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Affiliations below.

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Abstract:

ABSTRACT
Background and study aims
Optimal management for patients with low-grade dysplasia (LGD) in Barrett's esophagus (BE) is unclear. According to our national guideline, all patients with LGD with histologic confirmation of the diagnosis by an expert pathologist (i.e. “confirmed LGD”), are referred for a dedicated re-staging endoscopy in an expert center. We aimed to assess the diagnostic value of re-staging endoscopy by an expert endoscopist for patients with confirmed LGD.

Methods
In this retrospective cohort study, we included all patients with flat BE diagnosed in a community center who had confirmed LGD and were referred to one of the nine Barrett expert centers (BEC) in the Netherlands. Primary outcome was the proportion of patients with prevalent high-grade dysplasia (HGD) or cancer during re-staging in a BEC.

Results
Of the 248 patients with confirmed LGD, re-staging in the BEC revealed HGD or cancer in 23% (57/248). In 79% (45/57), HGD or cancer in a newly detected visible lesion was diagnosed. Of the remaining patients, re-staging in the BEC showed a second diagnosis of confirmed LGD in 68% (168/248), while the remaining 9% (23/248) had non-dysplastic BE.

Conclusion
One quarter of patients with apparent flat BE with confirmed LGD diagnosed in a community hospital turns out to have prevalent HGD or cancer after re-staging in an expert center. This endorses the advice to refer patients with confirmed LGD – also in the absence of visible lesions – to an expert center for re-staging endoscopy.

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Conflicts of interest

EN, SM, WC, AH, AB, AA, BS, AK, MS, TT, WN, JW, MH, ES, RP declared to have no disclosures relevant to this manuscript. BW received financial support for IRB-approved research from C2Therapeutics/Pentax Medical and Aqua Medical. JB received financial support for IRB-approved research from C2Therapeutics/Pentax Medical, Medtronic, and Aqua Medical.

Contributors

EN, SM, CK (Chessey Kroeze) and MS (Michael Siim) did data acquisition. EN, SM, JB, and RP coordinated study and data collection. EN, SM, RP and JB did the statistical analysis. SM, JB, RP contributed to data analysis and interpretation of data in research group meetings. EN drafted the manuscript. SM, WC, JB, ES, RP co-authored the manuscript. BW, LA, AB, AA, BS, ES, WC, AK, PJ, TT, WN, FP, JW, MH, JB, RP participated in annual meetings and were responsible for treatment of patients in their center. All authors critically edited, read, and approved the final manuscript.

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ABSTRACT
Background and study aims

Optimal management for patients with low-grade dysplasia (LGD) in Barrett’s esophagus (BE) is unclear. According to our national guideline, all patients with LGD with histologic confirmation of the diagnosis by an expert pathologist (i.e. “confirmed LGD”), are referred for a dedicated re-staging endoscopy in an expert center. We aimed to assess the diagnostic value of re-staging endoscopy by an expert endoscopist for patients with confirmed LGD.

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In this retrospective cohort study, we included all patients with flat BE diagnosed in a community center who had confirmed LGD and were referred to one of the nine Barrett expert centers (BEC) in the Netherlands. Primary outcome was the proportion of patients with prevalent high-grade dysplasia (HGD) or cancer during re-staging in a BEC.

Results

Of the 248 patients with confirmed LGD, re-staging in the BEC revealed HGD or cancer in 23% (57/248). In 79% (45/57), HGD or cancer in a newly detected visible lesion was diagnosed. Of the remaining patients, re-staging in the BEC showed a second diagnosis of confirmed LGD in 68% (168/248), while the remaining 9% (23/248) had non-dysplastic BE.

Conclusion

One quarter of patients with apparent flat BE with confirmed LGD diagnosed in a community hospital turns out to have prevalent HGD or cancer after re-staging in an expert center. This endorses the advice to refer patients with confirmed LGD – also in the absence of visible lesions – to an expert center for re-staging endoscopy.

Key words – Barrett’s esophagus; Low-grade dysplasia; Barrett’s neoplasia; Endoscopic treatment
INTRODUCTION

Barrett’s esophagus (BE) is the most important risk factor for development of esophageal adenocarcinoma (EAC). The malignant degeneration occurs through a stepwise process of phenotypic cellular changes: from non-dysplastic (ND) intestinal metaplasia (IM), to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and eventually EAC [1]. In advanced stages, EAC is a disease with a poor prognosis. Adequate surveillance strategies of BE patients are therefore essential to detect neoplasia at an early stage, amendable for curative endoscopic treatment [2,3].

