, dysplastic BE, and HGD/cancer continued to remain constant over the follow up duration (p=0.94, 0.88, and 0.94, respectively) (Supplementary Figure 1).

Similarly, when stratified by baseline histology pre-RFA, the hazard rate of any recurrence remained constant over the follow-up duration in all the 3 groups of NDBE/ID (p=0.15), LGD (p=0.20), and HGD/cancer (p=0.91) (Figure 2). The hazard rate of dysplastic recurrence also remained constant in all the 3 groups of NDBE/ID (p=0.62), LGD (p=0.74), and HGD/cancer (p=0.87) (Figure 3).

Recurrence location

BE recurred at the GEJ in 74.2% (n=112) of subjects and in the tubular esophagus in 25.8% (n=39) (Table 2). 24.1% (n=27) of recurrences at the GEJ were dysplastic. Out of those, 59.3% (n=16) were visible endoscopically (Cancer n=9, HGD n=5, LGD n=2) and 40.7% (n=11) were non-visible (HGD n=3, LGD n=8) and only detected on random biopsies of the GEJ.

82.1% (n=32) of recurrences in the tubular esophagus were visible endoscopically and 84.4% of those were detected within 5 cm of the GEJ (Figure 4A). 17.9% (n=7) were non-visible and only detected on random biopsies of the neo-squamous epithelium (Figure 4B) (Five were subsquamous and 2 had no mention of columnar mucosa on the endoscopy report, but histology showed IM with no squamous epithelium in the specimen

bottle). Six out of those 7 patients had NDBE at 2 cm (n=3); 7 cm (n=2); and 9 cm (n=1) from the GEJ. One patient had LGD at 4 cm from the GEJ. Therefore, the overall yield of random biopsy sampling for NDBE recurrence was only 1.0% (6/594) for any recurrence, and 0.2% (1/594) for dysplastic recurrence.

Predictors of recurrence

Baseline HGD/cancer but not LGD, predicted any recurrence (HR 1.95, 95%CI 1.07-3.56; p=0.029) (Supplementary Table 1) as well as dysplastic recurrence (HR 4.81, 95%CI 1.21-19.18; p=0.026) (Supplementary Table 2).

Supplementary Table 1: Multivariable model for any recurrence after complete remission of intestinal metaplasia with radiofrequency ablation.

Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits	P value
Age at CRIM	1.01	0.99-1.03	0.211
Male sex	0.83	0.53-1.29	0.398
Length of Barrett's cm (Prague M)	1.03	0.97-1.10	0.368
Presence of hiatal hernia	1.62	0.93-2.82	0.087
Baseline high grade dysplasia/cancer	1.95	1.07-3.56	0.029
Baseline low grade dysplasia	1.01	0.52-1.97	0.971
Endoscopic resection Pre-RFA	1.17	0.78-1.77	0.448

Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits	P value
Use of circumferential RFA device	1.17	0.75-1.83	0.495
Number of RFA sessions needed to CRIM	1.07	0.93-1.23	0.344
Use of other adjuvant ablation techniques	1.22	0.87-1.72	0.242

CRIM, complete remission of intestinal metaplasia; RFA, radiofrequency ablation.

Supplementary Table 2: Multivariable model for dysplastic recurrence after complete remission of intestinal metaplasia with radiofrequency ablation.

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits	P value
Age at CRIM	1.02	0.98-1.05	0.381

Male sex	1.77	0.58-5.39	0.317
Length of Barrett's cm (Prague M)	1.08	0.97-1.21	0.165
Presence of hiatal hernia	2.02	0.54-7.62	0.298
Baseline high grade dysplasia/cancer	4.81	1.21-19.18	0.026
Baseline low grade dysplasia	0.90	0.17-4.83	0.906
Endoscopic resection Pre-RFA	0.76	0.38-1.51	0.433
Use of circumferential RFA device	1.58	0.65-3.82	0.313
Number of RFA sessions needed to CRIM	1.09	0.85-1.38	0.508
Use of other adjuvant ablation techniques	1.92	1.04-3.57	0.039

CRIM, complete remission of intestinal metaplasia; RFA, radiofrequency ablation.

Discussion

Principal findings

In this large multicenter and international cohort study, recurrence rates of NDBE, any dysplasia, and HGD/cancer following initial CRIM after RFA did not appear to plateau over the first 5-6 years of follow up, suggesting that continued yearly surveillance remains important and arguing against extending surveillance intervals at present, particularly in those with HGD/cancer at baseline. The majority of recurrences (74.2%) developed at the

GEJ and approximately a quarter of those were dysplastic, out of which a significant proportion (40.7%) were non-visible endoscopically. Most (84.4%) visible recurrences in the tubular esophagus were located within 5 cm of the GEJ. Finally, the yield of tubular esophageal biopsies in the absence of visible recurrence was very low for NDBE (1.0%) and dysplastic BE (0.2%) which suggests that the requirement for random biopsies of the neo-squamous epithelium in the absence of visible recurrence may need to be re-evaluated.

A recent modelling study based on data from the US and UK RFA registries suggested surveillance endoscopies at one and three years after CRIM for patients with baseline LGD and endoscopies at three months, six months, one year, and then annually thereafter for those with baseline HGD or cancer.[11] The surveillance intervals were estimated only to a limit of five years to avoid extrapolation beyond available data. Therefore, there is a lack of clarity from current literature with regards to both the need for and the yield of surveillance beyond this time. Moreover, the latter model's estimates were based on dysplastic recurrences only and did not account for the non-dysplastic (NDBE) ones. NDBE recurrences following CRIM require therapy as those could represent an incompletely treated or missed prevalent disease and may therefore still have neoplastic potential if left untreated.[5] When NDBE recurrences at the GEJ were excluded (given concern that this may represent IM of the cardia rather than true BE recurrence[13]), the recurrence hazard rate across all grades of dysplasia remained constant (table 3 and supplementary figure 1). Our data suggests that continued surveillance beyond 5 years remains necessary. The recurrence rate in patients with LGD

at baseline also remained constant over time, suggesting that long term surveillance is warranted.

