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Clinical Relevance of Random Biopsies From the Esophagogastric Junction After Complete Eradication of Barrett's Esophagus is Low

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Clinical relevance of random biopsies after complete eradication of Barrett's esophagus

METHODS

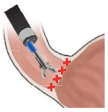
1,154 patients with early Barrett's neoplasia

↓

Succesful endoscopic eradication therapy in expert center

↓

4-quadrant biopsies from esophagogastric junction (EGJ)



- After treatment & during follow-up
- Incidence of intestinal metaplasia (IM)

RESULTS

		Never EGJ-IM (n = 971)	Persisting EGJ-IM (n = 78)	Recurrent EGJ-IM (n = 72)
Non-dysplastic recurrence	n (%)	83 (9)	9 (12)	13 (18)
	HR (95% CI)	-	1.2 (0.6-2.1)	1.2 (0.7-2.1)
Dysplastic recurrence	n (%)	33 (3)	2 (3)	1 (1)
	HR (95% CI)	-	0.7 (0.2-3.1)	0.3 (0-2.0)

CONCLUSION Random biopsies from the EGJ can safely be abandoned under condition that care is provided in expert centers and the esophagus is carefully inspected.

Clinical Gastroenterology and Hepatology

BACKGROUND & AIMS: **Although random histological sampling from the esophagogastric junction (EGJ) after complete eradication of Barrett's esophagus (BE) is recommended, its clinical relevance is questionable. This study aimed to assess the incidence and long-term outcomes of findings from random EGJ biopsies in a nationwide cohort with long-term follow-up.**

*Authors share co-first authorship.

Abbreviations used in this paper: BE, Barrett's esophagus; CE-BE, complete eradication of Barrett's esophagus; CI, confidence interval; EET, endoscopic eradication therapy; EGJ, esophagogastric junction; EGJ-IM, intestinal metaplasia at esophagogastric junction; HGD, high-grade dysplasia; IM, intestinal metaplasia; IQR, interquartile range; LGD, low-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; RFA, radiofrequency ablation.

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METHODS: **We included all patients with successful endoscopic eradication therapy (EET), defined as complete endoscopic eradication of all visible BE (CE-BE), for early BE neoplasia from the Dutch registry. Patients were treated and followed-up in 9 expert centers according to a joint protocol. Outcomes included the incidence of intestinal metaplasia (IM) at the EGJ (EGJ-IM) and the association between IM and visible (dysplastic) BE recurrence.**

RESULTS: **A total of 1154 patients were included with a median follow-up of 43 months (interquartile range, 22–69 months). At the time of CE-BE, persisting EGJ-IM was found in 7% of patients (78/1154), which was reproduced during further follow-up in 46% of patients (42/78). No significant association existed between persisting EGJ-IM at CE-BE and recurrent non-dysplastic or dysplastic BE (hazard ratio [HR], 1.15; 95% confidence interval [CI], 0.63–2.13 and HR, 0.73; 95% CI, 0.17-3.06, respectively). Among patients with no EGJ-IM at the time of CE-BE (1043/1154; 90%), EGJ-IM recurred in 7% (72/1043) after a median of 21 months (interquartile range, 15–36 months), and was reproduced during further follow-up in 26% of patients (19/72). No association was found between recurrent EGJ-IM and non-dysplastic or dysplastic recurrence (HR, 1.18; 95% CI, 0.67–2.06 and HR, 0.27; 95% CI, 0.04–1.96, respectively).**

CONCLUSION: **Because EGJ-IM was not associated with a higher risk for recurrent disease, we recommend to consider abandoning random EGJ sampling after successful EET, under the condition that care is provided in expert centers, and the esophagus, including the EGJ, is carefully inspected (Netherlands Trial Register, NL7309).**

Keywords: Barrett's Esophagus; Endoscopic Eradication Therapy; Radiofrequency Ablation; Random Biopsies.

Endoscopic eradication therapy (EET), consisting of endoscopic resection for visible abnormalities followed by ablation therapy, has proven to be safe and effective for the eradication of early Barrett's esophagus (BE) with neoplasia.[1-3] Although indications and treatment protocol for EET are well established, follow-up after successful treatment is less well-defined. It is generally accepted that histologic sampling is indicated when BE tissue and/or a new visible lesion recur during follow-up.[4-6]

However, in the case of an endoscopically normal appearing esophagus, there is lack of consensus on the need for random biopsies from the esophagogastric junction (EGJ). Current guidelines recommend random biopsies in 4 quadrants of the EGJ. [4-6] This procedure is not only time-consuming for endoscopists and pathologists, it also results in increased health care costs.[7,8] Moreover, it is our experience in daily clinical practice that the yield of these random EGJ biopsies is limited.

Recently, we published the treatment and long-term follow-up outcomes from a nationwide registry including all patients with BE that underwent EET in the Netherlands. The study reported a low recurrence risk of 1.0% per patient year for low-grade dysplasia (LGD), high-grade dysplasia (HGD), or cancer. A concise subanalysis showed that random biopsies from the EGJ showed intestinal metaplasia (IM) in 14%, of which none progressed to HGD or worse during median 3 years follow-up. [9] This brief analysis, however, lacked information on: (1) the difference between persisting IM after EET and recurrent IM during follow-up; (2) the relation between IM and the risk for recurrent non-dysplastic BE; (3) the pattern of IM recurrence during follow-up; and (4) formal analysis for an association between IM and visible BE recurrence. Therefore, in the current study, we aimed to assess the incidence and clinical relevance of findings from random EGJ biopsies in this previously described national cohort.

Methods

Study Population

This study is part of the Barrett Expert Center registry (Netherlands Trial Register, NL7309).[9] For the current study, we included all patients who underwent successful EET with radiofrequency ablation (RFA), defined as complete endoscopic eradication of all visible BE (CE-BE). Further details on the study population and treatment protocol are given in Supplementary Appendix 1.

End of Treatment

After all visible BE was endoscopically eradicated (ie, CE-BE), random 4-quadrant biopsies were taken from the EGJ (ie, <5 mm distally from the neosquamocolumnar junction) to histologically confirm eradication of IM. If IM persisted, one additional focal RFA of the EGJ was allowed, per discretion of the endoscopist.

Follow-up

Follow-up consisted of careful inspection of the esophagus during high-definition endoscopy. From 2008 to 2016, random 4-quadrant biopsies were taken from

the EGJ during every follow-up endoscopy. Due to a low yield of clinically relevant findings, the random EGJ biopsies were abandoned in 2016. Residual BE or visible lesions always remained indications for histological sampling. Similar to the sampling methods, the follow-up intervals also changed over time with less follow-up endoscopies during the first year as described previously.[9]

Histological Evaluation

Histological assessment of all biopsies at the end of treatment and during follow-up was performed by a dedicated BE expert pathologist. The training of these expert pathologists has been described in detail elsewhere.[10,11] In case the expert pathologist diagnosed indefinite for dysplasia, histology was revised by a second expert pathologist for a final diagnosis. If the second pathologist confirmed indefinite for dysplasia, biopsies were repeated during the next endoscopy.

Study Endpoints

Based on the definitions shown in Supplementary Table 1, we defined several outcomes:

I. Incidence of IM in random biopsies from a normal appearing EGJ (EGJ-IM) (Figure 1), with a distinction in the following subgroups:
   a. Never EGJ-IM, defined as random EGJ biopsies showing no IM at the time of CE-BE nor during follow-up;
   b. Persisting EGJ-IM after treatment, defined as random EGJ biopsies showing IM at the time of CE-BE;
   c. Recurrent EGJ-IM during follow-up, defined as random EGJ biopsies showing no IM at the time of CE-BE, but new IM during follow-up;

II. Association between EGJ-IM and recurrent dysplasia (ie, LGD or worse) and neoplasia (ie, HGD or worse) adjusted for potential confounders (ie, gender, age, BE length at baseline, baseline histology, new visible lesion during EET, and poor squamous regeneration after RFA [ie, <50% regression]);

III. Association between EGJ-IM and recurrent visible non-dysplastic BE (NDBE) tongues (Figure 2) adjusted for potential confounders (identical to II).

What You Need to Know

Background

Current guidelines recommend random histological sampling from the esophagogastric junction after successful endoscopic eradication therapy for Barrett's esophagus, although the clinical yield of these random biopsies is questionable.