The strongest predictor of progression to HGD/EAC in BE is a diagnosis of LGD confirmed by an expert pathologist (i.e. “confirmed LGD”). The histological diagnosis of LGD is challenging, because the distinction between dysplastic changes and reactive atypia of reflux-induced inflammation is difficult. Two prior studies demonstrated that LGD diagnosed by a community pathologist, was downgraded to NDBE in 73% - 85% after review by a BE expert pathologist. After downstaging to NDBE, the risk of progression to HGD/EAC was <1% per patient-year[4,5]. In contrast, for confirmed LGD, the risk of malignant progression increased to 9% - 13% per patient-year [6,7]. Therefore, current guidelines advise that a community-diagnosis of LGD is revised by an experienced pathologist[8–11].

In the Netherlands, BE treatment is centralized. While BE surveillance endoscopies are performed in community centers, endoscopic treatment is restricted to nine Barrett Expert Centers (BECs). Patients with visible lesions, HGD and/or cancer are directly referred to a BEC for endoscopic treatment. Since 2017, the Dutch guideline recommends that patients with confirmed LGD are also referred to an expert center for a dedicated re-staging endoscopy. This is based on the idea that LGD is a predictor for progression to HGD or cancer and that patients may benefit from dedicated re-staging endoscopies with the option for early intervention in case of visible lesions. Furthermore, several trials demonstrated significant risk reduction of progression from LGD to HGD/EAC after radiofrequency ablation (RFA) of the BE when compared to surveillance alone [12–14]. Most guidelines therefore state that prophylactic ablation of BE with a repetitive diagnosis of LGD should be considered [8,9].

In the current study we evaluated the diagnostic value of re-staging endoscopy performed in an expert center for patients with confirmed LGD.
METHODS

The BEC registry

All patients referred to a BEC in the Netherlands are registered in a uniform database, i.e. the BEC registry, which has been described in detail earlier [15]. For the current study, we retrospectively reviewed this database. To ensure completeness of data, an additional search in the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (ie, PALGA foundation) was performed. The PALGA database includes all pathology reports in the Netherlands. We selected all patients with confirmed LGD and referral to a BEC from the PALGA database.

Surveillance for non-dysplastic BE

Regular surveillance endoscopies for patients with NDBE are performed in community centers. Surveillance endoscopies consist of imaging followed by random biopsies according to the Seattle protocol (i.e. 4-quadrant biopsies at every 2cm) [10], and targeted biopsies from visible lesions. These biopsy specimens are read by the community hospital pathologist.

Patients with direct indications for treatment (i.e. HGD or worse, and/or a visible lesion) are referred to a BEC. For patients with a diagnosis of LGD assessed by the local pathologist, expert histologic revision is recommended, and referral to a BEC is advised in case the diagnosis of LGD is confirmed.

Expert panel histopathology revision

A central expert histopathology panel facilitates revision of LGD diagnoses. The panel consists of five core pathologists who have been dedicated in the field of BE for at least 15 years and have a median case load of seven cases per week, of which ≥25% are dysplastic [16,17]. Furthermore, all pathologists participated in the Dutch Barrett advisory committee for many years and participated in multiple training programs for endoscopists and pathologists (www.best-acedemia.eu). Nine other BE expert pathologists working in expert centers joined the panel more recently after quality assessment of 80 indefinite for dysplasia (IND) and LGD digital biopsy cases followed by group discussions with the core pathologists [4]. The performance of histopathology revision was extensively described previously [16].

For LGD diagnosed in the Netherlands, biopsy specimens are digitally transferred for revision by the panel. The expert panel diagnosis is sent to the endoscopist or pathologist who requested the revision.
Upon confirmation of LGD or upstaging to HGD/EAC, the advice is to refer patients to a BEC for a dedicated re-staging endoscopy. Upon downstaging of LGD to IND or no dysplasia, patients remain under endoscopic surveillance at the community hospital.

Barrett expert centers

As per national guideline, within 3-6 months of the diagnosis of LGD, patients are scheduled for a re-staging endoscopy in a BEC. There are 9 BECs in the Netherlands, where care is provided by 1-2 experienced pathologists and endoscopists per center, who participated in joint and specific training programs. Centers adhere to a joint treatment protocol and participate in quarterly meetings to guarantee homogeneity. This infrastructure has been established since 2008, when RFA was adopted for regular clinical care.