The number of endoscopies required to define CRIM remains a subject of debate. Intestinal metaplasia is known to be patchy and may be missed on random biopsies.[14] Therefore, two endoscopies with biopsies may be required to confidently rule out the presence of IM.[14] To our knowledge, there are no data comparing 2 vs. 3 or more negative endoscopies and this may be an area for further research. None of the three studies that defined CRIM on 2 negative endoscopies [6-8] evaluated the variation in the incidence of recurrence over time across all grades of dysplasia. In one single center study, 20% of patients had NDBE at baseline and no recurrences were reported after 3 years implying little benefit from surveillance beyond 3 years post CRIM.[6] This is in contrast to data from our study demonstrating that recurrence rate remained constant after 3 years.

Previously, two smaller, single center studies reported that the majority of dysplastic recurrences developed in the gastric cardia and the majority of those were non-visible.[10, 15] Eighty percent of recurrences in the tubular esophagus were visible endoscopically [10] and random biopsies >1 cm proximal to the GEJ had no yield for any recurrence.[15] Data from the current study from a larger multicenter cohort showed that 82% of tubular esophageal recurrences were visible and the yield of random biopsies >1 cm proximal to the GEJ was extremely low (1.2% yield for any recurrence and 0.2% for dysplastic recurrence). The true rate of non-visible, sub-squamous recurrence remains hard to measure, but is likely to be rare based on current data.[16] Volumetric laser endomicroscopy has been used to image post-RFA subsquamous glandular structures, but correlation with buried BE glands was poor in one study.[17] More cost-effective and

standardized imaging and sampling techniques are required in order to evaluate this outcome in a more systematic and precise manner. Moreover, data on the natural history of these recurrences are required.

Study strengths and limitations

This study has several strengths. We evaluated a large sample of patients over a long follow up duration, which are important factors to achieve more precise estimates of the recurrence rates. Data were collected from multiple centers located both in the UK and USA, which strengthens the validity and generalizability of our results. Furthermore, the vast majority of our patients (90%) received RFA for dysplastic BE which is representative of current clinical practice guidelines in contrast to several other studies of US populations where the larger proportion of patients (up to 46%)[11] have NDBE and therefore do not require RFA based on current evidence.[2] Databases were prospectively maintained in all participating centers in order to minimize selection and recall biases. While centralized pathology was not utilized, all centers had dedicated expert gastrointestinal pathologists reading all BE histology.

The study also has limitations. Biopsy sampling techniques and forceps size used were not standardized across centers and may therefore result in sampling error and case ascertainment bias. We attempted to minimize the latter by implementing a more conservative definition of CRIM with 2 negative endoscopies and biopsies for IM from both the GEJ and tubular esophagus. The multicenter nature of the study with different operators at centers of expertise, makes the study susceptible to variation in practices, but also helps to make our data more representative of real world practice. One caveat to the latter is that our study sample comes from tertiary referral centers, which may not

be representative of results in community practice. However, the overwhelming number of these procedures are currently performed in settings similar to ours based on current society guidelines.[2]

Conclusions and implications for clinical practice

This study demonstrates that the recurrence hazard rate of NDBE, dysplastic BE, and HGD/cancer remained constant over time during surveillance in patients who achieved CRIM after RFA when strict criteria for the definition of CRIM are applied. This suggests that diligent long term (at least) yearly endoscopic surveillance remains important in these patients. The majority of all recurrences developed at the GEJ and a significant proportion of dysplastic recurrences were non-visible endoscopically. This re-enforces the need for careful imaging and sampling of the GEJ despite the absence of any visible lesions. On the other hand, the majority of recurrences in the tubular esophagus are visible endoscopically and the yield of random biopsy sampling in the absence of visible lesions was very low in expert centers. These findings may need to be replicated in non-expert centers before further conclusions can be made with regards to the cost-effectiveness of this practice.

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Figure Legends:

Figure 1: Patient flowchart

Figure 2: The timeline of recurrent Barrett's esophagus (any recurrence; dysplastic recurrence; and high grade dysplasia (HGD)/cancer recurrence) following complete remission of intestinal metaplasia (CRIM).

Figure 3: The timeline of any recurrence stratified by baseline histology prior to radiofrequency ablation. NDBE: non-dysplastic Barrett's esophagus; LGD: low grade dysplasia; HGD: high grade dysplasia.

Figure 4: The timeline of dysplastic recurrences stratified by baseline histology prior to radiofrequency ablation. NDBE: non-dysplastic Barrett's esophagus; LGD: low grade dysplasia; HGD: high grade dysplasia.

Figure 5: The location of visible (panel A) and non-visible (panel B) recurrences in the tubular esophagus (blue cylinder). Histology of non-visible recurrences is also shown in panel B (NDBE: non-dysplastic Barrett's esophagus; LGD: low grade dysplasia).

Supplementary Figure 1: The timeline of recurrent Barrett's esophagus (any recurrence; dysplastic recurrence; and high grade dysplasia (HGD)/cancer recurrence) following

complete remission of intestinal metaplasia (CRIM) and after excluding non-dysplastic recurrences at the gastroesophageal junction.