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TOPIC HIGHLIGHT

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Low grade dysplasia in Barrett's esophagus: Should we worry?

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Abstract

The optimal management for low-grade dysplasia (LGD) in Barrett's esophagus is unclear. In this article the importance of LGD is discussed, including the significant risk of progression to esophageal adenocarcinoma. Endoscopic surveillance is a management option but is plagued by sampling error and issues of suboptimal endoscopy. Furthermore endoscopic surveillance has not been demonstrated to be cost-effective or to reduce cancer mortality. The emergence of endoluminal therapy over the past decade has resulted in a paradigm shift in the management of LGD. Ablative therapy, including radiofrequency ablation, has demonstrated promising results in the management of LGD with regards to safety, cost-effectiveness, durability and reduction in cancer risk. It is, however, vital that a shared-decision making process occurs between the physician and the patient as to the preferred management of LGD. As such the management of LGD should be "individualised."

Key words: Low grade dysplasia; Barrett's esophagus; Endoluminal therapy; Radiofrequency ablation; Esophageal adenocarcinoma

Core tip: Low-grade dysplasia (LGD) in Barrett's esophagus (BE) is an important entity and poses a significant risk of progression to esophageal adenocarcinoma. With the emergence of endoluminal therapy over the past decade there has been a paradigm shift in the management of LGD. Ablative therapy, such as radiofrequency ablation, has demonstrated promising results in the management of LGD with regards to safety, cost-effectiveness, durability and reduction in cancer risk. It is, however, critical that management should be through a shared-decision making process and "individualised". It is our belief that physicians should "*worry*" about LGD in BE.

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INTRODUCTION

Barrett's esophagus (BE) is an acquired condition, which represents an adaptive change to chronic gastro-esophageal reflux disease[1]. It is characterised by the presence of columnar mucosa within the tubular esophagus, which demonstrates specialized intestinal metaplasia (goblet cells). This metaplastic change is thought to represent a precursor for esophageal adenocarcinoma (EAC)[2]. It is postulated that there is a multi-step process during which the mucosa progresses through a metaplasia-dysplasia-carcinoma sequence[3]. Current guidelines, therefore, recommend endoscopic surveillance for patients with BE to detect early changes in the esophageal mucosa[4,5].

Dysplastic changes within the esophageal mucosa

include low-grade dysplasia (LGD) and high-grade dysplasia (HGD), which are regarded as intraepithelial neoplasia. Due to the high risk of progression to EAC[6] and the risk of coexisting EAC[7,8], the management of HGD includes either endoluminal therapy or an esophagectomy. Controversy, however, exists as to the optimal management for patients with LGD. In this article we discuss the evidence on the management of LGD and explain why we should "*worry*" about LGD.

LOW-GRADE DYSPLASIA: DEFINITION AND DIAGNOSIS

Dysplasia is defined as neoplastic epithelium that is confined within the basement membrane of the gland from which it arises differentiating it from invasive adenocarcinoma[9,10]. The revised Vienna classification standardizes the diagnosis of gastrointestinal epithelial neoplasia and adopts a five-tiered system when evaluating BE[11]. LGD is characterized by the relative preservation of glandular architecture but with cellular atypia (adenomatous or non-adenomatous changes) including nuclear hyperchromatism, pleomorphism, mucin depletion and absence of goblet cells. Identifying loss of surface maturation is important to aid in the differentiation between true dysplasia and regenerative atypia. In the presence, however, of inflammation/ulceration the epithelium may mimic that of LGD[12]. An important feature is the presence of crypt cells, which are significantly higher in number in patients with LGD who progress to EAC[13].

The Vienna classification system is reproducible amongst gastrointestinal pathologists and provides high specificity and predictive value even with LGD[14]. Even so the diagnosis of LGD can be difficult especially amongst non-gastrointestinal pathologists[15] especially when trying to differentiate between indefinite for dysplasia and LGD. Indeed the absence of well-defined cut off points with dysplasia makes such a differentiation difficult. Furthermore differentiating between LGD and HGD can also pose a diagnostic challenge with κ values for intra-observer and inter-observer variability being 0.64 and 0.45 respectively[16]. It is therefore recommended that pathologists who are experts in esophageal histopathology confirm the diagnosis of dysplasia in BE[4,5]. Consensus diagnosis of LGD among gastrointestinal pathologists[16] is vital as the degree of dysplasia is a key determinant for further management of patients with BE.