Re-staging consists of careful imaging endoscopy with high-definition endoscopes with virtual chromoendoscopy. Patients are generally under sedation and most centers schedule dedicated timeslots for BE endoscopies. The Barrett segments is described using the Prague C&M classification[18]. Visible lesions are described using the Paris classification[19] and either biopsied or endoscopically resected directly. In addition, random biopsies following the Seattle protocol are taken from the flat Barrett segment[20].

Endoscopic management

Visible lesions are removed with endoscopic resection techniques. If the specimen shows dysplasia or early cancer, RFA of the remaining BE is generally advised. For flat BE, a diagnosis of HGD, or a repeated diagnosis of confirmed LGD during two separate endoscopies (i.e. twice LGD) are indications for prophylactic RFA [12].

When the re-staging endoscopy shows flat BE with IND or no dysplasia, patients are scheduled for surveillance endoscopies in the BEC after 12 months. If no dysplasia is found at these endoscopies, patients are referred to the community center and surveyed according to the regular NDBE surveillance protocols.

Study population

We included cases that fulfilled all of the following criteria:

- Flat BE in absence of visible lesions with LGD in a community center; and
- Confirmed LGD upon expert pathologist revision; and
- Referral to a BEC between January 2017 and October 2019
Since 2017, guidelines advise expert histopathology review including referral to a BEC in case of confirmation or upstaging to HGD/EAC.

Cases with visible lesions assessed in the community center were excluded for this study cohort.

**Study endpoints**

We defined several endpoints:

- Proportion of patients with HGD or cancer during re-staging in the BEC. Proportion of patients with visible lesions during re-staging in the BEC;
- Proportion of patients with high-risk EAC during re-staging in the BEC, defined as cancer with deep submucosal invasion (i.e. sm2/3), and/or poor differentiation grade, and/or presence of lymphovascular invasion. In contrast, low-risk EAC was defined as any mucosal or superficial submucosal EAC (i.e. ≤ sm1) in absence of poor differentiation and in absence of lymphovascular invasion.
- Proportion of patients with an indication for (prophylactic) endoscopic treatment upon re-staging. Indications for treatment consisted of confirmed LGD at two separate endoscopies, HGD or EAC[8].

**Statistics**

Statistical analysis was performed using the Statistical Software Package IBM SPSS Statistics version 24.0.0.1 for Windows (SPSS, Chicago, Illinois, USA) and R version 3.4.1 for Windows. Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR) for normally distributed or skewed data, respectively. Categorical variables were presented as counts with percentages. Adjusted 95% confidence intervals (95%-CI) were obtained using simple bootstrapping with 10000 samples. Chi-square test was performed to compare binary, unpaired results.

**Ethics**

The Institutional Review Board of the Amsterdam University Medical Centers declared that the registry was not subject to the Medical Research Involving Human Subjects Act and waived the need for formal ethical review and patient-informed consent. Still, written informed consent was obtained for all patients who underwent endoscopic treatment [15]. Patients who had not undergone endoscopic treatment were approached through an opt-out card with the possibility to object to participation in the study.
RESULTS

We identified 258 patients with confirmed LGD. In total, 248/258 patients (96%) were referred to a BEC for a re-staging endoscopy between January 2017 and October 2019 and were included in the analysis. The remaining 10 patients remained in the community center and were not referred for varying reasons, including limited life expectancy and/or patient preference.

Baseline characteristics are shown in Table 1. The majority of patients was male (78%) with a median age of 69 years (IQR 64-75). 149 (60%) had a history of Barrett surveillance in a community hospital during median 7 years.

Re-staging endoscopy in the BEC was performed at median 3 months (IQR 0-3) after the community center endoscopy during which confirmed LGD was diagnosed.

HGD or cancer during re-staging

In total, 57 patients (23%) had HGD or cancer during re-staging in the BEC. This included a diagnosis of HGD (32 patients; 13% [95% CI 9-18]), low-risk EAC (23 patients; 9% [95% CI 6-14]), or high-risk EAC (2 patients; 1% [95% CI 0.01-2]) (Table 2).

In 168/248 (68%; [95% CI 62-74]) a second diagnosis of confirmed LGD was found during re-staging in the BEC. In the remaining 23 patients (9% [95% CI 6-14]), the initial finding of dysplasia was not reproduced (Figure 1).

