Review Article

Endoscopic therapy for confirmed low-grade dysplasia in Barrett's esophagus

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Abstract: Barrett's esophagus (BE) is a premalignant condition characterized by replacement of the esophageal lining with metastatic columnar epithelium. To date, the management in case of confirmed low-grade dysplasia (LGD) remains controversial. In this article we summarize the available endoscopic options and their results in terms of efficacy and safety in the treatment of confirmed LGD in BE.

Keywords: Barrett's esophagus (BE); dysplasia; endoscopy; personalized medicine

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Introduction

Barrett's esophagus (BE) is a metaplastic process in which the normal squamous epithelium in the esophagus is replaced by intestinal-type mucosa comprised of columnar epithelium and goblet cells (1). This condition is a significant risk factor for esophageal adenocarcinoma (EAC), following the d1ysplasia-carcinoma sequence, from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and progressing ultimately to carcinoma (2). Regarding the management of patients with LGD on random biopsies, both European and American guidelines agree on the need of confirmation of LGD by a second pathologist with expertise in gastrointestinal pathology (3,4). If LGD is not confirmed at 6-month endoscopy, a standard surveillance for patients with nondysplastic BE can be carried out, while in case of confirmed LGD, that is a strong risk factor for progression to EAC, a tailored endoscopic treatment should be proposed to patients (5). Curvers *et al.* (6) found that in 147 patients with a diagnosis of LGD, it was downgraded in 85% to no dysplasia or indefinite for dysplasia after histologic review, while patients with confirmed LGD had a higher progression rate (27 fold more) per year to HGD/EAC than those downgraded to non-dysplastic Barrett's esophagus (NDBE). Moreover, this risk of progression increases further when two or three pathologists agreed on the LGD diagnosis (7,8). Persistent LGD (confirmed LGD at baseline and subsequent endoscopy), as shown in a large cohort study (9), had a risk of progression to HGD/EAC of 7.65% *vs.* 2.32% in patients without persistent LGD. Therefore, patients with diagnosis of confirmed and persistent LGD deserve a specific management. Endoscopic procedures have become increasingly widespread and advanced not only in the diagnosis and monitoring, but also in the treatment of BE (10) even if the treatment of LGD continues to be controversial and guidelines that allow standardization on endoscopic treatment for confirmed LGD-BE are still not comprehensive.

In this article we summarize the available endoscopic options and their results in terms of efficacy and safety in

the treatment of confirmed LGD in BE.

Several endoscopic techniques have been evaluated for the ablation of BE, aimed to eradicate dysplasia and intestinal metaplasia (IM) and prevent the progression to EAC (11-14).

Thermal treatment

Radiofrequency ablation (RFA)

RFA is an ablative thermal technique for BE that consisting in the application of energy with variable density (10–12 J/cm^2), with ablative effect limited in depth (700 μm) which determines hyperthermia (100 °C), cellular damage and drying effect. It is the gold standard for patients with non-nodular LGD-BE. Two randomized controlled trials have directly examined the efficacy of RFA compared to surveillance in limiting progression to HGD or EAC in patients with LGD. Shaheen *et al.* published the first prospective randomized, sham controlled, trial that compared 127 patients with dysplastic BE treated with RFA *vs.* a sham ablation (15). Complete eradication of LGD (CE-D) was achieved in 90% of patients in RFA arm and 23% with the sham procedure (P<0.001) at 1-year of follow-up. Specifically, for LGD, the progression to HGD of patients in RFA group was 5%, compared with 14% in surveillance arm, while none of both arms developed EAC (7). Overall, RFA group showed a complete eradication of intestinal metaplasia (CE-IM) in 77.4% of patients, while 2.3% in the control arm (P<0.001). Subsequently, also the SURF study, compared RFA *vs.* surveillance in 136 patients with confirmed LGD. The progression to HGD or EAC in the surveillance and RFA groups was 26.5% and 1.5%, respectively (P<0.001) at 2 years of follow-up and the study was stopped earlier due to the treatment efficacy (16). Among patients in RFA group, CE-D occurred in 92.6% and CE-IM in 88.2% while in the control group CE-D occurred in 27.9% and CE-IM in 0.0% (P<0.001). A recent retrospective analysis also confirmed these results (17). The progression to HGD or EAC per year was 6.6% in the surveillance arm compared to 0.77% in the RFA group, showing as demonstrated in the European SURF trial, that RFA is an effective treatment for LGD not only in clinical trials but also in clinical practice. Finally, in a meta-analysis (18) of 19 published studies including a total of 2,746 patients, the risk ratio of disease progression for BE-LGD treated with RFA compared with surveillance was 0.14% (95% CI: 0.04–0.45). This indicates that RFA resulted in an 86% reduction in the risk of disease progression to HGD/EAC when compared to surveillance, with a number needed to treat of 9.2. These interesting data demonstrate that endoscopic ablation with RFA have advantages in terms of effectiveness in reducing the progression of LGD-BE to HGD or EAC compared to endoscopic surveillance. Moreover, the high percentage of neoplastic progression in patients under surveillance alone, the low NNT to avoid progression to HGD or cancer and the good safety profile of RFA reported to date provide further evidences to consider RFA as the treatment of choice for LGD-BE. However, the major limitation of clinical trial and studies is the short follow-up period (36 median months). Therefore, Kahn *et al.* (19) conducted a retrospective analysis comparing the long-term results of RFA *vs.* surveillance in clinical practice. Of 173 patients, 79 (45.7%) underwent RFA while 94 (54.3%) were not treated, with a 90-month median follow-up. Considering the results of this study in which about 9% of patients treated with RFA progressed in HGD or EAC compared to 15% of patients in surveillance (P=0.44), RFA was found to be not associated with a statistically significant reduction in progression to HGD or EAC in a long follow-up period. This is an important consideration that support the recommendation of the ACG guidelines (4) to consider endoscopic surveillance as a possible alternative to RFA for LGD-BE patients and in order to find risk stratification models for patients with LGD-BE, guiding physicians in patient's selection for ablative therapy.