Findings

In this nationwide cohort, random biopsies from the esophagogastric junction did not result in any clinically relevant findings such as high-grade dysplasia or worse. The most common finding, intestinal metaplasia, was not associated with recurrent Barrett's esophagus.

Implications for patient care

Random sampling of the esophagogastric junction after successful eradication therapy can safely be abandoned in expert centers. Eventually, this will save time and costs due to shorter procedure times and elimination of histopathologic evaluation.

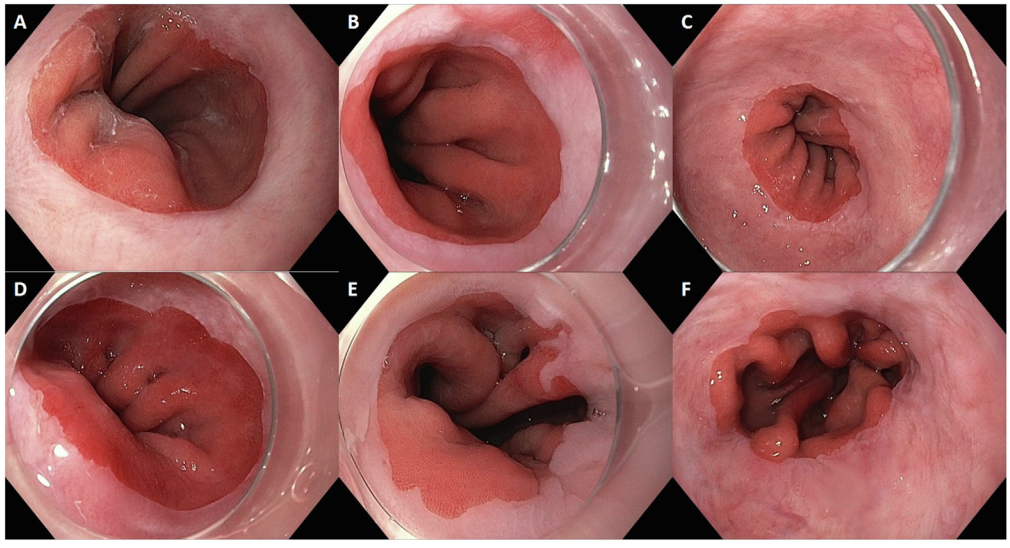

Figure 1. Endoscopic images of a normal appearing EGJ. These examples of a normal EGJ after successful endoscopic eradication therapy illustrate the wide variety in possible endoscopic appearances (*A–F*).

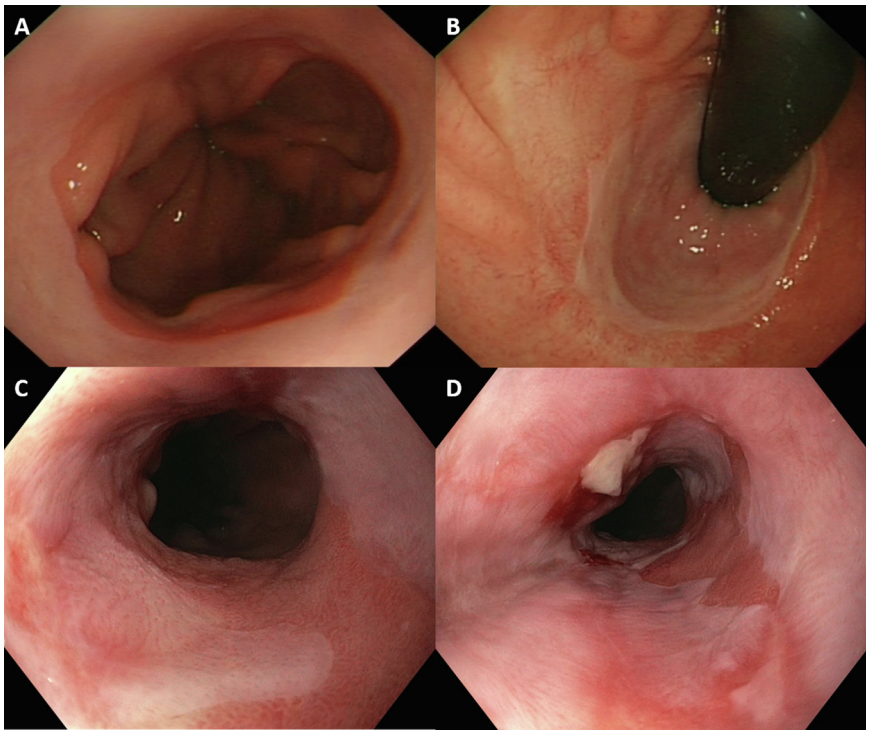

Figure 2. Endoscopic images of recurrent visible non-dysplastic BE after initial CE-BE. Example of a patient with initial C1M3 flat BE with low-grade dysplasia who underwent successful endoscopic eradication therapy. After 4 radiofrequency ablation treatments, CE-BE was achieved with a normal appearing esophagogastric junction and absence of intestinal metaplasia in random biopsies (*A–B*). Seven years post-treatment, recurrent C1M2 flat BE along with severe reflux esophagitis was detected during endoscopic follow-up (*C–D*).

Data Collection

All data were collected in an online database by medical students after reviewing endoscopy and pathology reports, and other relevant clinical information from electronic patient files. To guarantee the high quality of collected data, an independent review of a random 50% of the study population was performed by a dedicated research fellow. The images of all patients with recurrent visible BE, and/or an irregular EGJ during follow-up were centrally reviewed by 2 members of the study team (RP and JB) for presence of recurrent visible BE. Discrepancies were resolved in a consensus meeting. All authors had access to the study data and reviewed and approved the final manuscript.

Statistics

Statistical analysis was performed using RStudio version 3.6.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). For descriptive statistics, frequencies and proportions were computed for categorical variables, and mean with standard deviation and median with interquartile range (IQR) for continuous variables with normal or skewed distribution, respectively. We used R packages for survival and recurrent event analysis and adjusted for possible confounders. Risk for recurrent disease was calculated as an annual risk with 95% confidence intervals (CIs) using bootstrapping.

Results

Baseline characteristics and outcomes of the cohort have been described previously (Supplementary Table 2).[9] In short, we included 1154 patients with a median follow-up duration of 43 months (IQR, 22–69 months) and with a median of 4 (IQR, 1–5) follow-up endoscopies per patient. Recurrence of dysplasia occurred in 38 patients (3%; annual risk, 1.0%; 95% CI, 0.8%–1.4%), whereas neoplasia recurred in 24 patients (2%; annual risk, 0.7%; 95% CI, 0.4%–1.0%).

Incidence of IM at EGJ After CE-BE

At the time CE-BE was established, random EGJ biopsies showed no IM in 988 patients (86%) and IM in 136 patients (11%). In 30 patients (3%), no biopsies were taken per discretion of the endoscopist (Supplementary Appendix 2). Among the 136 patients with persisting EGJ-IM, 68 patients (50%) were additionally treated with a single focal RFA of the EGJ (Figure 3). The majority of these patients (63/68; 93%) had a prior focal RFA during the initial EET phase, which included full treatment of the EGJ. The remaining 5 patients (5/68; 7%) had no prior focal RFA owing to a motivated protocol deviation, after they achieved CE-BE after a single circumferential RFA. Additional focal RFA of the EGJ resulted in no IM in 55 of 68 patients (81%), whereas EGJ-IM persisted in 10 of 68 patients (15%).