Visible lesions during re-staging

Overall, re-staging in the BEC resulted in detection of a visible lesion in 58/248 patients (23%). Figure 2 displays a composite image of a patient with a visible lesion detected in a BEC. Stratified for worst pathology found during re-staging, all 25 patients with EAC were diagnosed with a visible lesion (100%, [95% CI 86-100]) (Table 2). For patients diagnosed with HGD, a visible lesion was found in 20/32 (62%; [95% CI 44-79]). Among patients with a second diagnosis of confirmed LGD, 12/168 patients (7%; [95% CI 4-12]) had a visible lesion. Finally, 1 patient (4% [95% CI 0.1-2]) with non-dysplastic BE was found to have a visible lesion that appeared suspicious for neoplasia during endoscopy and was removed with ER, but the final pathology reading showed no dysplasia.

Overall, 51/58 patients (88%) had a flat-type lesion (i.e. type 0-II) according to the Paris classification, most commonly type 0-IIa (Table 1).
High-risk cancer during re-staging

Two patients (2/248; 1%) were diagnosed with high-risk EAC during re-staging.

One patient was found to have a visible lesion upon re-staging in the BEC. The patient had no history of surveillance for BE in the community hospital. Time between first community hospital endoscopy and re-staging endoscopy in the BEC was 3 months. ER specimen showed a deep submucosal cancer (>500µm), with lymphovascular invasion and moderate differentiation, with negative deep resection margins. Additional baseline examinations showed lymph node- and distant metastasis.

The second patient, also without BE surveillance history, was found to have a visible lesion upon re-staging and ESD was initiated but prematurely aborted due to deep invasion in the proper muscle layer. Additional baseline examinations showed bone metastasis. Time between first community hospital endoscopy and re-staging was 3 weeks.

Indication for endoscopic treatment

After re-staging in the BEC, 91% of patients (225/248; [95% CI 86-94]) had an indication for endoscopic treatment according to current guidelines. Treatment indications consisted of EAC (n=25), HGD (n=32), or two diagnosis of confirmed LGD (n=168).

Follow-up after re-staging

Endoscopic treatment

All patients with HGD (n=32) and low-risk cancer (n=23) underwent direct endoscopic treatment. Treatment was also initiated in 142/168 patients with a second diagnosis of confirmed LGD. Complete endoscopic eradication was achieved in the majority of patients with a second diagnosis of confirmed LGD, HGD, or cancer (i.e., 94% vs. 100% vs. 86%, respectively). Treatment outcomes were described in detail in a separate manuscript [15].

Endoscopic surveillance after a second diagnosis of confirmed LGD

Despite a repeated diagnosis of confirmed LGD, 26/168 patients (15%) underwent endoscopic surveillance instead of prophylactic RFA, due to limited life expectancy and/or patient preference. Median BE length in this group was C5M6 (IQR C1-8; M4-10). Patients were followed for median 15 months (IQR 10-23) with median 2 FU endoscopies (IQR 1-2).

Two patients progressed to HGD (2/26; 8%; annual risk 6%). One patient had HGD at first FU after 6 months. The second patient developed HGD at 42 months after baseline staging, with LGD.
reproduced during each of the three prior FU endoscopies. At the moment of progression to HGD, endoscopic treatment was initiated for both patients, with outcomes pending.

*Endoscopic surveillance after a single confirmed LGD diagnosis*

A finding of dysplasia was not reproduced during re-staging in 23 patients. Patients were followed for median 19 months (IQR 12-25) with median 1 (IQR 1-2) FU endoscopy after restaging. Two patients (2/23; 9%; annual progression risk 6%) developed HGD, one after 6 months and one after 30 months after several diagnosis of confirmed LGD.

Overall, when comparing results from all 9 expert centers, there was no significant difference between the centers.

**DISCUSSION**

We assessed the impact of a dedicated re-staging endoscopy by an expert endoscopist upon a diagnosis of flat BE with LGD confirmed by an expert pathologist. To that end, we included 248 patients who were referred with flat BE to a Barrett Expert Center in the Netherlands and in whom confirmed LGD was diagnosed. In 23% of patients, prevalent HGD or cancer was found during re-staging. This was diagnosed through targeted sampling from a visible lesion in the majority of patients. Overall, 91% of patients had an indication for endoscopic treatment after the re-staging endoscopy. Our results suggest that patients with confirmed LGD should undergo a re-staging endoscopy by an expert endoscopist.