LGD AND PROGRESSION TO ESOPHAGEAL ADENOCARCINOMA

It is well established that the presence of dysplasia is associated with an increased risk of adenocarcinoma and in clinical practice it is the only recognised predictor of developing cancer. The neoplastic potential of LGD, however, is poorly defined. The development of cancer is associated with interplay of complex cellular, genetic and molecular mechanisms[3]. The natural history of dysplastic changes, therefore, is difficult to predict particularly on an individualised patient basis. This unpredictability serves further fuel to the argument that the diagnosis of dysplasia of any grade should be cause for concern.

Table 1 Molecular biomarkers predicting progression of dysplastic Barrett's esophagus

Molecular biomarker	Technique	Ref.
Overexpression of p53	IHC	[24-27]
Loss of heterozygosity (17p)	PCR	[28-30]
Hypermethylation of genes	PCR	[32]
Aneuploidy (2N)/Tetraploidy (4N)	Flow cytometry	[33-35]
Ki-67[1]	IHC	[23]

[1]Facilitates differentiation between non-dysplastic and dysplastic mucosa. IHC: Immunohistochemistry; PCR: Polymerase chain reaction.

It is largely assumed that a stepwise progression occurs from LGD to HGD and subsequent EAC, a sequence of events that was first proposed by Naef *et al*[17]. In clinical practice the timescale of this sequence is unknown and hence it may not be seen to occur; as such dysplastic BE of any grade could therefore progress to EAC. Evidence suggests that patients with LGD progress to EAC at a higher rate than patients with non-dysplastic BE. Two large population-based studies have demonstrated that the risk of progression for LGD is 0.5%-1.4%/year, in comparison to only 0.12%/year for non-dysplastic BE[18,19]. A large multicenter cohort study demonstrated that LGD persisted in 21% and progressed to HGD/EAC in 13%[20]. Although a significant number (66%) regressed, one may argue that a number of these may represent overdiagnosis or misdiagnosis rather than true regression. A more recent study demonstrated that the cumulative risk of progression to HGD or EAC was 85%, with an incidence rate of 13.4% per patient year for patients with confirmed LGD[21]. Whilst this statistic is alarming, it should be qualified by the observation by Curvers *et al*[21] that 85% of patients were downstaged from LGD to non-dysplastic BE. Thus discordance and limitations in pathological assessment make it difficult for physicians to make management plans based on histopathology alone. However, it has been demonstrated that when gastrointestinal pathologists make a consensus diagnosis of LGD the risk of progression to HGD or EAC is significant[16,22].

Due to the limitations of histological analysis, investigators have attempted to identify tissue biomarkers to help predict the risk of progression to EAC (Table 1). The cell cycle is dysregulated in dysplastic BE with abnormal expression of Ki67 on the surface epithelium, which aids in the differentiation of non-dysplastic and dysplastic BE[23]. It is, however, the overexpression of p53 in LGD that is associated with an increased risk of progression to HGD/EAC[24-26]. The concomitant diagnosis of aberrant p53 increased the positive predictive value of neoplastic progression from 15% to 33%[27]. Further the presence of 17p loss of heterozygosity (LOH), which is thought to represent inactivation of

p53 has been demonstrated to be a strong predictor of progression in BE[28]. Indeed LOH at the sites of known tumour suppressor genes (*APC*, *DCC*, *AND*, *TP53*) may be potential biomarkers of progression in BE[29,30]. As well as loci abnormalities, epigenetic changes including hypermethylation-induced inactivation of p16 have been demonstrated to be prevalent in BE[31] and associated with an increased risk of progression in LGD[32]. Hypermethylation of *RUNX3* and *HPP1* genes in BE may also represent risk factors for progression[32]. Flow cytometric analysis can also demonstrate DNA content abnormalities in patients with BE. The presence of aneuploidy or tetraploidy in patients with LGD is associated with an increased cumulative incidence of EAC[33-35]. There are, however, a number of caveats to the use of biomarkers in BE. Biomarker analysis is not universally applicable or feasible, especially in clinical practice. The current studies are potentially underpowered and there will undoubtedly be concerns regarding reproducibility between laboratories. There are also issues regarding costs and the requirement for complex analytical techniques including immunohistochemistry and flow cytometry. Indeed, the American Gastroenterological Association currently do not recommend the use of biomarkers to risk stratify patients with BE[5]. Nevertheless the above abnormalities in BE demonstrate promise in biomarker-based prediction and may reduce the inter-observer variability amongst pathologists. Further studies are necessitated before biomarkers can be utilised routinely in prediction of progression.

