

## Esophageal strictures after extensive endoscopic resection: hope for a better outcome?

Today, endoscopy permits the complete removal of esophageal superficial tumors, even when they cover large areas in an almost circumferential pattern. Use of extensive endoscopic submucosal dissection (ESD) for mucosal squamous cancer has been advocated, because it allows en bloc curative resection of cancers at nominal risk for nodal or distant metastases, provides ad-hoc pathology specimens, and decreases the risk of recurrence.<sup>1</sup> High-grade intraepithelial neoplasia and (sub)mucosal cancer complicating Barrett's esophagus are appealing indications for the "en bloc" radical resection of the lesion and the entire metaplastic mucosa in a single step. This is opposed to the cumbersome repetition of stepwise endoscopic radical resection<sup>2</sup> or the combination of focal resection and multiple sessions of radiofrequency ablation, which the most recent guidelines for management of neoplastic Barrett's esophagus recommend.<sup>3</sup>

However, this more aggressive treatment strategy has a major drawback: it carries a particularly high rate of strictures, mostly related to the extent of circumferential resection. In particular, esophageal strictures were reported to complicate more than 90% of esophageal ESD cases involving the entire lumen circumference.<sup>4</sup> The resultant dysphagia substantially decreased patients' quality of life, requiring multiple sessions of endoscopic dilatation.<sup>5</sup>

Preventive measures or more effective therapies are necessary for handling or avoiding this adverse event. In this issue of *Gastrointestinal Endoscopy*, Sato et al<sup>6</sup> reported that oral corticosteroid therapy dramatically reduced the need for endoscopic balloon dilation (EBD). The authors analyzed a retrospective cohort of patients treated with oral corticosteroids (prednisolone, 30 mg daily, started 2 days post-circumferential ESD, gradually tapered, and discontinued after 8 weeks) and EBD, comparing those cases with patients for whom dilatation was the only method of managing benign esophageal strictures after circumferential ESD. They studied 23 consecutive patients who had undergone complete circumferential ESD for superficial esophageal carcinoma (22 squamous cell carcinomas and 1 adenocarcinoma associated with Barrett's esophagus). Main outcome measurements were the total number of EBD sessions and the total EBD period. Sato

et al showed that patients undergoing corticosteroid therapy required fewer sessions ( $13.8 \pm 6.9$  vs  $33.5 \pm 22.9$ ,  $P < .001$ ) and a shorter management period ( $4.8 \pm 2.3$  vs  $14.2 \pm 17.5$  months,  $P < .01$ ) than the group that only received dilation. In addition, Sato et al<sup>6</sup> reported that late administration of corticosteroids had no beneficial effect. The need for dilation was not, however, suppressed, because 6 to 20 sessions were still reported in the corticosteroid group. This may be because of the relatively low corticosteroid dose used in the study (30 mg prednisolone) and the 2-day delay between ESD and starting oral corticosteroid intake. Low efficacy was observed in

**Oral prednisolone, often combined with early balloon dilation, offers the sole validated and affordable treatment option for preventing intractable postprocedural stricture of the esophagus.**

some Western centers, mainly after the circumferential resection of Barrett's neoplasia (this based on our own unpublished experience).

Corticosteroids are thought to locally inhibit the deposition of collagen and enhance its breakdown, reducing scar tissue formation. Corticosteroids can be administered orally or injected locally. Each approach carries advantages and disadvantages. Oral steroids are easy to administer and, thanks to a stable steroid concentration in the serum, achieve a continuous effect, although at the expense of developing systemic adverse effects.<sup>7</sup> By contrast, the endoscopic injection of triamcinolone is locally effective and avoids the systemic effects and adverse events associated with oral corticosteroid use.<sup>8</sup> Positive results have been shown in peptic strictures, for which the injection site is easy to target. It seems trickier, however, to perform multiple steroid injections in largely denuded resected areas. After extensive mucosal and submucosal resection, what is the target? The muscle itself? The periesophageal fat and mediastinum? And what are the risks of perforation and infection after local injection in a naked muscle?

What other approaches might be taken? Increasing corticosteroid doses to 150 mg/day, as recently suggested?