It is well-known that LGD is a challenging diagnosis and guidelines therefore recommend expert pathologist revision for each LGD diagnosis[8–11]. The differentiation between reactive inflammatory changes and early dysplasia is complex. Prior studies showed that up to 85% of LGD diagnoses made in a community center, is down-staged to NDBE after expert revision[6][7]. Most importantly, LGD that was down-staged to NDBE progressed at an annual rate <1%, comparable to “normal” NDBE, whereas LGD that was confirmed had an annual progression risk of 9–13%. Of note, in the current study we selectively included patients with LGD that was confirmed by an expert pathologist.

“Expert pathologists” in the current study were defined as pathologists dedicated in the field of BE with a median case load of seven cases a week, of which ≥25% are dysplastic[16,17]. Moreover, pathologists participated in multiple joint training programs with quality assessments followed by group discussions[4].

**Accepted Manuscript**

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Some comparisons with prior studies can be drawn. The aforementioned two studies that assessed progression risks after confirmed LGD did not report a proportion of HGD/EAC and/or visible lesions detected at re-staging. However, steep Kaplan-Meier curves during the first 6 months suggest that HGD/EAC was already present referral to the expert center [6,7]. In the screening cohort of the SURF study, a randomized intervention study comparing RFA to surveillance for patients with LGD, 20/247 (8%) patients initially diagnosed with confirmed LGD were found to have HGD or cancer during first re-staging in a BEC [21]. In addition, in a recently published retrospective study, the authors aimed to determine the proportion of prevalent HGD or EAC detected by BE referral units in patients referred from the community with a recent expert confirmed diagnosis of LGD. Similarly to our study, the authors concluded that worse grades of dysplasia (HGD/EAC) are found in a Barrett referral unit after referral for confirmed LGD in approximately a quarter (20/75, 27%) of patients, plausibly representing prevalent HGD/EAC [22]. We may speculate about several explanation for our findings. First, the quality of the endoscopy in the community hospital likely plays an important role. This is mainly determined by the quality of imaging and the quality of histologic sampling. It is well-known that detection of visible lesions in BE is challenging. This is especially the case when exposure to visible lesions is low, as in a surveillance setting. Partly due to the subtle appearance of early neoplasia, but mainly because general endoscopists are unfamiliar with the endoscopic appearance of neoplasia, since progression to neoplasia is rare (<1% annual risk) [23–25]. A prior study compared detection rates of visible lesions in community centers and after referral in BECs and showed that expert endoscopists detected a visible lesion in 87%, compared with 60% at the community hospitals (P < 0.01) [26]. However, this study selectively included patients with HGD/EAC. The endoscopists in the expert center may therefore have been biased and were looking for a lesion, knowing that the patient had HGD/EAC.

An American study showed that nearly 25% of endoscopies performed in BE patients were not adherent to Seattle protocol [27]. This finding is confirmed in a recent systematic review showing poor adherence to the Seattle protocol, especially in non-expert centers and in longer BE segments [28]. Adherence may be low due to increased procedure time or wrong perception of an individual patients’ risk of neoplastic progression.

A second explanation relies to the quality of the endoscopy in the expert center. Endoscopic examination consists of high-definition endoscopy with optical chromoendoscopy by an experienced endoscopists under optimal circumstances with the majority of patients under sedation and with the use of dedicated timeslots for BE endoscopies.
Still, if imaging and sampling may be less accurate in a community hospital, why were these patients with a visible lesion containing HGD or cancer then diagnosed with LGD? It seems unlikely that random biopsies with confirmed LGD in the community center were accidentally obtained from the visible lesion, and that these biopsies were then read as LGD but not as HGD or cancer. From a pathophysiological perspective, it may be that patients with HGD or cancer have a larger field defect with dysplastic changes. This large field defect with more wide-spread dysplastic changes may be easier to pick up with random biopsies than a solitary visible lesion. The current study shows that detection of confirmed LGD, even if the BE is deemed completely flat in a community center, defines a cohort with a substantial risk for more advanced histology.