As well as biomarkers, the risk of progression is also related to clinical and endoscopic factors, including age, male gender, multifocality and length of the BE segment[18,36]. As LGD maintains a constant risk of progression to EAC[19] diagnosis at an early age is clinically relevant, as these individuals would have more life-years to potentially progress.

What is important, however, is the persistence of LGD with surveillance alone. Persistent LGD, a "pre-malignant lesion", only serves to further concern both the physician and patient and it is well established that BE has a significant decrement in health-related quality of life[37]. Anecdotally it is known that the natural history of dysplasia differs from patient to patient and this only adds to the inability to inform patients of their specific risk of neoplastic progression. If physicians are unable to accurately identify which patients with LGD will go on to develop HGD or EAC, surely intervention should be an option that is considered? Although most deaths are not cancer-related, a significant number of patients with LGD develop esophageal cancer[38], which in itself is associated with significant morbidity and burden to both the patient and the healthcare system.

LGD: SURVEILLANCE ALONE?

Guidelines currently recommend that patients with LGD undergo endoscopic surveillance every 6-12 mo until two consecutive biopsies demonstrate non-dysplastic BE[4,5]. Surveillance alone, however, is not without limitations. Firstly, and most importantly there has been no randomised, prospective trial demonstrating that surveillance has a survival advantage over no surveillance or intervention. The United Kingdom BOSS trial (DOI 10.1186/ISRCTN54190466) aims to answer this to a degree by establishing whether surveillance in BE (including LGD) is beneficial. In the meantime surveillance is based solely on a weak recommendation with moderate quality evidence[5].

For surveillance to have any survival advantage strict adherence to an endoscopic biopsy protocol (Seattle Protocol) is necessitated[39]. Adherence to such protocols has been demonstrated to be suboptimal, decreasing further with increasing length of BE and resulting in reduced detection of dysplasia[40,41]. Sampling error[42] and a mosaic of dysplastic and non-dysplastic areas are other key issues to be aware of. Standard high-resolution white light endoscopy only allows the detection of macroscopically obvious abnormalities. The adoption of narrow band imaging[43,44], autofluorescence imaging[44] chromoendoscopy and virtual chromoendoscopy[45,46] could significantly improve the detection of dysplasia. A promising technique is that of confocal laser endomicroscopy (CLE), which allows *in vivo* visualisation of the mucosal histology. CLE affords targeted biopsies, improving diagnostic yield even in the absence of macroscopic abnormalities[47,48]. Although CLE can improve the sensitivity of detecting mucosal changes, the technique is limited to tertiary-referral centres thus limiting its use in surveillance[49]. These advanced techniques need further validation, including a cost-benefit analysis before they can be routinely recommended for endoscopic surveillance.

Although not demonstrated HGD may co-exist amongst LGD and as such managing LGD with surveillance alone may be detrimental in such cases. More troublingly is that patients can develop HGD/EAC even with two consecutive biopsies revealing non-dysplastic BE[20]. Critically there is no prospective data to demonstrate that surveillance in BE is cost effective or improves mortality from EAC. All in all, strategies based on surveillance alone in LGD are exposed to limitations that can have far reaching implications. Further, patients' perceptions and concerns are important issues to consider with surveillance, especially with a premalignant condition. Crucially, following intervention for dysplasia, quality of life is improved through the perception that the risk of EAC is reduced[50].

As an adjunct to surveillance, chemopreventive strategies have been used in BE. The cornerstone of medical therapy is the proton-pump inhibitor (PPI), which is associated with a lower incidence of EAC[51] and is superior to H_2-receptor antagonists in reducing progression to dysplasia or EAC[52,53]. Interestingly, PPI therapy reduces cell proliferation in BE[54,55]. Evidence regarding PPI therapy is, however, indirect at best and merely associative. There is also a paucity of prospective, controlled clinical studies examining the role of PPI therapy in

BE and the development of EAC. Furthermore, even with symptom control persistent acid and bile refluxate is present in patients taking PPI therapy[56,57], thereby not eliminating the key factor in the pathogenesis of BE. Non-steroidal anti-inflammatory drugs and aspirin, which exert their effect by inhibition of the COX-1 and -2 enzymes may play a role in reducing progression to EAC[58,59]. In contrast selective inhibition of COX-2 (associated with colonic carcinogenesis) did not prevent progression of dysplasia to EAC[60]. It is clear that carcinogenesis in BE is a complex interplay of numerous factors, which may not necessarily be influenced by chemopreventive strategies. The results of the United Kingdom AspECT trial (ClinicalTrials.gov NCT00357682) are awaited and may help answer what role aspirin and PPI play in the progression of BE to EAC. Until then the American Gastroenterological Association do not recommend aspirin in patients with BE in the absence of cardiovascular disease.