Outcomes for Patients With Never EGJ-IM After CE-BE

Overall, 1043 patients had no IM in the random EGJ biopsies at the time of CE-BE or after additional focal RFA of the EGJ (Figure 3). These patients were followed for a median of 40 months (IQR, 22–70 months) with a

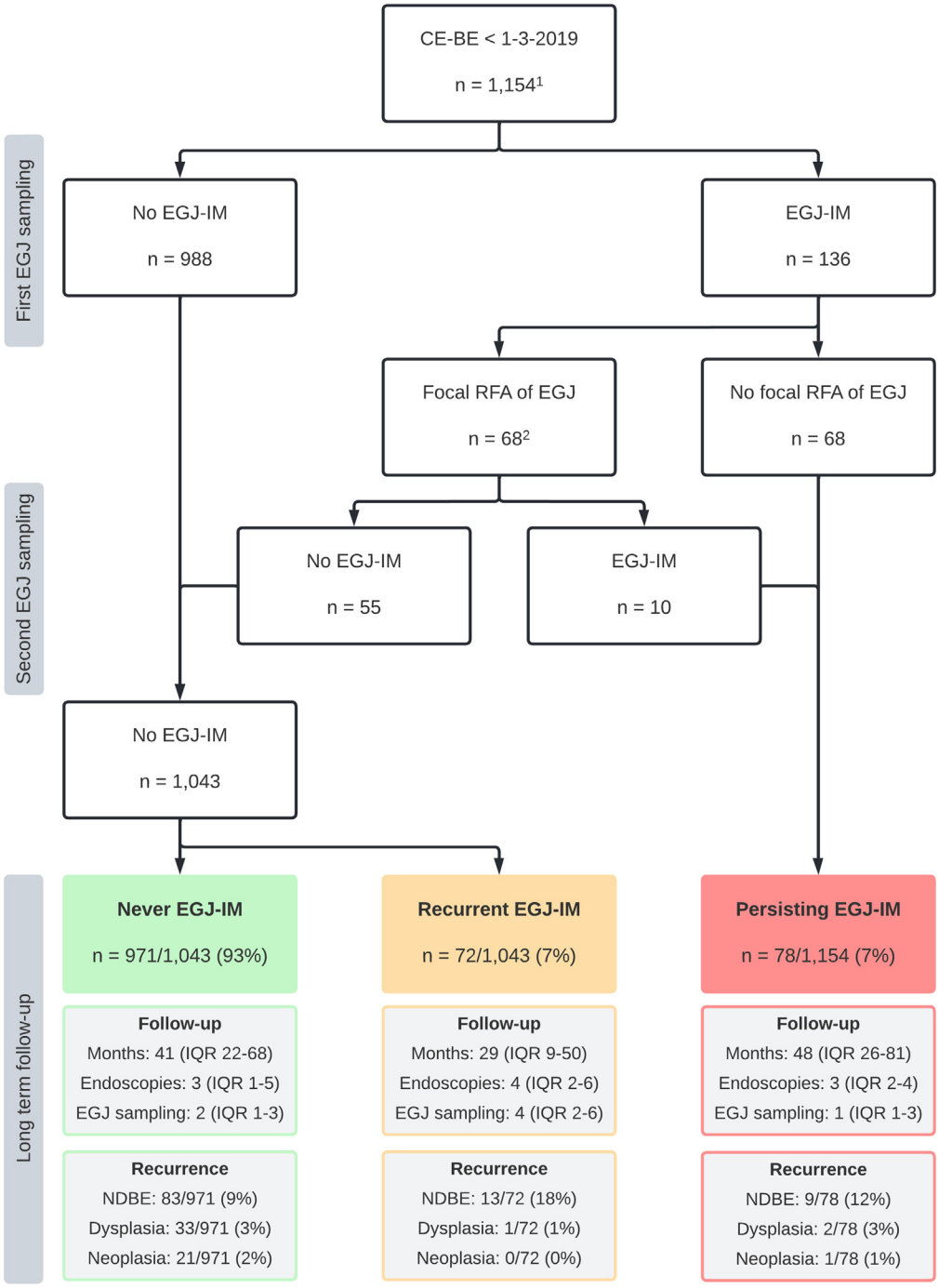

Figure 3. Patient flow chart.

[1]No EGJ biopsies were taken in 30 patients at the moment of CE-BE.
[2]No EGJ biopsies were taken in 3 patients after additional focal RFA of EGJ.

median of 4 (IQR, 3–6) endoscopies. Random EGJ biopsies were obtained in 71% of the follow-up endoscopies (2552/3600), showing no IM at any time point in a total of 971 of 1043 patients (93%).

In these patients with never EGJ-IM, recurrent visible NDBE occurred in 83 of 971 patients at an annual risk of 2.1% (95% CI, 1.7%–2.7%). The majority of these patients (68/83; 82%) had recurrent small BE islands. The remaining 15 patients (18%) had recurrent BE tongues over a median length of C0M2. One patient progressed 12 months after detection of a C1M2 NDBE segment to flat HGD. The remaining patients with visible NDBE had no progression to dysplasia during a median follow-up of 24 months with 2 endoscopies.

Recurrent dysplasia and neoplasia occurred in, respectively, 33 of 971 patients (3%; annual risk, 0.9%; 95% CI, 0.6%–1.2%) and 21 of 971 patients (2%; annual risk, 0.6%; 95% CI, 0.4%–0.9%), as shown in Supplementary Table 3.

Outcomes of Patients With Persisting EGJ-IM After CE-BE

A total of 78 patients had persisting EGJ-IM after successful EET (Figure 3), with a median follow-up of 48 months (IQR, 26–81 months) with 3 endoscopies (IQR, 2–4). Random EGJ biopsies were obtained in 73% of follow-up endoscopies (170/233). Overall, EGJ-IM was reproduced in 46% (36/78) of patients and in 41% (70/170) of follow-up endoscopies (Supplementary Figure 1).

Recurrent visible NDBE occurred in 9 of 78 patients (12%; annual risk, 2.9%; 95% CI, 1.6%–5.6%) (Table 1). A majority (6/9; 67%) of recurrent NDBE consisted of small BE islands, whereas the remaining 3 patients (33%) had recurrent NDBE over a median length of C1M2 (IQR, C0-1 to M0-2). The annual risk for recurrent NDBE tongues was 1.0% (95% CI, 0.3%–2.9%).

Recurrent dysplasia was seen in 2 of 78 patients (2.6%; annual risk, 0.7%; 95% CI, 0.2%–2.4%). One patient had persisting EGJ-IM after EET, which was reproduced during further follow-up endoscopies. Three years after end of EET, a BE island was found proximal in the esophagus with HGD. The second patient had persisting IM after EET, and during the next endoscopy, LGD was found in random biopsies from a normal EGJ. This patient showed persisting LGD during further follow-up but no progression during 3 years with 3 endoscopies. Neoplasia recurred in 1 patient as described above (annual risk, 0.3%; 95% CI, 0.0%–1.9%).

Outcomes of Patients With Recurrent EGJ-IM After CE-BE

In the patients with initially no IM in random EGJ biopsies after EET, recurrent EGJ-IM was found in 7% of patients (72/1043) and in 4% of endoscopies (103/2552) with random EGJ sampling (Figure 3). EGJ-IM recurred at a median 21 months (IQR, 15–36 months) after EET was finished and at an annual risk of 1.7% (95% CI, 1.3%–2.1%). These 72 patients were followed for a median of 29 months (IQR, 9–50 months) with 4 endoscopies (IQR, 2–6) after this finding. EGJ biopsies were obtained in 75% of the follow-up endoscopies (213/283). The finding of EGJ-IM was reproduced in 26% of patients (19/72) and in 23% of the endoscopies (50/213) with EGJ sampling (Supplementary Figure 2).

Recurrent visible NDBE occurred in 13 of 72 patients at an annual rate of 1.8% (95% CI, 0.9%–3.6%). Of these patients, 7 of 13 (54%) had small BE islands, whereas the other 6 patients (46%) had recurrent NDBE tongues over a median length of C0M2 (annual risk, 0.5%; 95% CI, 0.2%–1.7%).

Recurrent dysplasia was detected in 1 of 72 patients at an annual risk of 0.2% (95% CI. 0.0%–1.3%). This patient had no IM in random EGJ biopsies directly after EET, but the next endoscopy after 12 months showed IM. Another 12 months later, LGD was found in the EGJ, after which additional focal RFA was performed successfully. Neoplasia occurred in none of the patients with recurrent EGJ-IM (annual risk, 0.0%; 95% CI, 0.0%–0.9%).

Association Between EGJ-IM and Recurrent Disease

Unadjusted associations between EGJ-IM and recurrent visible NDBE, BE tongues, dysplasia, and neoplasia are shown in Figure 4 and Supplementary Figure 3. We found no association between EGJ-IM and any of these outcomes. Additionally, we performed adjusted analysis with correction for potential confounders. No association was found between the detection of EGJ-IM and any of these outcomes (Table 2).