Based on our results, we recommend that patients with confirmed LGD in a flat BE diagnosed in a community center, are referred to an expert center for a dedicated re-staging endoscopy. Most importantly, one quarter of these patients turned out to have a visible lesion with HGD or cancer. One percent of patients was even found to have a high-risk cancer. If these patients would have been treated with RFA in a community center due to apparent “flat BE”, this would have been inadequate therapy and the risk for progression to advance disease would be substantial.

On the other hand, if these patients with confirmed LGD would not have been referred for re-staging in an expert center, surveillance would have been done after 6 months, with a risk of progression in patients with prevalent HGD/EAC. Moreover, a subtle lesion may also have been missed during the second endoscopy with a new delay and risk for progression. The Dutch and European BE guideline advise to refer patients with confirmed LGD to an expert center for re-staging within 3 months; whereas US guidelines advise re-staging after 3-6 months with high-definition and (optical) chromoendoscopy not necessarily in an expert center [8–10,29,30]. Considering the high rates of worse histopathology found at the expert endoscopy, we would advocate for re-staging within 3-6 months upon referral in an expert center as advised by the Dutch and European guideline.

This study has important strengths. This is the first report of a nationwide cohort of BE patients with confirmed LGD who were referred to expert centers for re-staging and has direct implications for clinical care. Our data are homogeneous: all endoscopists and pathologists participated in a specific and joint training program and all centers followed a uniform treatment and follow-up protocol. We included all patients in the Netherlands who underwent endoscopic re-staging upon confirmed LGD in one of the BECs. We provide high-quality data that were collected by dedicated researchers.

We have to address some limitations as well. This is a retrospective study with a risk for selection bias. Most importantly, we could have missed patients with confirmed LGD that were not included in our database. In order to minimize this risk and to ensure complete data, apart from the BEC registry,
we performed an additional search in the national pathology database. There also is a risk that not all
patients with confirmed LGD were referred to an expert center, but only the patients with
anticipated high risk for neoplasia, such as those with long BE segments. This would result in an
overestimation of the proportion of prevalent HGD in our study. However, since only 10 patients with
confirmed LGD were not referred, the effect would be minimal. Finally, although guidelines
recommend confirmation of each LGD diagnosis, some endoscopists may have chosen not to apply
for pathology revision. If specifically those patients with an assumed low risk for prevalent HGD, such
as patients with short segment BE, were not applied for pathology revision, than again the reported
rate for prevalent HGD would overestimate the actual rate. Still, our study outcomes do reflect
current clinical care and recommendations therefore still hold.

In a minority of community hospital LGD cases (15%), revision was performed by one local expert
pathologist instead of revision by the panel upon referral, since panel revision is advisable, but not
mandatory regarding to the Dutch guideline [8]. Since the endoscopists in the BEC were informed
about the presence of LGD in advance, inspection may have been even more meticulous and the
threshold to resect visible lesions may have been lower. However, instead of this being a limitation
or bias, we feel that this reflects real-life clinical practice and only supports the advice to refer
patients with confirmed LGD to an expert center for re-inspection. Unfortunately, we have no data
on adherence to the Seattle protocol in the community center. Therefore, we could not draw any
conclusions to adherence to the Seattle biopsy protocol or possible sampling error. Follow-up data
for confirmed LGD that was not treated in our study may be prone to confounding by indication.
Down-staging to NDBE during re-staging may either indicate actual down-staging, but more likely
reflects sampling error of focal LGD area(s), but it is impossible to make this difference for patients in
the current study. Unfortunately, we had no data on type of endoscope and use of optical
chromoendoscopy. Finally, data may be less generalizable worldwide, due to our homogeneous care
setting in The Netherlands.

Our study shows that re-staging by an expert endoscopist upon confirmed LGD is valuable, since a
quarter of the patients in fact had prevalent HGD or cancer. Furthermore, 91% of these patients has
an indication for endoscopic treatment upon re-staging. Confirmed LGD entails a high risk of
synchronous worse histopathology that can easily be overlooked by inexperienced endoscopists. We
advocate for expert endoscopy for all patients with confirmed LGD.
REFERENCE LIST


Figure legends:

Figure 1. Expert center endoscopic assessment of confirmed LGD – Patient flow

Figure 2: Endoscopic images of a patient referred with confirmed LGD in random biopsies, no visible lesions were detected at the referring hospital

Images community hospital:
A, B. Images in white light endoscopy (WLE) of a C4M5 Barrett segment without signs of reflux esophagitis. The endoscopist reported no visible abnormalities and took random biopsies at 3 levels (i.e., unclear whether these were taken by following Seattle protocol or not). Histopathology analysis showed low-grade dysplasia in all 3 levels, with p53 expression. Panel revision confirmed the diagnosis.