LGD: ROLE OF ENDOLUMINAL THERAPY

The aim of endoluminal therapy is to eradicate both dysplastic BE and non-dysplastic BE, achieving reversion to neosquamous epithelium and thus reducing the risk of progression to EAC. Endoluminal therapies include endoscopic mucosal resection (EMR) for visible abnormalities (nodular BE) or ablative techniques such as radiofrequency ablation (RFA), photodynamic therapy (PDT) and argon plasma coagulation (APC).

It is currently recommended that EMR is an alternative to esophagectomy for patients with either HGD or intramucosal adenocarcinoma[5,61]. Further, EMR is also invaluable as both a diagnostic and staging procedure, the latter helping to differentiate between a mucosal or submucosal adenocarcinoma. Importantly, EMR significantly improves interobserver agreement on the diagnosis of both LGD and HGD in comparison to a standard biopsy technique[62]. However, there are no recommendations for the use of EMR for the management of LGD, particularly in the absence of a visible/nodular abnormality.

An early trial using PDT for ablation LGD showed promising results with an efficacy of 92.9%[63]. Further trials from the United Kingdom demonstrated that PDT was similarly efficacious in eradicating LGD[64,65]. Likewise a study utilising APC to ablate LGD demonstrated complete eradication of dysplasia at one year[66]. When comparing the two ablative therapies, PDT achieved higher rates of LGD eradication[67]. There are, however, concerns about the side effect profile of PDT with high stricture rates and photosensitivity being reported[63,68,69]. Of greater concern with any ablative technique is the risk of subsquamous intestinal metaplasia, which can develop into a subsquamous adenocarcinoma[68,70].

The ablation of intestinal metaplasia (AIM) trials, which adopted the technique of circumferential RFA (cRFA, Halo© 360) and focal RFA (fRFA Halo© 90), were pivotal in the management of both dysplastic and non-dysplastic BE. Initial studies were based on the identification of dose-response, safety and efficacy of cRFA in non-dysplastic BE[71]. A pilot study of patients with LGD, demonstrated that a combination of cRFA and subsequent fRFA (stepwise regimen) had a 100% complete response for dysplasia at 2-year follow up[72].

It was, however, the AIM dysplasia trial, which provided the first real evidence that RFA had a role in the management of LGD[73]. This prospective, multicenter, sham-controlled trial demonstrated that RFA resulted in complete eradication of LGD in 90.5% in comparison to 22.7% in the control group at 12 mo ($P < 0.001$). Eradication of non-dysplastic BE was demonstrated in 81% of patients undergoing RFA compared to 4% in the sham-control group. At follow-up with as required fRFA complete eradication of LGD was attained in 98% and 100% at 2- and 3-years respectively[74]. Importantly, for patients with LGD undergoing RFA overall disease progression was 2.04%/patient/year, with a 0.51%/patient/year progression rate to EAC[74]. The annual progression rate in sham-control group was 16.3%. This evidence demonstrated for the first time that endoluminal therapy in the form of RFA for dysplastic BE was potentially anti-neoplastic. Indeed no disease progression-related morbidity or mortality was demonstrated in this study.

More recently prospective studies from the United Kingdom[75] and the Netherlands[76] have verified the efficacy of RFA in eradicating dysplastic BE. The United Kingdom National Halo RFA Registry demonstrated following EMR (for nodular lesions), serial RFA eradicated dysplasia in 81% of patients at 12 mo with 94% remaining clear of dysplasia at 19 mo. Similarly, the smaller study from the Netherlands demonstrated following serial RFA (with or without EMR), 90% of patients remain in remission at 5-years.

There have, however, been concerns about the durability, risk of subsquamous intestinal metaplasia, safety and cost of RFA for dysplastic BE. For patients with LGD achieving complete eradication of dysplasia, 90% remained free of dysplastic BE and > 75% remained free of non-dysplastic BE at 3-years without additional RFA therapy[74]. Anti-reflux surgery (ARS), which reduces refluxate into the lower esophagus, may improve the durability of RFA. Understandably the elimination of acid reflux, a known risk factor for BE, may have a beneficial effect on neoplastic progression. Studies have demonstrated that concomitant fundoplication is safe, effective at eradicating dysplasia and improves durability when compared to RFA and subsequent PPI therapy[77,78]. There is, however, no data supporting the role of ARS as an anti-neoplastic intervention. It is clear that further prospective data is clearly necessitated to address the long-term durability of RFA with or without ARS. Our current understanding of the oncogenic potential of the neosquamous epithelium is limited. Yet it has been demonstrated this epithelium has no persistent molecular abnormalities (Ki-67, p53) or "buried" metaplasia following RFA. This is in contrast to other ablative techniques such as PDT where genetic abnormalities can