This scheme looks very promising, but high doses might induce serious side effects. Another option may be to start corticosteroid administration during the perioperative period rather than waiting 48 to 72 hours after resection, as several reports, fearing early refeeding, have proposed. Should other antifibrotic agents and biological agents be tested in this experimental setting? Or should temporary prophylactic stenting with either fully-covered expandable metal stents or biodegradable stents be considered? Prophylactic stenting should be approached with caution, because it may induce other adverse events, including stent migration, bleeding, stent-related strictures, intractable pain, and hyperplastic regenerative changes in the esophageal wall that make neoplastic residues and inflammatory changes difficult to distinguish.

More promising are reports on the innovative transplantation of autologous tissue-engineered epithelial cell mucosal grafts.<sup>9</sup> Ohki et al<sup>10</sup> performed an open-label, single-arm study in which they showed that sutureless endoscopic transplantation of carrier-free cell sheets composed of autologous oral mucosal epithelial cells safely and effectively promoted re-epithelialization of the esophagus after ESD. They collected specimens of oral mucosal tissue from patients with superficial esophageal neoplasms. Epithelial cell sheets were fabricated ex vivo by culturing isolated cells on temperature-responsive cell culture surfaces. After a reduction in temperature, these sheets were endoscopically transplanted directly to the ulcer surfaces in patients who had just undergone ESD. Complete re-epithelialization occurred within a median time of 3.5 weeks. No patients experienced dysphagia, stricture, or other adverse events after the procedure, except 1 patient who displayed a full circumferential ulceration that expanded into the esophagogastric junction. Circumferential resection may therefore require a more systemic approach. Further, the high costs of these techniques may limit their expanded use.

In conclusion, as the availability and effectiveness of extensive mucosal resection in the esophagus improve, the management of postoperative strictures will remain the topic of translational and clinical research. Well-designed prospective trials should help define the best strategy for avoiding adverse events. This will allow for a broader acceptance of the endoscopic total resection of neoplastic and preneoplastic mucosal lesions in a single step, as opposed to the repetition of focal resections and multiple ablation sessions that recent expert consensus recommend. At the present time, however, oral prednisolone,

often combined with early balloon dilation, offers the sole validated and affordable treatment option for preventing intractable postprocedural stricture of the esophagus.

## DISCLOSURE

*The author disclosed no financial relationships relevant to this publication.*

**Pierre H. Deprez**

Department of Hepatogastroenterology  
Cliniques universitaires Saint-Luc  
Université Catholique de Louvain  
Brussels, Belgium

Abbreviations: EBD, endoscopic balloon dilation; ESD, endoscopic submucosal dissection.

## REFERENCES

1. Oyama T, Tomori A, Hotta K, et al. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005;3(Suppl 1): S67-70.
2. Pouw RE, Peters FP, Sempoux C, et al. Stepwise radical endoscopic resection for Barrett's esophagus with early neoplasia: report on a Brussels' cohort. *Endoscopy* 2008;40:892-8.
3. Bennett C, Vakili N, Bergman J, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi Process. *Gastroenterology* 2012;143: 336-46.
4. Ono S, Fujishiro M, Niimi K, et al. Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. *Endoscopy* 2009;41:661-5.
5. American Society for Gastrointestinal Endoscopy. Esophageal dilation. Guidelines for clinical application. *Gastrointest Endosc* 1991;37:122-4.
6. Sato H, Inoue H, Kobayashi Y, et al. Control of severe strictures after circumferential endoscopic submucosal dissection for esophageal carcinoma: oral steroid therapy with balloon dilatation or balloon dilatation alone. *Gastrointest Endosc* 2013;78:248-55.
7. Yamaguchi N, Isomoto H, Nakayama T, et al. Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Gastrointest Endosc* 2011;73:1115-21.
8. Hashimoto S, Kobayashi M, Takeuchi M, et al. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. *Gastrointest Endosc* 2011;74:1389-93.
9. Kanai N, Yamato M, Ohki T, et al. Fabricated autologous epidermal cell sheets for the prevention of esophageal stricture after circumferential ESD in a porcine model. *Gastrointest Endosc* 2012;76:873-81.
10. Ohki T, Yamato M, Ota M, et al. Prevention of esophageal stricture after endoscopic submucosal dissection using tissue-engineered cell sheets. *Gastroenterology* 2012;143:582-8.