Images Barrett Expert Center:
C, D. Images in WLE and narrow band imaging (NBI) of the same patient with a Barrett segment containing a Paris type 0-IIa visible lesion of 25mm in diameter, 2cm above the gastroesophageal junction, 7-11 o’clock in neutral position.
E. Endoscopic view through the Duette cap: lesion delineated with electrocoagulation markers before starting the endoscopic resection procedure.
F. View on the wound after resection and removal of the cap.

Histopathology analysis showed esophageal adenocarcinoma invading the submucosa, with good differentiation, without signs of lymphovascular invasion.

Abbreviations
BE – Barrett’s esophagus
BEC – Barrett’s expert center
CE-BE – Complete eradication of Barrett’s esophagus
CI – Confidence interval
CT – Computed tomography
EAC – Esophageal adenocarcinoma
EMR – Endoscopic mucosal dissection
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All (n=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Age, years, Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>Male, n (%)</td>
</tr>
<tr>
<td></td>
<td>BMI Mean ± SD</td>
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<tr>
<td></td>
<td>Smokers*, n (%)</td>
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<tr>
<td></td>
<td>Current</td>
</tr>
<tr>
<td>History</td>
<td>History of surveillance prior to referral, n (%)</td>
</tr>
<tr>
<td></td>
<td>Duration of prior surveillance, Median (IQR)</td>
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<tr>
<td></td>
<td>History of LGD prior to referral, n (%)</td>
</tr>
<tr>
<td>Endoscopic BE characteristics</td>
<td>Prague classification for Length BE segment, cm, Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>Circumferential</td>
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<tr>
<td></td>
<td>Maximum</td>
</tr>
<tr>
<td></td>
<td>Hiatal hernia, n (%)</td>
</tr>
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<td></td>
<td>Esophagitis, n (%)</td>
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<tr>
<td>Visible lesions (n=58)</td>
<td>Paris classification of visible lesions (primary component)**, n (%)</td>
</tr>
<tr>
<td></td>
<td>Type 0-IIa</td>
</tr>
<tr>
<td></td>
<td>Type 0-IIb</td>
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<tr>
<td></td>
<td>Type 0-IIc</td>
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<td></td>
<td>Type 0-Is</td>
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</tbody>
</table>

*73 (29%) missings

**6 (10%) missings

Abbreviations: IQR – interquartile range; SD – standard deviation; PPI – proton pump inhibitors; LGD – low-grade dysplasia; BE – Barrett esophagus.
Table 2. Histopathology findings during re-staging in the BEC

<table>
<thead>
<tr>
<th>Diagnosis during re-staging in BEC</th>
<th>Total cohort (N=248)</th>
<th>No visible lesion detected in BEC (histology based on random biopsies)</th>
<th>Visible lesion detected in BEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia not reproduced, n (%)</td>
<td>23 (9)</td>
<td>22 (96)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>New diagnosis of confirmed LGD, n (%)</td>
<td>168 (68)</td>
<td>156 (93)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>HGD, n (%)</td>
<td>32 (13)</td>
<td>12 (37)</td>
<td>20 (63)</td>
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<tr>
<td>EAC, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>LR-EAC</td>
<td>25 (10)</td>
<td></td>
<td>25 (100)</td>
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<tr>
<td>HR-EAC</td>
<td>23 (9)</td>
<td></td>
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<td></td>
<td>2 (1,0)</td>
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</tr>
</tbody>
</table>

Abbreviations: BEC – Barrett Expert Center; y – year; LGD – low-grade dysplasia; HGD – high-grade dysplasia; EAC – esophageal adenocarcinoma; LR – low-risk; HR – high-risk
Referred to a BEC with confirmed flat LGD
N=248 (100%)

- Single diagnosis of confirmed LGD, not reproduced in BEC
  N=23 (9%)

- Second diagnosis of LGD in BEC
  N=168 (68%)
    - Visible lesion detected in BEC
      N=12 (7%)
      - Treated with ER +/- RFA
        N=142 (85%)
    - Visible lesion detected in BEC
      N=45 (76%)
      - Treated with ER +/- RFA
        N=55 (96%)

- HGD/EAC detected in BEC
  N=57 (23%)