Incidence of Dysplasia at EGJ After CE-BE

None of the random EGJ biopsies after EET showed HGD or worse. Nine patients with CE-BE had LGD in random EGJ biopsies. All 9 patients were considered as treatment failures due to persisting dysplasia after EET and, as a result, not included in this analysis.[9] These patients were followed up for a median of 35 months (IQR, 20–61 months) with a median of 4 endoscopies (IQR, 2–6). A single patient developed a subtle Paris type 0-IIa visible lesion just distally from the EGJ, which was removed with en-bloc EMR and showed LGD with focal HGD. Subsequent random EGJ biopsies during further follow-up after EMR showed persisting LGD. Six patients had persisting LGD during further follow-up, but no progression to HGD or worse. Two patients had no LGD or IM during further follow-up.

Table 1. Annual Risks for Non-dysplastic, Dysplastic, and Neoplastic Recurrence per Subcategory for Findings at Random Esophagogastric Sampling

	Recurrent NDBE	Recurrent NDBE tongues	Recurrent dysplasia	Recurrent neoplasia
	Annual risk [95% CI]	Annual risk [95% CI]	Annual risk [95% CI]	Annual risk [95% CI]
Never EGJ-IM	2.1 [1.7–2.7]	0.6 [0.2–1.4]	0.9 [0.6–1.2]	0.6 [0.4–0.9]
Persisting EGJ-IM	2.9 [1.6–5.6]	1.0 [0.3–2.9]	0.7 [0.2–2.4]	0.3 [0.0–1.9]
Recurrent EGJ-IM	1.8 [0.9–3.6]	0.5 [0.2–1.7]	0.2 [0.0–1.3]	0.0 [0.0–0.9]

CI, Confidence interval; EGJ-IM, intestinal metaplasia at esophagogastric junction; NDBE, non-dysplastic Barrett's esophagus.

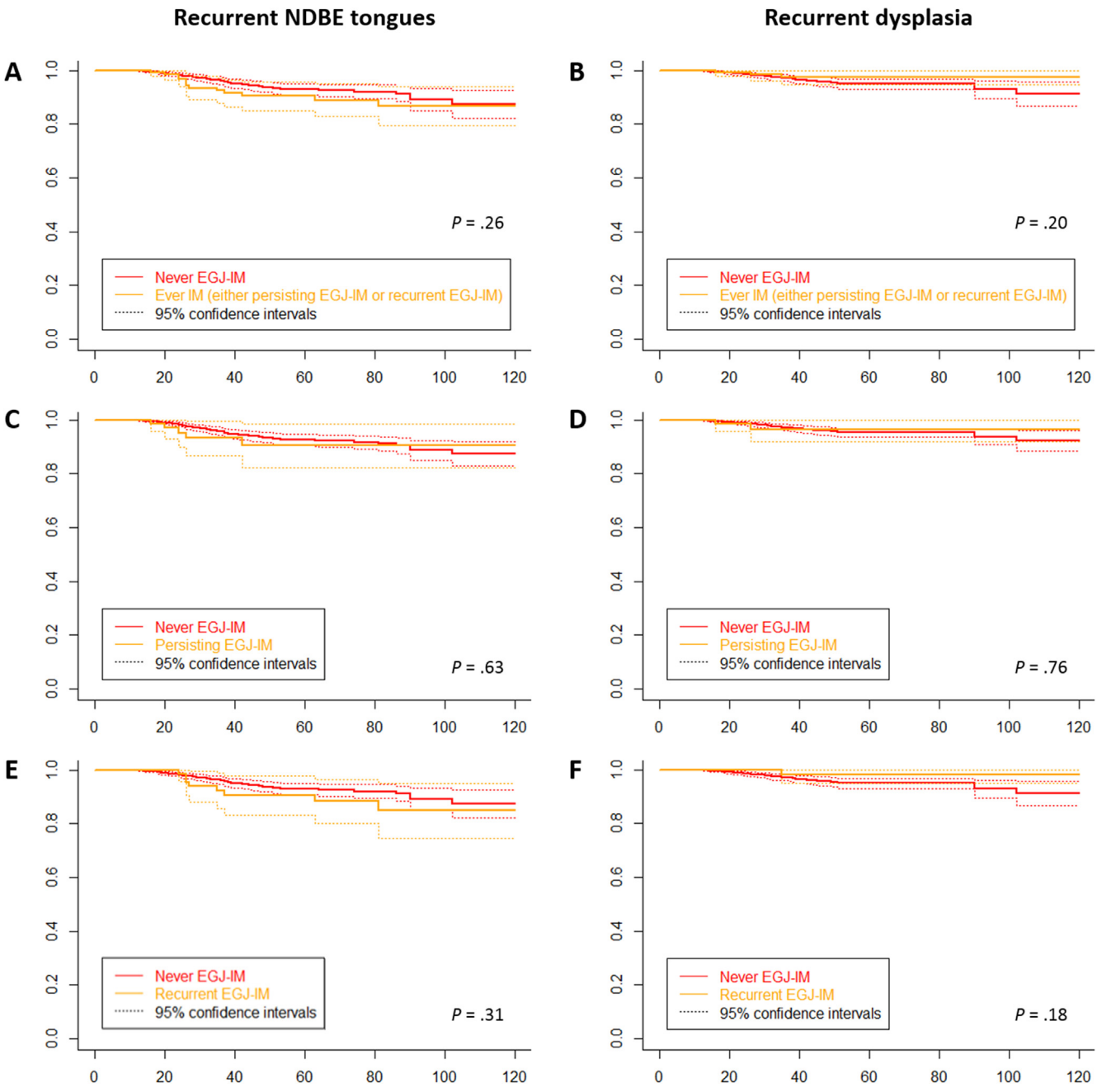

Figure 4. Association between EGJ-IM and recurrent disease. These figures show the unadjusted associations between, respectively, recurrent tongues of NDBE and dysplasia and patients with ever EGJ-IM (*A–B*), persisting EGJ-IM (*C–D*), and recurrent EGJ-IM (*E–F*) as compared with patients with never EGJ-IM.

During follow-up, random EGJ biopsies showed LGD in 0.8% of patients, all defined as recurrences, and none of these patients progressed to HGD or worse. None of the random EGJ biopsies showed HGD or worse. An overview of all patients with dysplastic recurrences is given in Supplementary Appendix 3, Supplementary Figure 4, and Supplementary Table 3.

Discussion

In this nationwide cohort of 1154 patients that underwent successful EET for early BE neoplasia in expert centers, we found no association between persisting or recurrent EGJ-IM and any clinically relevant outcome. Moreover, in the majority of patients with EGJ-IM, this was a single finding not reproduced during further follow-up. All HGD or cancer recurrences were detected through targeted biopsies from recurrent visible lesions or recurrent flat BE but not from random EGJ biopsies. Therefore, we believe that, in expert centers, random EGJ biopsies after successful EET and during follow-up can safely be abandoned. In case of a normal appearing esophagus, as is the case in the vast majority of follow-up endoscopies, this will save time and costs due to shorter

Table 2. Association Between Intestinal Metaplasia at Esophagogastric Junction and Recurrent Disease

	Recurrent NDBE		Recurrent NDBE tongues		Recurrent dysplasia		Recurrent neoplasia	
	HR [95% CI][a]	*P*	HR [95% CI][a]	P	HR [95% CI][a]	P	HR [95% CI][a]	P
Persisting EGJ-IM	1.15 [0.63–2.13]	.66	1.14 [0.45–2.85]	.79	0.73 [0.17–3.06]	.67	0.49 [0.67–3.67]	.49
Recurrent EGJ-IM	1.18 [0.67–2.06]	.56	1.46 [0.68–3.12]	.33	0.27 [0.04–1.96]	.19	NA[b]	NA[b]
Ever EGJ-IM	1.18 [0.76–1.82]	.45	1.36 [0.73–2.54]	.32	0.45 [0.14–1.48]	.19	0.19 [0.03–1.42]	.11

CI, Confidence interval; EGJ-IM, intestinal metaplasia at esophagogastric junction; HR, hazard ratio; NA, not applicable; NDBE, non-dysplastic Barrett's esophagus.
[a]Adjusted for gender, age, Barrett's esophagus length at baseline, baseline histology, new visible lesion during treatment, and poor squamous regeneration after radiofrequency ablation.
[b]No recurrent neoplasia was observed in the group with recurrent EGJ-IM.

procedure times and elimination of subsequent histopathologic evaluation. Furthermore, patients can be informed about the findings directly after the endoscopy instead of during a separate consultation.

