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Addressing Controversies in the Management of Barrett's Oesophagus with Low Grade Dysplasia

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Abstract

There are multiple international guidelines on the management of non dysplastic Barrett's oesophagus (NDBE) and Barrett's oesophagus with high grade dysplasia (HGD). Despite the numerous studies in the literature pertaining to the management of Barrett's oesophagus with low grade dysplasia (LGD), there is still no agreement due to the lack of evidence in respect to the diagnosis, progression rate and best management of Barrett's oesophagus with LGD. This review discusses the current controversies in the management of LGD, including surveillance intervals and techniques, effectiveness and safety of radiofrequency ablation (RFA), cost effectiveness of RFA, natural history of LGD, and risk factors for progression from LGD to HGD or oesophageal adenocarcinoma (OAC), and ultimately addressing the ideal management strategy for patients with Barrett's oesophagus with LGD.

Introduction

Barrett's oesophagus is defined as columnar epithelium which extends above the gastro-oesophageal junction with histological evidence of intestinal metaplasia with mucin-containing goblet cells [1,2]. Progression of Barrett's oesophagus is thought to be a multistep process, where histology changes from non-dysplastic Barrett's oesophagus (NDBE) to low grade dysplasia (LGD) to high grade dysplasia (HGD) before reaching oesophageal adenocarcinoma (OAC) [3,4]. Currently there are clear recommendations from multiple international guidelines regarding the management of NDBE and Barrett's oesophagus with HGD [1,2,5,6]. The aim of these guidelines is to improve survival of patients with Barrett's oesophagus by reducing the risk of progression to OAC. Current guidelines suggest surveillance of NDBE every 3-5 years for patients with short segment (<3 cm) Barrett's oesophagus and every 2-3 years for patients with long segment (>3 cm) Barrett's oesophagus [5]. Endoscopic eradication therapy is recommended for patients with confirmed HGD within Barrett's segment [1,2,5,6].

Controversies in Management of LGD

There is no consensus regarding the management of patients with LGD. Current guidelines suggest either close surveillance with 6-12 monthly gastroscopies and biopsies or referral to an expert centre for endoscopic eradication therapy [7]. This lack of consensus is mainly due to conflicting evidence concerning the diagnosis, progression rate and best management of LGD.

Surveillance Intervals and Techniques

The current gold standard for performing surveillance endoscopies is by high definition white light examination (HD-WLE) with biopsies as per the Seattle protocol [3,8]. This may be used in conjunction with chromoendoscopy with methylene blue or acetic acid. In addition, advanced imaging techniques such as narrow band imaging (NBI), autoflorescence imaging and confocal laser endomicroscopy (CLE) may be used for improved accuracy to enable targeted biopsies [3]. Jayasekera "et al." [9] performed a cross-sectional study assessing a total of 1190 individual biopsy points in 50 consecutive patients with dysplastic Barrett's oesophagus in an expert Barrett's Unit. They demonstrated that the sensitivity, specificity and accuracy of detecting HGD or OAC were: HD-WLE 79.1%, 83.1% and 82.8%; NBI, 89%, 80.1% and 81.4%; and CLE, 75.7%, 80.0% and 79.9% respectively. They also demonstrated that all mucosal points with OAC and patients with HGD were detected by targeted biopsies using a combination of HD-WLE and NBI. Performing surveillance endoscopies for patients with Barrett's oesophagus have been shown by numerous observational studies to be effective in early detection of OAC and hence improve survival when compared to

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patients with Barrett's oesophagus who are not undergoing surveillance [10,11]. Furthermore, Cameron "et al." [12] demonstrated a 56% increase in OAC detection rate when the assessment was performed in an expert Barrett's Unit compared to that in the community. Regarding LGD, some international guidelines suggest 6 monthly surveillance [2,5,6] while others suggest 12 monthly surveillance [13]. These recommendations are based on expert opinions due to the fact that there are no randomised controlled trials looking at the effect of surveillance and mortality [3].

Effectiveness and Safety of Radiofrequency Ablation

In a randomised controlled trial by Shaheen "et al." [14]. 127 patients with dysplastic Barrett's oesophagus were randomly assigned in a 2:1 ratio to receive either radiofrequency ablation (RFA) or a sham procedure. RFA successfully eradicated 90.5% of LGD compared to 22.7% of those in the control group. Patients in the RFA group also had lower progression rate to HGD or OAC 3.6% vs. 16.3%. A subsequent follow-up study looking at the durability of RFA in dysplastic Barrett's oesophagus showed that dysplasia remained eradicated in >85% of patients after 3 years without maintenance therapy [15]. Moreover, according to a randomised controlled trial by Phoa "et al." [16] 136 patients with LGD were randomised in a 1:1 ratio to receive either RFA or surveillance. RFA in LGD is superior to surveillance in reducing risk of neoplastic progression. RFA is an effective therapy for dysplastic Barrett's oesophagus, however it is not without complications; moreover, there is also a significant recurrence rate. For instance, Cameron "et al." [17] illustrated in a prospective observational study of 137 patients receiving RFA for dysplastic Barrett's oesophagus that adverse events occurred in 4% of patients, of which majority were strictures followed by bleeding; 1.3% and 0.9% respectively. They also demonstrated that 9% of patients have recurrence of dysplasia and 28% of patients have recurrence of intestinal metaplasia after initial eradication after a median follow up time of 12.4 months. Similarly, Shaheen "et al." [15] showed that of the 127 patients, 3.9% of patients had a serious adverse event while 15% and 25% of patients had a recurrence of dysplasia and intestinal metaplasia respectively.