Regarding safety of the procedure, recent meta-analyses (18-20), showed that strictures are the most common reported adverse events, followed by pain. Bleeding and perforation were rare. The pooled incidence of any recurrence after RFA (IM and dysplasia) was 7.3/100 patient per year (21). No strong risk factors are significantly linked to the risk of recurrence, that in any case can be retreated, and a possible link with inflammation or BE extension need further investigations and confirmations.

Argon plasma coagulation (APC)

APC as ablative technique for BE was used more widely in the 2000s. Two randomized controlled trials of APC ablation *vs.* endoscopic surveillance in BE patients managed with PPIs (medical trial) or fundoplication (surgical trial) as a method for reflux control were published. The results were that ablation using APC was feasible and effective to achieve a stable neo-squamous epithelium at 5 years of follow-up (22,23). More recently, the same group also

evaluated the longer-term outcomes of APC ablation for BE. In this study, 129 patients with BE (NDBE or LGD-BE) were randomized to APC ablation or surveillance. The eradication was achieved in more than 95% of patients treated with APC ablation and this result persisted in 47 of 56 patients at short-term (12 months) follow-up, in 33 of 49 patients at mid-term (42–75 months) and in 21 of 32 patients at long-term (>84 months) follow-up (24). Even if more data exist about APC and HGD-BE, in the setting of LGD-BE this work demonstrated that APC ablation is an effective ablative technique for BE and this outcome is held in some cases over time. However, these results do not allow the use of this method in daily clinical practice and head to head RFA studies are needed to demonstrate its real efficacy. Moreover, considering the reported risk of stricture formation in about 10% of patients, Manner *et al.* presented new exciting safety data of the "Hybrid-APC" technique, which combines submucosal injection of sodium chloride 0.9% plus APC on BE mucosal residue of at least 1 cm after endoscopic treatment for early Barrett's neoplasia (25). Even if they showed a more favorable safety profile, with a lower number of strictures and minor adverse events, no sufficient evidences are available in the setting of LGD-BE and to date this technique cannot be not recommended in the management of BE.

Cryoablation

The spray cryotherapy using low-pressure liquid nitrogen has been also tested in the past years as ablative endoscopic technique for BE (26,27) and showing a good profile of safety and efficacy (28), but available data concern HGD-BE. In 2015 the first multicenter, prospective open-label registry (29) enrolling also LGD-BE was performed, with interesting rates of eradication that was about 90% for dysplasia and 60% for IM. These results were even more intriguing in patients with short Barrett and any dysplasia, achieving in these cases more than 95% of CE-D and about 75% of CE-IM and suggesting that cryotherapy is an effective ablative technique for LGD-BE and short Barrett. Recently, the first single-arm prospective clinical trial has been published (30). In this paper a new ablative option is well explained, using a new cryoballoon system that freezes esophageal mucosa with nitrous oxide. The device contains liquid nitrous oxide in a capsule that converts to gas within a low-pressure balloon. The contact between the cryogen and the balloon freezes the mucosa to –85 ℃, with a system able to rotate and ablate targeted area of pathological mucosa (31). In this study, BE with confirmed LGD, HGD and/or intramucosal EAC with or without prior ablation, were treated with cryoablation, repeated every 3 months (at maximum 5 times) to obtain the eradication. Finally, they found very good rates of complete eradication of dysplasia and IM that were about 95% and 88% respectively, including patients who failed previous treatments and difficult-to-treat BE. Specifically, CE-D rate was 100% in LGD-BE, with no difference between naive and experienced patients. The overall post-cryoablation stricture rate was 9.8% (4/41 and two of them were treatment-naive), successfully treated with balloon dilation. Post-procedural pain requiring medical treatment was less that found in spray cryotherapy trial (29).

