

EDITORIAL

Is Complete Endoscopic Resection Still a Viable Option for Barrett's-Related Dysplasia and Neoplasia?



Barrett's esophagus (BE) can progressively lead to the development of low-grade dysplasia (LGD), high-grade dysplasia (HGD), intramucosal carcinoma (IMC), and advanced esophageal cancer.¹ Endoscopic resective and/or ablative treatment modalities have widely replaced surgery as the standard for the complete elimination of BE and BE-related early neoplasia.¹⁻⁴ Resective modalities, of which endoscopic mucosal resection (EMR) is the most common, are effective for both curing and obtaining tissue for pathologic assessment, but these may be associated with stricture formation. Ablative techniques, of which radiofrequency ablation (RFA) is the most common, are effective for treating BE-related neoplasia, but there is a lack of histologic correlation.⁵⁻⁷ Although each RFA and widespread EMR have been used alone,⁸⁻¹³ current guidelines recommend a hybrid approach for the optimal treatment of BE and related neoplasia; this hybrid approach consists of focal EMR for visible nodular or depressed neoplasia, followed by ablation (usually RFA) of the residual BE.^{1,3,14} However, many uncertainties remain. Is hybrid therapy always indicated, or are there subpopulations of patients who would benefit more from EMR or RFA alone? When should these modalities be combined, and what is the ideal combination? What are the long-term results of each treatment modality, either alone or combined, and how should future research be oriented?

The article by Konda et al¹⁵ in this issue of *Clinical Gastroenterology and Hepatology* provides an important addition to the literature concerning the management of BE-related early neoplasia by resective modalities alone.

This retrospective analysis of prospectively collected data describes patients who were referred to a single center for the treatment of BE-related HGD/IMC during a nearly 10-year period. It is an expansion of previously reported experience by the same group.¹⁶ The primary outcome of the study was the efficacy of achieving complete Barrett's eradication by EMR (CBE-EMR), which was defined as complete eradication of all Barrett's tissue and BE-related neoplasia. Secondary outcomes included safety, durability, and accuracy of diagnosis. Overall, 107 patients were included in the CBE-EMR protocol, which was performed either in a single session (radical EMR) or in a multistep fashion every 2-6 months until complete eradication of all BE was achieved (stepwise EMR). Overall, 74 patients (69%) were considered for durability analysis because they were followed for a mean of 40.6 months (median, 33 months).

The authors found that at the end of the treatment phase, BE was completely eradicated in 80% of the

patients on the basis of intention-to-treat analysis and 99% of patients on the basis of per-protocol analysis.

After EMR, patients were closely followed with upper gastrointestinal endoscopies and biopsies after 3-6 months and then again yearly. Notable recurrence during follow-up included 6 cases of LGD (8.1%), 1 case of HGD (1.4%), and 1 case of IMC (1.4%). All were successfully treated with another session of EMR. One patient (0.9%), who was followed outside of the authors' center, developed metastatic cancer. Overall, CBE-EMR showed good durability because at the end of follow-up, nearly three-fourths (72%) of the patients were in complete remission from intestinal metaplasia (IM), and all (100%) were in complete remission from neoplasia.

The most common complication was esophageal stricture, which occurred in 44 cases (41%), and there was consequent symptomatic dysphagia in 40 patients (38%). Esophageal stenosis was successfully treated with an average of 2.3 (range, 1-9) endoscopic dilation sessions per patient. The radical one-step approach was more commonly associated with this complication compared with the stepwise approach (51% vs 26%, $P < .01$). The authors speculated that the higher surface area involved and the presence of more directly opposing areas of ulceration might be responsible for this observation. Three patients experienced perforations, 2 (1.9% of cases) during EMR and 1 (2.2% of cases) during dilation. One of the first 2 patients died of surgery-related complications. The second patient was managed conservatively, and the third was treated surgically.

The authors concluded that complete EMR for BE-related HGD/IMC was an effective, durable, and relatively safe technique.

Strengths and Weaknesses

The study has numerous strengths. It spans over a decade, includes a large number of patients, and has a long follow-up. All histologic specimens were evaluated by the same 2 expert pathologists. Strict criteria for diagnosis, inclusion, and follow-up were also applied.

The study also has some weaknesses, which the authors acknowledged. These include the retrospective, single-center, single-operator design of the study, the lack of a control group, and the presence of a substantial subset of patients followed elsewhere after EMR.

Comparison With Other Studies in the Field

The study¹⁵ compares well with others in the field. Early studies reporting resection-only modalities^{10,17-19} showed similarly good eradication rates but high

stricture rates. These studies were relatively small and provided only short mid-term results.