Cost Effectiveness of RFA

A number of studies have demonstrated the cost effectiveness of RFA for Barrett's oesophagus with HGD suggesting potentially increasing life expectancy by 3 quality adjusted life years for a cost of <$6000 when compared to no intervention [18,19]. Regarding treatment of LGD, even though RFA is more effective at reducing the risk of progression, it is significantly more expensive than endoscopic surveillance [20], and therefore may not be cost effective. Ultimately the cost effectiveness of using RFA for LGD depends on the long-term effectiveness of ablation, progression rate of LGD to HGD or OAC and whether surveillance endoscopy can be discontinued after successful ablation. Furthermore, there is still no adequate long term data about the durability of RFA. Shaheen "et al." [15] reported on a 3 year follow up of his cohort from 19 sites, suggesting that dysplasia remained eradicated in >85% and intestinal metaplasia remained eradicated in >75% of patients. Most subjects with recurrences could again attain complete eradication of intestinal metaplasia with further treatment. While this data is promising, there is no certainty regarding maintaining long term durability of neosquamous mucosa and hence suggests that further surveillance and therapeutic endoscopies are still warranted post eradication therapy.

Natural History of LGD

The revised Vienna classification defines LGD as characterised by cytological atypia such as hyperchromatic and stratified nuclei with relatively preserved glandular architecture [21]. Pathological diagnosis of LGD is challenging, due to a degree of subjectivity in assessment of the criteria, some variation and difficulty interpreting the significance of changes in the context of reactive atypia and inflammation [22]. Consequently, there is a large interobserver variability among community and even expert pathologists in the differentiation of NDBE, indefinite for dysplasia and LGD [12,23,24]. This interobserver variability between community and expert pathologists has also contributed to the over diagnosis of LGD in the literature. Reported progression rates for LGD range from 0.4% to 13.4% [24-27]. For instance, Curvers "et al." [24] demonstrated in a multicentre study that 85% of 147 patients had their diagnosis of LGD down staged after being reviewed by an expert pathologist. For those with a confirmed diagnosis of LGD, the progression rate to HGD or OAC was as high as 13.4% per patient per year, while for those who had been downgraded to NDBE, their progression rate was 0.49%. The true progression rate and natural history of LGD is difficult to determine due to the literature containing many studies with over-diagnosis of LGD, variability in outcomes between community and expert centres, and interobserver variability between pathologists.

Risk Factors for Progression from LGD to HGD or OAC

The risk of progression is determined primarily by the degree of dysplasia within a Barrett's segment. There is a substantial variation in the reported progression rate from LGD to HGD and OAC. This progression rate from LGD may be underestimated if there is an over diagnosis of LGD reported by a single community pathologist [28,29], conversely, this progression rate may also be overestimated if multiple expert GI pathologists agree on the diagnosis of LGD [24,30]. While there are uncertainties about the natural progression of LGD, there have been several studies, which identify risk factors for progression. These risk factors for progression include, confirmation of LGD by an expert pathologist, consensus among an increased number of expert GI pathologists, persistent LGD and multifocality of Barrett's related dysplasia [4,27,30,31]. Duits "et al." [31] showed in a retrospective analysis of 255 patients with LGD that the number of pathologists confirming the diagnosis of LGD is strongly associated with the risk of progression. In their study, there was a significant increase in risk when all 3 pathologists agreed upon the diagnosis of LGD (odds ratio (OR), 47.14; 95%CI, 13.10-169.70). In addition, when there is persistent LGD on 2 or more consecutive gastroscopies, the risk of progression is also increased (OR 9.28; 95%CI, 4.39-19.64). Furthermore, Srivastava in an observational study looking at baseline biopsies from 77 dysplastic Barrett's oesophagus patients demonstrated that the extent of LGD as measured by a total patient crypt count such as multifocal dysplasia is also a significant risk factor for progression to OAC.

Surveillance vs. Radiofrequency Ablation

Owing to the many uncertainties of diagnosis and management of Barrett's oesophagus with LGD in the literature; the question of surveillance or treatment with radiofrequency ablation currently is best addressed on a case by case basis and involving the patient in a thorough discussion regarding the potential risks and benefits of treatment options. As the current evidence stands, it would be

beneficial for all patients with LGD be referred to an expert Barrett's Unit for an assessment endoscopy and review of pathology by at least one expert GI pathologist. If there are risk factors for progression identified, then RFA should be considered, otherwise it is reasonable to continue with 6 monthly surveillance endoscopies.

Conclusion

This article highlights the many controversies surrounding the diagnosis and management of patients with Barrett's oesophagus related LGD. Further studies identifying endoscopic, clinical and histological related risk factors for progression of LGD will improve our capacity to risk stratify patients and identify those who would most benefit from RFA compared to surveillance. In addition, standardised histological criteria to characterise LGD will greatly reduce the diagnostic uncertainties and allow us to better understand the natural history of LGD.

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