COMMENTARY
Print ISSN 2234-2400 / On-line ISSN 2234-2443
Clin Endosc 2014;47:124-126
http://dx.doi.org/10.5946/ce.2014.47.2.124

Open Access

When Is Pre-Emptive Treatment Necessary after Endoscopic Mucosal Resection of Early Esophageal Neoplasm?

Hyung Gil Kim

Division of Gastroenterology, Department of Internal Medicine, Inha University College of Medicine, Incheon, Korea

See "Predictors of Esophageal Stricture Formation Post Endoscopic Mucosal Resection" by Bashar Qumseya, Abraham M. Panossian, Cynthia Rizk, et al., on page 155-161

Endoscopic mucosal resection (EMR) is emerging as the treatment of choice and an alternative to esophagectomy in the treatment of Barrett's esophagus with early neoplasia and superficial esophageal cancer limited to the mucosal layer.[1] EMR of larger lesions requires piecemeal resection which allows the risk of higher local recurrence than in cases with *en bloc* resection. Endoscopic submucosal dissection (ESD) has been successfully applied for the treatment of early esophageal cancer including squamous cell carcinoma and Barrett's adenocarcinoma (BA).[2]

Esophageal strictures are among the most common and problematic complications of EMR and endoscopic ablation therapy in early esophageal neoplasm and the leading cause of long-term morbidity.[3-6] Symptomatic stricture formation has been reported after the use of EMR, photodynamic therapy, and combination therapy in 13% to 50% of patients.[3-6]

Esophageal strictures often require multiple dilations to resolve dysphagia; however, risk factors for esophageal stricture and dysphagia have not been clearly defined. Their determination would make it possible to identify those patients who may benefit from early pre-emptive intervention such as prophylactic dilation.[7]

In an early study, Katada et al.[8] reported that resection of >75% of the esophageal circumference was associated with a high rate of stricture formation in patients with superficial esophageal squamous cell carcinoma (SESCC) and that mucosal defects longer than 30 mm were associated with greater stenosis severity. Thus, they emphasized that removal of excess mucosa should be avoided.

Mizuta et al.[9] analyzed regional and technical factors between cases with and without post-ESD stenosis in SESCC. Regional factors included location, endoscopic appearance, longitudinal and circumferential tumor size, invasion depth, and lymphatic and vessel invasion. The technical factors included longitudinal and circumferential sizes of mucosal defects, muscle disclosure and cleavage, perforation, and *en bloc* resection. The longitudinal and circumferential sizes of the tumors and mucosal defects were significant predictive factors for post-ESD stenosis. Receiver operating characteristic analysis showed the highest sensitivity and specificity for a circumferential mucosal defect size of more than 71% and a circumferential tumor size of more than 59%.

Another study on SESCC reported that in addition to longitudinal and circumferential diameters of the resected specimens and the proportion of extension to the whole circumference of the lumen, histological depth and procedure time were also associated with stricture formation.[10] In recent studies on SESCC, the rate of post-ESD stricture was reportedly 5% to 18%.[10,11]

Chung et al.[7] reported complete Barrett's excision (CBE) by stepwise endoscopic resection in short-segment Barrett's high-grade dysplasia and BA. In this study, esophageal dilation was required in 33% of cases. Independent risk factors for requiring dilation included the number of mucosal resections during the index procedure and the maximal extent of the Barrett's segment. Additionally, circumferential Barrett's excision in a single session increases the likelihood of esophageal stricture.

Lewis et al.[12] reported factors associated with esophageal stricture formation after EMR monotherapy for neoplastic Barrett's esophagus. Resection of >50% of the circumference was strongly associated and a tobacco use history ≥25 pack-

Received: February 5, 2014 **Accepted:** February 12, 2014

Correspondence: Hyung Gil Kim
Division of Gastroenterology, Department of Internal Medicine, Inha University College of Medicine, 366 Seohae-daero, Jung-gu, Incheon 400-103, Korea
Tel: +82-32-890-2548, **Fax:** +82-32-890-2549, **E-mail:** kimhg@inha.ac.kr

years showed a tendency toward stricture formation. Total number of pieces resected and number of EMR sessions were also associated with stricture formation on univariate analysis.

In this present study by Qumseya et al.,[13] among 136 patients with adenocarcinoma or dysplasia of Barrett's esophagus, 27% had esophageal stricture. Most patients underwent EMR followed by ablation therapy. The size of the excised lesion and the number of lesions removed in the index procedure were associated with an increased risk of developing stricture. The number of EMR sessions, EMR methods, and additional ablation modalities after EMR were not significantly associated with stricture formation. These data suggest that EMR followed by ablation therapy may have a similar rate of stricture formation as that of CBE.

These authors did not have reliable information about the resected circumferential extent of the esophagus or the vertical length of Barrett's segment. The maximal diameter of the resected specimen and the number of resections were thought to correlate with the circumferential area of the resection. However, pre-emptive therapy for stricture may require more measurable predictors of stricture. The authors suggest that EMR in separate sessions is advantageous in reducing the risk of stricture formation when the lesions appear to be low risk and when the patient is young and a nonsmoker with no family history of esophageal cancer. As they mentioned, this requires prospective evaluation.