What is the clinical value of EGJ sampling at the end of EET, defined as the time when complete endoscopic eradication of all visible BE has been achieved? We found that 11% of patients had persisting EGJ-IM at the time CE-BE was established. When compared with patients with no EGJ-IM after EET, patients with persisting EGJ-IM had no increased risk for recurrent non-dysplastic (hazard ratio [HR], 1.15; 95% CI, 0.63–2.13) or dysplastic BE (HR, 0.73; 95% CI, 0.17–3.06) during follow-up. This is in contrast to a recent published meta-analysis that included 24 studies evaluating the recurrence rate after successful EET with RFA and reported a higher risk of dysplastic recurrence in patients with persisting IM (relative risk, 2.95; 95% CI, 1.64–5.29). However, this meta-analysis should be interpreted with caution considering the small sample size in the majority of the included studies, the significant heterogeneity in treatment protocols with only 6 studies reporting circumferential ablation of the EGJ, the substantial differences in sampling and follow-up strategies, the high attrition rate for patients with persistent IM, and the mixture of expert and non-expert centers.[12] In our cohort, one-half of the patients with persisting EGJ-IM underwent additional focal RFA of the EGJ. Although this successfully eradicated IM in 81%, the lack of an association between persisting IM and clinically relevant outcomes suggests that this additional focal RFA is redundant. Random biopsies showed LGD in a small minority of patients (ie, 0.8%), and this finding was associated with a benign course during further follow-up. None of the random EGJ biopsies showed HGD or cancer. We therefore recommend that random EGJ biopsies after eradication of all visible BE can safely be abandoned in expert centers.

What is the clinical value of EGJ sampling for detection of IM during follow-up endoscopies? Patients with no EGJ-IM directly after EET had a 26% risk of developing IM in EGJ biopsies during follow-up, whereas this risk was 46% for patients with persisting EGJ-IM after EET. This is supported by prior literature, reporting an incidence of EGJ-IM after successful EET in 11% to 35%.[1,13-21] However, the finding of IM was not reproduced in the majority of patients, which was confirmed in prior studies.[1,13-17] As shown in Supplementary Figures 1 and 2, a finding of EGJ-IM often occurs in an "on-off" pattern, which may reflect sampling error. Most importantly, we found no association between recurrent EGJ-IM during follow-up and recurrent visible NDBE (HR, 1.18; 95% CI, 0.67–2.06) or recurrent dysplasia (HR, 0.27; 95% CI, 0.04–1.96), which is in line with prior studies reporting a low risk for future dysplasia.[1,13,14,21] Therefore, we conclude that recurrent IM is not a relevant outcome, and this finding does not justify EGJ sampling during follow-up in expert centers.

What is the clinical value of EGJ sampling for detection of other abnormalities during follow-up endoscopies? In 9 of 1154 patients (0.8%), random biopsies of a normal appearing EGJ were found to harbor LGD.[9] None of these patients progressed to HGD or cancer during follow-up, which is comparable to previous studies showing a low incidence (<1.3%) and benign course for LGD in a normal appearing EGJ.[17,20,22] Based on these results, LGD at the EGJ is an uncommon finding that appears to be of low clinical relevance. In addition, none of the biopsies in our cohort with a total of 2722 random EGJ samplings showed HGD or cancer. Therefore, we believe that random EGJ sampling during follow-up can safely be abandoned in expert centers. In case of (doubt about the presence of) visible abnormalities, targeted biopsies should always be performed at a low threshold.

The abovementioned recommendations rely on the definition of a "normal appearing EGJ." In our study, we defined this as the squamocolumnar junction coinciding with the top of the gastric folds in absence of any visible Barrett's mucosa or islands (Figure 1). Simultaneously as for the initial diagnosis of BE, irregular EGJ <1 cm should not be defined as recurrent BE.[4,5,23,24] We realize that the interpretation of this definition may be hampered by subjectivity, and, therefore, all images of patients with

potential BE tongues and/or irregular EGJ were reviewed centrally by 2 expert endoscopists. In those cases when the endoscopist is in doubt whether a (small) BE tongue of >1 cm persists, the endoscopist may perform a biopsy from this area of interest for further information.

An important requirement to safely abandon random sampling is the stringent treatment of the EGJ. Our protocol dictated circumferential ablation of the EGJ each time a focal RFA catheter was used. Eventually, the EGJ was treated circumferentially with focal RFA at least once in the majority of the patients (1099/1154; 95%), and even twice in more than one-half of the patients (607/1154; 53%) (Supplementary Table 2). In addition, another prerequisite is the ability of an endoscopist to detect new visible abnormalities in the esophagus. This can especially be challenging at the EGJ, which needs to be carefully inspected both in antegrade and retrograde positions. Assuming not every endoscopist is well-trained and experienced in this approach, random biopsies should therefore still be considered during follow-up in non-expert centers.

This study has several important strengths. Our data originated from a large, nationwide cohort with long-term follow-up. All patients were subjected to centralized treatment by experts who adhered to a joint treatment and follow-up protocol. Moreover, high quality of data was guaranteed through involvement of dedicated research fellows in data collection. In addition, all patients with recurrent visible BE or an irregular EGJ were centrally reviewed by 2 expert endoscopists.

Our study also has several limitations. From 2016, we stopped random biopsies of an endoscopically normal appearing EGJ during follow-up as opposed to the recommendations from international guidelines at the time. As a result of this change in follow-up strategy, EGJ sampling was not performed in a large proportion of the follow-up endoscopies (1111/3833; 29%). EGJ sampling was also omitted in a selected subgroup of patients, who were often characterized by a complicated treatment course. Furthermore, any inter-observer variability in the endoscopic assessment of the EGJ could not be eliminated, despite that treatment and follow-up were exclusively performed by BE experts and that images were reviewed centrally. Lastly, our results and recommendations cannot be automatically extrapolated to treatment in community centers, because all patients underwent treatment and follow-up in expert centers.

In conclusion, in our national cohort of patients with BE treated in expert centers with long-term follow-up, persisting or recurrent EGJ-IM after successful EET was not associated with recurrence of BE with or without dysplasia. In fact, random sampling from a normal appearing EGJ did not result in clinically relevant findings. Therefore, we recommend abandoning random sampling of the EGJ after successful EET and during further follow-up, under condition that care is provided in expert centers, the esophagus including the EGJ is carefully inspected, and targeted biopsies are taken at a low threshold in case of visible abnormalities or recurrent BE. Ultimately, this will save time and costs for the endoscopist, the pathologist, and the patient.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.11.012.

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Conflicts of interest

These authors disclose the following: Charlotte Frederiks has received speaker's fees from Pentax Medical. Jacques Bergman is a consultant for Medtronic, Cook Medical, and Boston Scientific; and has received financial support for institutional review board-approved research from Pentax Medical, Medtronic, and Aqua Medical. Roos Pouw is a consultant for MicroTech; and has received speaker's fees from Medtronic. Bas Weusten has received financial support for institutional review board-approved research from Pentax Medical. The remaining authors disclose no conflicts.

Supplementary Appendix 1. Details of Study Population and Treatment Protocol

Study Population

This study is part of the Barrett Expert Center registry (Netherlands Trial Register, NL7309), which captures outcomes for all patients who underwent endoscopic eradication therapy (EET) for early Barrett's esophagus (BE) related neoplasia in the Netherlands between January 1, 2008, and December 31, 2018.[1] In the Netherlands, the treatment for BE neoplasia is centralized in 9 Barrett Expert Centers, with the implication that only specifically trained endoscopists and expert gastrointestinal pathologists are involved in the care for patients with dysplastic BE. For the current study, we included all patients with successful EET, defined as complete endoscopic eradication of all visible BE (CE-BE), established at least 1 year before the moment of data collection (ie, before March 1, 2019). The Institutional Review Board of the Amsterdam University Medical Centers declared that the Barrett Expert Center registry was not subject to the Medical Research Involving Human Subjects Act. The need for formal ethical review was waived accordingly, and patients were approached with an opt-out with the possibility to oppose against participation.

Treatment Protocol

Patients with histologically confirmed low-grade dysplasia (LGD), high-grade dysplasia (HGD), or low-risk esophageal adenocarcinoma (ie, mucosal or superficial submucosal [sm1] cancer, well to moderately differentiated, no lymphovascular invasion, radical vertical resection margin) had an indication for EET in an expert center. Visible lesions were removed by means of endoscopic resection, and radiofrequency ablation (RFA) was performed at 3-month intervals to eradicate (residual) flat BE as described previously.[2,3] The esophagogastric junction (EGJ) was treated circumferentially with a focal RFA catheter at least once. After RFA, touch-up treatment was allowed using endoscopic resection for residual areas >10 mm or argon-plasma coagulation (maximum 2 sessions) for residual islands <10 mm.