Presented data mean that cryoablation not only may have higher rates of complete eradication of both any dysplasia and IM than liquid nitrogen cryotherapy (81% of CE-HGD; 91% of CE-LGD, about 80% of CE-IM) but also, it is associated with a lower number of treatments (median of 3) compared to CO2 spray cryotherapy (32). In conclusion, these results are extremely interesting and encouraging and create the assumption for designing more conclusive randomized clinical trials.

Non-thermal treatment

Endoscopic mucosal resection/endoscopic submucosal dissection (ESD)

Although nodular BE is more common in patients with HGD/EAC, it may also be present in patients with LGD and it is up to the endoscopist to look carefully and highlight the presence of nodules or mucosal irregularities. In fact, patients with nodular BE with LGD have higher rate of progression to HGD/EAC than patients with only flat IM with LGD (17). The management of nodular BE should include, as first approach, the EMR or ESD, in order to have a complete resection and staging of the lesion (33,34), because the presence of nodules often predicts higher grade of dysplasia (35-37). In subjects with LGD and complete resection of the nodule, the endoscopic ablative therapy generally follows the endoscopic resection, until a complete eradication of dysplasia and IM has been achieved, finally reducing the potential recurrence of any dysplasia or intestinal metaplasia.

Photodynamic therapy (PDT)

PDT with profiler sodium was considered for the

eradication of dysplastic BE in a clinical trial with promising results for HGD-BE patients (38,39). No evidences exist in the setting of LGD-BE. The only head-to-head comparison of PDT *vs.* RFA for the ablation of dysplasia in BE was performed in a consecutive case series (40). In this study were compared patients with dysplasia treated with PDT or RFA (both focal or circumferential), showing a rate of complete eradication of dysplasia that was about 55% for PDT and 89% for RFA (P=0.001). Despite in this study the authors tried to compare PDT and RFA, this was not a randomized trial and patients had different BE dysplasia grading, so that even if PDT could be potentially useful as ablative technique, for head-to-head comparison more evidences are necessary.

Discussion

Innovation in endoscopic therapy, in the last years, has allowed not only to increase the number of patients fit for BE treatment, but also, at the same time, has reduced the need for surgery in this population. Considering the evolving of endoscopic technologies and devices, it is mandatory for endoscopists to be supported by scientific evidences and guidelines in their clinical decisions. Taking in account these considerations and clinical data presented, the endoscopic ablation seems to be more efficacy compared to endoscopic surveillance in the management of LGD-BE. To date, the high risk of progression to HGD/EAC during surveillance, the good results of RFA in terms of efficacy, safety and tolerability by patients, support us to consider it as the first therapeutic endoscopic option for confirmed LGD-BE. At the moment, RFA is the endoscopic technique on which we have more data including both randomized controlled trials (15) and meta-analyzes (16-20). They demonstrate that it is a safe and effective technique that allows a complete eradication rate of dysplasia in more than 90% of cases and that can be considered as the gold standard for the treatment of LGD-BE. However, these results can be supported only if the procedure is performed in centers of reference for BE, in which is possible a multidisciplinary evaluation of the patient and expert endoscopists who perform the procedure (41). This is crucial, considering the pivotal role of the endoscopist in the selection of patients, establishing an accurate diagnosis, a risk stratification and subsequently a tailored endoscopic plan of treatment.

Conclusions

Finally, promising data recently published about the cryoballoon ablation, with rates of 95% and 88% for CE-D and CE-IM respectively, suggest a potential role for cryoablation in the treatment of LGD-BE. However, the small sample size and the lack of a control arm in the unique non-randomized study allows us to say that more research is needed to validate real efficacy of this novel ablative technique for BE. So that, to date, the treatment of choice for confirmed LGD-BE remains RFA, as other endoscopic options (APC or Hybrid APC, PTD, cryotherapy) are not sufficiently supported by scientific evidences or head-to-head comparison studies in this setting of patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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