The pathogenesis of post-EMR esophageal stricture may be multifactorial with patient-related and technical factors.[7,14] The diathermy setting, procedure time, muscle layer injury, EMR or ESD, additional ablation therapy for Barrett's neoplasm, and longitudinal and circumferential excision extents are potential modifiable technical aspects. Smoking status, degree of esophageal mucosal exposure to refluxed gastric acid content, esophageal luminal diameter (upper esophagus and esophagogastric junction are narrower than the mid-esophagus) may be patient-related factors.[7]

There are some differences in the definitions of esophageal stricture among studies. In some studies, esophageal stenosis was defined when a standard endoscope (9.8 mm in diameter) failed to pass through the stenosis,[9] while other authors defined stricture as an endoscopically identified stenosis producing patient complaints of dysphagia.[13] In the present study, the author defined esophageal stricture as a narrowing of the esophageal lumen regardless of the presence of dysphagia and classified as mild, moderate, and severe according to resistance to the passage of a standard endoscope (9.8 mm in diameter). Some authors reported that multiple patients with stricture >10 mm in diameter had clinically significant dysphagia that could be caused by motility disorders that occurred after EMR or ablation therapy as well as mechanical obstruction.[14] Further studies may be needed to define a practical and widely acceptable definition of esophageal stricture.

Interestingly, smoking may be associated with stricture formation following EMR or ablation therapy for early neoplasm of the esophagus. Some authors reported that patients with a heavy smoking history tended to experience stricture formation,[12] whereas other authors reported that current or ex-smokers were at a lower risk of developing stricture compared with patients who had never smoked.[14]

Pre-emptive therapy for post-EMR esophageal stricture can be programmed in high-risk groups of patients, especially when up to 75% of the esophageal circumference is resected in a single session. Although endoscopic balloon dilation has been a treatment of choice, esophageal stricture following semicircular or complete circular ESD is sometimes refractory to endoscopic dilation and should be treated by multiple weekly pre-emptive endoscopic balloon dilation.[11] The endoscopic injection of triamcinolone, a long-acting steroid derivative, may prevent esophageal stricture after widespread ESD.[15] The use of oral prednisolone reduced the number of endoscopic balloon dilation sessions after complete circular ESD (15.6 vs. 1.7).[12] Ohki et al.[16] produced tissue-engineered cell sheets and investigated the safety and efficacy of endoscopic transplantation of tissue-engineered autologous oral mucosal epithelial cell sheets for preventing stricture formation after semicircular ESD. Eight of nine patients did not experience dysphagia or stricture following the procedure.

In conclusion, esophageal stricture and dysphagia following endoscopic resection of early esophageal neoplasm decrease patient quality of life. Patient, regional, and technical factors of esophageal stricture formation should be considered and prophylactic therapy following semi-circumferential or circumferential endoscopic resection is recommended. Prophylactic therapy to prevent dysphagia and stricture formation could be performed with scheduled endoscopic dilation, triamcinolone injection, tissue-engineered cell sheet transplantation, and oral prednisolone administration.

Conflicts of Interest

The author has no financial conflicts of interest.

REFERENCES

1. Fujishiro M. Perspective on the practical indications of endoscopic submucosal dissection of gastrointestinal neoplasms. World J Gastroenterol 2008;14:4289-4295.
2. Takahashi H, Arimura Y, Masao H, et al. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video). Gastrointest Endosc 2010;72:255-264.
3. Chennat J, Konda VJ, Ross AS, et al. Complete Barrett's eradication endoscopic mucosal resection: an effective treatment modality for high-grade dysplasia and intramucosal carcinoma--an American single-center experience. Am J Gastroenterol 2009;104:2684-2692.

4. Vilsteren FG, Pouw RE, Seewald S, et al. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicenter randomized trial. Gut 2011;60:765-773.
5. Prasad GA, Wu TT, Wigle DA, et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. Gastroenterology 2009;137:815-823.
6. Yachimski P, Puricelli WP, Nishioka NS. Patient predictors of esophageal stricture development after photodynamic therapy. Clin Gastroenterol Hepatol 2008;6:302-308.
7. Chung A, Bourke MJ, Hourigan LF, et al. Complete Barrett's excision by stepwise endoscopic resection in short-segment disease: long term outcomes and predictors of stricture. Endoscopy 2011;43:1025-1032.
8. Katada C, Muto M, Manabe T, Boku N, Ohtsu A, Yoshida S. Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. Gastrointest Endosc 2003;57:165-169.
9. Mizuta H, Nishimori I, Kuratani Y, Higashidani Y, Kohsaki T, Onishi S. Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer. Dis Esophagus 2009;22: 626-631.
10. Ono S, Fujishiro M, Niimi K, et al. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. Gastrointest Endosc 2009;70:860-866.
11. Isomoto H, Yamaguchi N, Minami H, Nakao K. Management of complications associated with endoscopic submucosal dissection/endoscopic mucosal resection for esophageal cancer. Dig Endosc 2013;25 Suppl 1:29-38.
12. Lewis JJ, Rubenstein JH, Singal AG, Elmunzer BJ, Kwon RS, Piraka CR. Factors associated with esophageal stricture formation after endoscopic mucosal resection for neoplastic Barrett's esophagus. Gastrointest Endosc 2011;74:753-760.
13. Qumseya B, Panossian AM, Rizk C, et al. Predictors of esophageal stricture formation post endoscopic mucosal resection. Clin Endosc 2014; 47:155-161.
14. Prasad GA, Wang KK, Buttar NS, Wongkeesong LM, Lutzke LS, Borkenhagen LS. Predictors of stricture formation after photodynamic therapy for high-grade dysplasia in Barrett's esophagus. Gastrointest Endosc 2007;65:60-66.
15. Hashimoto S, Kobayashi M, Takeuchi M, Sato Y, Narisawa R, Aoyagi Y. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. Gastrointest Endosc 2011;74:1389-1393.
16. Ohki T, Yamato M, Ota M, et al. Prevention of esophageal stricture after endoscopic submucosal dissection using tissue-engineered cell sheets. Gastroenterology 2012;143:582-588.