Supplementary Appendix 2. Outcomes of Patients With No Esophagogastric Junction Sampling After Complete Eradication of Barrett's Esophagus

In 33 patients, no esophagogastric junction (EGJ) biopsies were obtained after endoscopic eradication therapy (EET). The majority of patients had a complicated treatment course, and no further biopsies were performed since this would have no consequences for eventual additional treatment. These patients were followed for a median of 27 months (interquartile range [IQR], 16–35 months) with 1 endoscopy (IQR, 0–2), in all patients without random EGJ sampling.

Recurrent visible non-dysplastic Barrett's esophagus (NDBE) occurred in 3 of 33 patients (9%; annual risk, 3.8%; 95% confidence interval [CI], 1.3%–10.6%). Two patients had BE islands after 10 and 16 months. The third patient had recurrent C0M2 NDBE at 21 months after EET.

Two patients (2/33; 6%) developed recurrent neoplasia (annual risk, 2.5%; 95% CI, 0.5%–8.9%). Both patients experienced a complex treatment course with poor squamous regeneration after radiofrequency ablation (RFA) and repeated new visible lesions that appeared during the course of EET. Ultimately, both patients achieved complete eradication of Barrett's esophagus (CE-BE), but it was decided to obtain no biopsies because no additional treatment would be performed. One patient developed a recurrent visible lesion after 1 year, in the scar of prior endoscopic resection. The second patient had sustained CE-BE during 5 years with annual endoscopies, but again 1 year later, a BE island with high-grade dysplasia (HGD) was found 8 cm above the EGJ.

Supplementary Appendix 3. Description of All Dysplastic or Neoplastic Recurrences

Overall, recurrent low-grade dysplasia (LGD), high-grade dysplasia (HGD), or cancer occurred in 38 patients and recurrent HGD or cancer in 24 patients (Supplementary Figure 3; Supplementary Table 3).

All 24 patients with recurrent HGD or worse were detected through targeted biopsies from a visible lesion or from recurrent Barrett's esophagus (BE). Prior esophagogastric junction (EGJ) sampling after endoscopic eradication therapy showed no intestinal metaplasia (IM) in most of these patients (21/24; 88%), whereas 1 patient (1/24; 4%) had persisting EGJ-IM. The remaining 2 patients (2/24; 8%) had no prior EGJ sampling during follow-up. These patients have been described in detail in Appendix 2.

In total, 14 patients had recurrent LGD. Nine patients (9/14; 64%) had LGD in a normal appearing EGJ detected through random biopsies. In 2 patients (2/9; 22%), this finding of LGD was preceded by EGJ-IM (recurrent, $n = 1$; persisting, $n = 1$), whereas the other 7 patients (7/9; 78%) had no prior EGJ-IM. A single of these 9 patients underwent additional RFA. The remaining 8 were followed for a median of 2 years (interquartile range [IQR], 2–5 years) with 2 endoscopies (IQR, 2–5), and no patient progressed to neoplasia (0%; 95% confidence interval [CI], 0%–40%]). The other 5 of 14 patients (36%) with recurrent LGD had a visible BE recurrence containing LGD. None of these patients had prior EGJ-IM.