The results of this study¹⁵ overlap with 2 recent, large, multicentric, retrospective studies that reported the long-term results of stepwise radical EMR for the treatment of BE-related HGD/IMC.^{8,10} These studies included 169 patients who were followed for a median of 32 months¹⁰ and 90 patients followed for a mean 65 months.⁸ In both studies, high rates of complete HGD/IMC and IM eradications were observed, and this ranged from 90% to 97% and 81% to 85%, respectively. Neoplastic tissue (HGD/IMC) recurred in 2%–6% of cases, whereas non-neoplastic BE recurred in 20%–40%. All were successfully treated with other EMR sessions.^{8,10} In the first study,¹⁰ neoplasia progressed to a fatal outcome in 1 patient under treatment (0.6%). Similar recurrence rates were also observed in recent long-term studies with the hybrid (EMR + RFA) treatment.^{9,11,12} These studies highlight the need for prolonged (more than 5 years) surveillance in dysplastic BE.

In both widespread resection studies,^{8,10} esophageal stricture formation was the most common complication, involving nearly half of patients. This required a 2-fold increase in the number of total endoscopies per patient (mostly for dilations, much less for stent placement or incision therapy), compared with the group that did not experience stricture formation (6 vs 3 endoscopic sessions).^{10,20} In one of the studies, 2 dilations (2.3%) were associated with perforations, of which one required surgery.¹⁰ Barrett's length was associated with both recurrence⁸ and symptomatic stricture formation.¹⁰ In 2 recent studies only extensive (>50% of the circumference) stepwise EMR was associated with stricture formation in half of the patients, whereas focal (<50% of the circumference) EMR had a stricture rate of only 1%–4%,^{13,21} which was similar to the 1%–9% rates observed with the hybrid approach.^{9,11,12}

Comparison With the Hybrid Approach

The high stenosis and complication rates observed with the CBE-EMR treatment have led many authors to question its validity, especially when an alternative exists. According to current major guidelines, the hybrid approach, rather than CBE-EMR, is the modality of choice for treating dysplastic/neoplastic BE, especially for BE > 5 cm.^{1–3} This modality has shown similar overall long-term outcomes with CBE-EMR but with much lower complication rates,^{9,11,12} and it is also technically less demanding. In a recent randomized trial comparing the 2 approaches,²⁰ more strictures developed (88% vs 14%, $P < .001$), more endoscopies per patient were required (6 vs 3, $P < .001$), and more severe complications occurred (24% vs 0%) in the widespread resection group. The other efficacy indicators appeared to be equivalent, even though the study was underpowered for their assessment. Long-term, prospective randomized

trials would be necessary to decisively assess the difference in efficacy between the 2 methods. Yet, the design of such a study appears to be unrealistically large and may be unethical.^{20,22}

Quality of life indicators are also necessary for the overall assessment of the 2 methods, because a lower quality of life might reasonably be expected with the resective-only approach because of higher dysphagia rates. These indicators would thus need to be included in future prospective studies.

Two options are open to the endoscopist who wishes to salvage the CBE-EMR approach. The first, which was taken by the authors in the present study,¹⁵ is to hypothesize a subgroup of patients who would benefit more from the CBE-EMR rather than the hybrid approach. The authors identified some disease characteristics such as multifocal disease, diffuse nodularity, deep BE glands, and regenerative tissue as being more amenable to complete resection. Similar risk factors have been observed in other studies.²³ This hypothesis might be tested in future prospective studies. The other option is to apply stricture-preventing treatments after widespread EMR, which was a possibility only hinted at by the authors. They mentioned performing prophylactic pneumatic dilation 7 days after circumferential EMR in recent years, but no further data were given on the efficacy and risks of this method.¹⁵ The authors also did not comment on other possible stricture-preventing modalities such as oral or site injection of steroids, topical or site injection of mitomycin, placement of biodegradable stents, or application of autologous cells.^{24–28} Our group has anecdotally observed early success with oral viscous budesonide for stricture prevention in this setting. If these methods prove successful in preventing, or even significantly reducing, stricture formation, then they may tip the balance in favor of the tissue-acquiring CBE-EMR therapy.

Finally, considering that currently economic considerations have assumed critical importance, cost-analysis studies are strongly needed.²⁹ Future studies may consider the economic burden associated with the CBE-EMR approach compared with the hybrid one. Which is more cost-effective, focal EMR followed by 3–4 sessions of RFA or widespread EMR followed by 3–4 sessions of dilations? In this last analysis, we also need to include the costs associated with 2% perforation rate during EMR and 2% perforation rate during dilation as well as the related need for surgery, as observed in this study. These considerations might also serve to tip the balance toward one approach or the other in the decision-making process.

Conclusion

In summary, this study shows that long-term eradication of BE and BE-related dysplasia/early neoplasia by means of widespread endoscopic resection is feasible. However, this approach is associated with a high rate of stricture formation, is more technically demanding, and

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