persist[79]. Although, the actual occurrence of subsquamous intestinal metaplasia post RFA is low[76] and can also occur without ablative therapy[80]. Furthermore, the incidence of subsquamous intestinal metaplasia is lower following RFA (0.9%) compared to PDT (14.2%)[80]. In the AIM dysplasia trial no perforations or procedure related deaths occurred over the 3-years. There were, however, a very small number of adverse events thought to be related to the procedure, with 7.6% of patients developing a stricture that required dilatation[74]. Although the incidence of adverse events is higher than that with endoscopy alone, it does vary with the type of procedure[81]. Indeed RFA has a better safety profile than PDT, which is associated with high rates of photosensitivity and stricture formation[68]. Ablative therapy has been shown to be cost-effective for HGD in a United Kingdom-based analysis[82]. Critics, however, question the cost-effectiveness of ablative therapy for LGD in comparison to surveillance. In a cost-utility analysis, if ablative therapy could eradicate more than 28% of LGD, ablation would be favoured over surveillance[83]. Furthermore RFA is only cost-effective in patients with confirmed and stable LGD[84], which defines the importance of consensus agreement for LGD. Evidently the cost-effectiveness depends on the durability of ablative therapy. Discontinuation of surveillance would reduce long-term costs, but this is not recommended as recurrence (dysplastic and non-dysplastic) can occur[85,86] Thus following ablative therapy, surveillance is recommended in all patients to identify potential changes in the mucosa.

CONCLUSION

The emergence of endoluminal therapy over the past decade has resulted in a paradigm shift in the management of dysplastic BE. As such, the American Gastroenterological Association has recommended that RFA is a therapeutic option for patients with confirmed LGD[5].

Critics, however, claim that there are caveats to this recommendation. Firstly there are concerns regarding the diagnostic uncertainty with LGD, in particular the inter- and intra-observer variability amongst pathologists. As such, ablative therapy may result in over-treating patients who merely have non-dysplastic BE. The natural history of LGD is unclear and the literature demonstrates marked heterogeneity, especially with regards to progression risk. It is thought that patients with LGD and non-dysplastic BE have a similar low risk of developing EAC[20]. However, if patients with BE are truly being overdiagnosed, this would mean that studies looking at the natural history of LGD are being "contaminated" with non-dysplastic BE leading to an underestimation of progression and malignant potential. Thus, all patients diagnosed with LGD require a consensus from two or more gastrointestinal pathologists.

The purpose of any intervention for LGD is to reduce the incidence of EAC. Trials have demonstrated short-term benefits for ablative therapy, but critics claim that there is no long-term data demonstrating the prevention of EAC. Indeed there is paucity of long-term data but a recent meta-analysis demonstrated that ablative therapy reduced the risk of EAC in patients with LGD[87]. There is, however, heterogeneity amongst the literature and this reflects the molecular and biological differences in dysplasia amongst patients.

Finally opponents of ablative therapy for LGD, claim the side-effect profile does not justify intervention over surveillance alone. Furthermore, ongoing surveillance is necessitated following ablation and as such has an impact on the cost-effectiveness and quality of life. Although PDT has an unfavourable side-effect profile, RFA has been demonstrated to be safer and better tolerated. The requirement of ongoing surveillance will no doubt be addressed once the long-term efficacy and durability of RFA has been established. Results from an ongoing randomised trial (ClinicalTrials.gov NCT01360541) comparing RFA against surveillance for LGD will provide answers to the queries posed by opponents to ablative therapy

Despite the above caveats it is the authors' belief that consensus defined LGD is an important entity and warrants consideration of ablative therapy. The authors believe that management of LGD should be "individualised" and based on known risk factors for progression. Indeed the panacea would be to identify reliable biomarkers or predictors of progression to EAC. However, until then we need to rely on clinically relevant factors to help with risk stratification. Thus a young, male patient with long segment BE and multifocal LGD would be regarded as "high risk" and should therefore be considered for ablation. It is, however, not as simple as that in clinical practice and the uncertainty with progression should encourage physicians to consider ablative therapy as an alternative to surveillance alone. Most importantly as per the American Gastroenterological Association's recommendation there should be shared-decision making process between the physician and the patient as to the preferred management of LGD.

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