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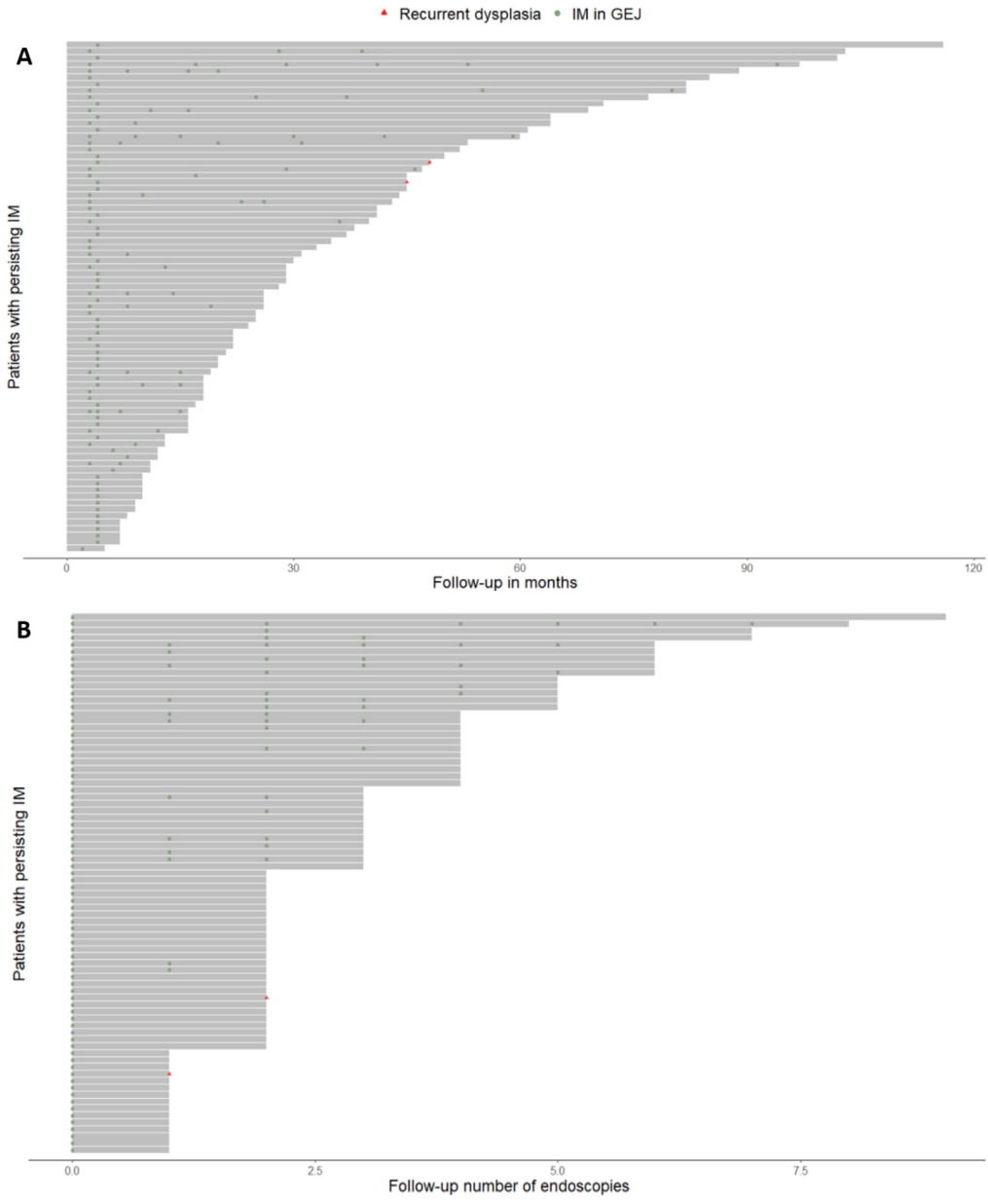
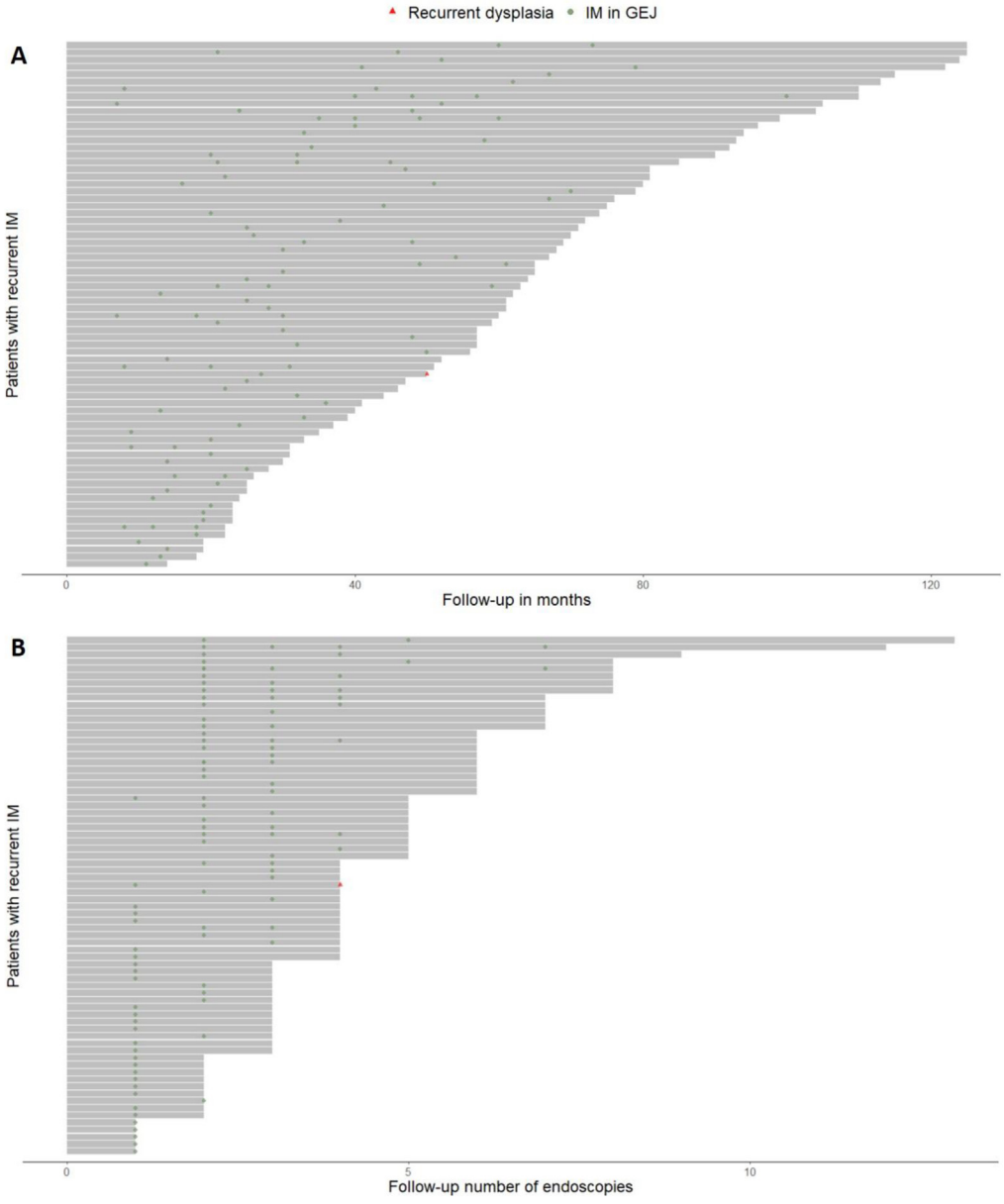
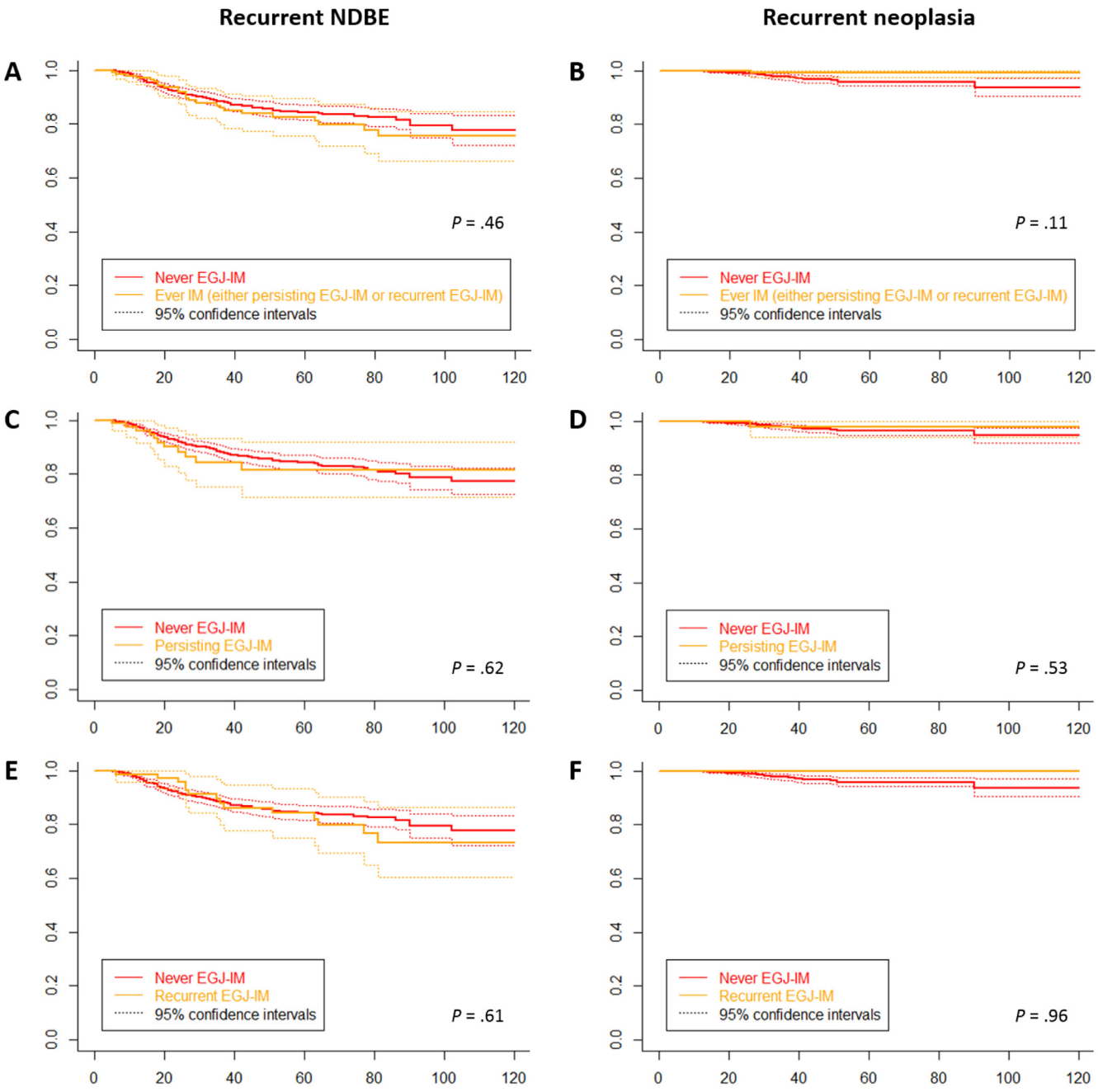


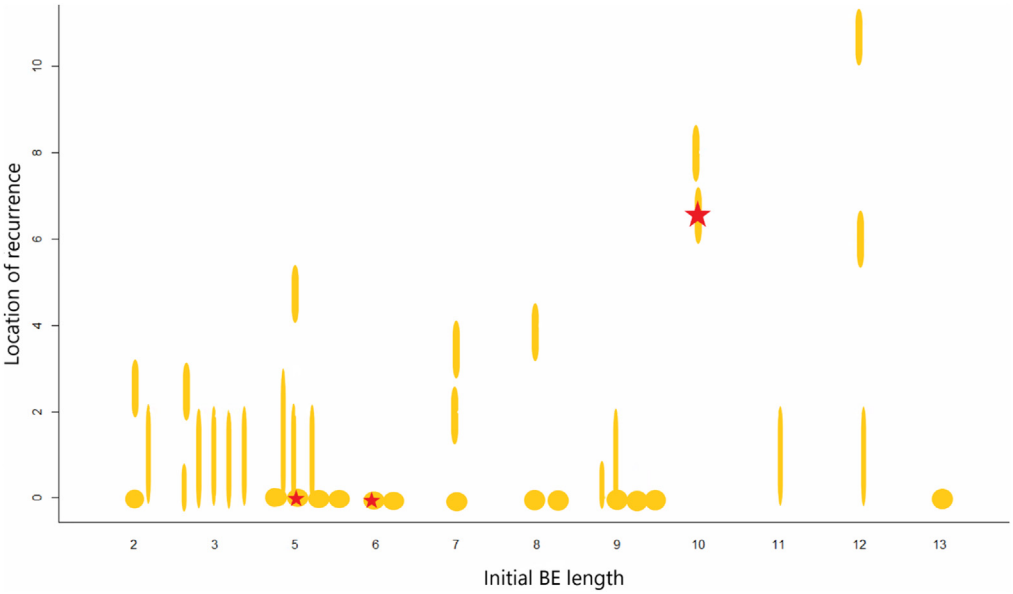
Supplementary Figure 1. Follow-up details of 78 patients with persisting EGJ-IM. These plots show all 78 patients with CE-BE but persisting EGJ-IM when follow-up was initiated, with each horizontal grey bar representing a single patient. *Green spots* indicate the moment of IM detection, which was in a minority of cases reproduced during further follow-up, represented by multiple *green spots*. *Red spots* indicate recurrent dysplasia. The upper figure (*A*) shows the follow-up results plotted against time in months, whereas the lower figure (*B*) is plotted against the number of endoscopies with esophagogastric sampling.



Supplementary Figure 2. Follow-up details of 72 patients with recurrent EGJ-IM. These plots show all 72 patients with CE-BE and no EGJ-IM when follow-up was initiated, who developed recurrent EGJ-IM during follow-up, with each horizontal grey bar representing a single patient. *Green spots* indicate the moment of IM detection, which was in a minority of cases reproduced during further follow-up, represented by multiple *green spots*. *Red spots* indicate recurrent dysplasia. The upper figure (*A*) shows the follow-up results plotted against time in months, whereas the lower figure (*B*) is plotted against the number of endoscopies with esophagogastric sampling.



Supplementary Figure 3. Association between EGJ-IM and recurrent disease. These figures show the unadjusted associations between respectively recurrent NDBE including islands and neoplasia, and patients with ever EGJ-IM (*A–B*), persisting EGJ-IM (*C–D*), and recurrent EGJ-IM (*E–F*) as compared with patients with never EGJ-IM.



Supplementary Figure 4. Location of dysplastic BE recurrences. This graph shows all 38 dysplastic recurrences in our cohort, plotted against initial BE length prior to treatment (*X-axis*) and location of recurrence (*Y-axis*). A *yellow stripe* indicates recurrent disease. A *red star* means that this patient had a prior finding of EGJ-IM, before recurrence was detected.

Supplementary Table 1. Definitions

Term	Definition
CE-BE	Complete eradication of all endoscopically visible Barrett's mucosa, which was the endpoint for endoscopic eradication therapy.
EGJ-IM	IM in random biopsies from a normal appearing EGJ.
Persisting EGJ-IM	IM in random biopsies from a normal appearing EGJ at the moment of CE-BE.
Never EGJ-IM	No IM in random biopsies from a normal appearing EGJ at the moment of CE-BE nor in all random EGJ biopsies during further follow-up.
Normal appearing EGJ	The squamocolumnar junction coinciding with the upper end of the gastric folds in absence of any endoscopically visible Barrett's mucosa or islands.
Recurrent EGJ-IM	New IM in random biopsies from a normal appearing EGJ during follow-up after initially random EGJ biopsies at the moment of CE-BE showed no IM.
Recurrent visible non-dysplastic BE	Endoscopically visible Barrett's mucosa, either islands or tongues of >1 cm, during follow-up after CE-BE.
Recurrent dysplasia	Histological evidence of LGD or worse during follow-up after CE-BE.
Recurrent neoplasia	Histological evidence of HGD or cancer during follow-up after CE-BE.

BE, Barrett's esophagus; CE-BE, complete eradication of Barrett's esophagus; CE-IM, complete eradication of intestinal metaplasia; EGJ, esophagogastric junction; HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia.

Supplementary Table 2. Baseline Characteristics of the Cohort

		Patients with CE-BE before March 1, 2019 (n = 1154)
Demographics		
Male gender		947 (82)
Age, *y*		64 (9)
BMI, kg/m^2		28 (4)
BE history		
Prior fundoplication		21 (2)
Surveillance history		759 (66)
Surveillance duration, *y*		3 (0–8)
Imaging		
Hiatal hernia		1099 (95)
Hiatal hernia size, *cm*		3 (2–4)
Esophagitis		38 (3)
Stenosis		42 (4)
BE length, *cm*	Circumferential	2 (0-5)
	Maximum	4 (3-7)
Visible lesion		718 (62)
Primary Paris type[a]	0–Ip/s	63 (5)
	0–IIa	419 (36)
	0–IIb	90 (8)
	0–IIc	22 (2)
Lesion size, *mm*		15 (10–20)
Pathology		
Worst overall histology	LGD	306 (27)
	HGD	362 (31)
	Low–risk EAC	486 (42)
Treatment		
Endoscopic resection		718 (62)
Endoscopic resection technique	Cap–based EMR	688 (60)
	ESD	20 (2)
RFA treatment	C–RFA	1 (0-1)
	F–RFA	2 (1-2)
	Total	2 (1-3)
Total number of F-RFA treatments	0	55 (5)
	1	492 (43)
	2	427 (37)
	3	148 (13)
	≥4	32 (3)
Touch-up APC		462 (40)
Touch-up endoscopic resection		74 (6)
Endoscopic resection for new visible lesion		44 (4)

Note: Data are presented as number (%), median (IQR), or mean (SD).
APC, Argon plasma coagulation; BE, Barrett's esophagus; BMI, body mass index; CE-BE, complete endoscopic eradication of Barrett's esophagus; C-RFA, circumferential RFA; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; F-RFA, focal RFA; HGD, high-grade dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; SD, standard deviation.
[a]Missing for 124 patients with a visible lesion at baseline.

Supplementary Table 3. Overview of 38 Patients With Dysplastic or Neoplastic Recurrences

Patient	Follow-up time, *mo*	Follow-up endoscopies, n	Endoscopies with EGJ sampling, n	Findings of EGJ sampling	Type of recurrence	Detection method	Histology
Progression to advanced neoplasia							
#1	25	3	3	No IM	BE island with visible lesion	Target biopsies	Advanced cancer
#2	38	3	3	No IM	Tongue with visible lesion	Target biopsies	
#3	19	2	2	No IM			
#4	16	2	0	No biopsies			
#5	39	2	2	No IM	Visible lesion at EGJ	Target biopsies	
Recurrent dysplasia, amendable for repeat endoscopic treatment							
#6	12	1	1	No IM	BE island with visible lesion	Target biopsies	Low risk cancer
#7	28	2	2	No IM			Low risk cancer
#8	51	4	4	No IM			Low risk cancer
#9	14	2	2	No IM			Low risk cancer
#10	24	3	2	No IM			Low risk cancer
#11	35	5	5	No IM			HGD
#12	26	3	3	Persisting IM			HGD
#13	42	4	4	No IM	Tongue with visible lesion	Target biopsies	Low risk cancer
#14	51	4	3	No IM			Low risk cancer
#15	32	1	1	No IM			Low risk cancer
#16	32	3	2	No IM			Low risk cancer
#17	19	1	1	No IM			Low risk cancer
#18	12	1	1	No IM			HGD
#19	41	5	5	No IM			HGD
#20	56	5	0	No biopsies			HGD
#21	90	6	5	No IM	Visible lesion at EGJ	Target biopsies	Low risk cancer
#22	37	6	5	No IM			Low risk cancer
#23	22	2	2	No IM			HGD
#24	18	6	2	No IM			LGD
#25	49	4	3	No IM	Flat BE tongue	Random biopsies BE tongue	HGD
#26	90	7	7	No IM			LGD
#27	30	4	4	No IM			LGD
#28	26	2	2	No IM			LGD
#29	28	3	3	No IM			LGD

Supplementary Table 3. Continued

Patient	Follow-up time, *mo*	Follow-up endoscopies, n	Endoscopies with EGJ sampling, n	Findings of EGJ sampling	Type of recurrence	Detection method	Histology
LGD in random biopsies from normal appearing EGJ							
#30	44	4	4	No IM	Normal appearing EGJ	Random EGJ biopsies	LGD
#31	18	3	2	No IM			LGD
#32	21	1	1	No IM			LGD
#33	102	6	5	No IM			LGD
#34	31	2	1	No IM			LGD
#35	14	1	1	No IM			LGD
#36	45	7	5	No IM			LGD
#37	35	4	4	Recurrent IM			LGD
#38	16	2	1	Persisting IM			LGD

BE, Barrett's esophagus; EGJ, esophagogastric junction; HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia.