ORIGINAL ARTICLE

Technical feasibility of endoscopic submucosal dissection for local failure after chemoradiotherapy or radiotherapy for esophageal squamous cell carcinoma

Keiichiro Nakajo, MD, Yusuke Yoda, MD, Keisuke Hori, MD, PhD, Kenji Takashima, MD, Kensuke Sinmura, MD, PhD, Yasuhiro Oono, MD, Hiroaki Ikematsu, MD, PhD, Tomonori Yano, MD, PhD

Kashiwa, Japan

Background and Aims: Salvage endoscopic submucosal dissection (ESD) after chemoradiotherapy can be technically difficult as a result of radiation-induced fibrosis. We aimed to evaluate the technical feasibility of ESD for local failure after chemoradiotherapy for esophageal squamous cell carcinoma (ESCC) and for other primary lesions within the irradiation field.

Methods: Consecutive patients treated with ESD for superficial ESCC between December 2009 and May 2017 were investigated retrospectively and stratified into group A (33 patients, 35 lesions; local failure at the primary site after chemoradiotherapy), group B (25 patients, 34 lesions; second primary lesions within the irradiation field), and group C (550 patients, 596 lesions; radiotherapy-naïve superficial ESCC). We evaluated procedural success rate, en bloc resection rate, 1-year local relapse-free survival (LRFS) rate, procedure time, and incidence of major adverse events.

Results: The rates of procedural success and en bloc resection, respectively, were significantly lower in group A (89%, 86%) than in groups B (100%, 100%) and C (100%, 98%). The 1-year LRFS rates were 86%, 100%, and 99% in groups A, B, and C, respectively, and significantly lower in group A than in group C. Serious adverse events including perforation were not observed in groups A and B; perforation occurred only in group C (2.8%).

Conclusions: ESD is technically feasible in patients with local failure, especially as initial salvage treatment and as treatment for second primary lesions within the irradiation field. (Gastrointest Endosc 2018;■:1-10.)

INTRODUCTION

Although definitive chemoradiotherapy (CRT) is a curative treatment option for esophageal cancer,[1–4] local failure is seen in 32% to 50% of patients receiving definitive CRT[5,6]; salvage treatment for local failure is required in these patients. We previously reported that salvage EMR is a curative treatment option when the residual or recurrent tumor is localized and superficial, without lymph-node or distant metastasis.[7–9] However, for lesions with severe fibrosis in the submucosal layer after CRT, the en bloc and complete resection rates of EMR are relatively low.[7–9] Endoscopic submucosal dissection (ESD), developed in the early 2000s, aims to improve the curability of widespread superficial esophageal cancer managed via EMR.[10] ESD has been widely adopted due to its effectiveness and safety, because it facilitates en bloc resection for superficial esophageal cancer and reduces the risk of local recurrence.[10–12] Moreover, ESD is used as salvage endoscopic treatment for local failure

Abbreviations: CT, computed tomography; CRT, chemoradiotherapy; DSS, disease-specific survival; ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; LRFS, local relapse-free survival; OS, overall survival; PDT, photodynamic therapy; RT, radiotherapy.

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Current affiliation: Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan.

Reprint requests: Tomonori Yano, Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan.

If you would like to chat with an author of this article, you may contact Dr Yano at toyano@east.ncc.go.jp.

after CRT.[7–9,13–15] However, because radiation-induced fibrosis is often noted in the submucosal layer after CRT, salvage ESD is considered a technically difficult procedure with increased risk of severe adverse events, including bleeding or esophageal perforation.[7–9,13–15] Few reports have evaluated the effectiveness and safety of salvage ESD for residual or recurrent tumors after CRT.[13,14]

This study aimed to clarify the effectiveness and safety of salvage ESD in patients with residual or recurrent tumors after CRT. We compared salvage ESD for local failure after CRT, ESD for second primary lesions after CRT, and conventional ESD.

PATIENTS AND METHODS

Study design and definitions

We analyzed consecutive patients treated with ESD for superficial esophageal squamous cell carcinoma (ESCC) between December 2009 and May 2017 at the National Cancer Center Hospital East in Kashiwa, Japan. Patients who had undergone ESD for ESCC previously were excluded. The patient cohort was stratified into 3 groups: group A, salvage ESD after CRT or radiotherapy (RT); group B, ESD for second primary lesions after CRT or RT; and group C, conventional ESD for RT-naïve lesions. Salvage ESD was defined as ESD for local failure after CRT or RT. Local failure was defined as a residual lesion just after CRT, or as local recurrence after complete response with CRT or RT. Second primary lesions were defined as lesions developed within the irradiation field at a different site than that of the primary tumor noted before CRT. Conventional ESD was defined as endoscopic resection for RT-naïve superficial ESCC. All recurrent lesions were diagnosed through endoscopic observation and confirmed histologically according to the presence of cancer cells in the biopsy specimens. Definitive CRT comprised external beam irradiation of 50 Gy or more, with concurrent fluoropyrimidine-based chemotherapy with or without a platinating agent. RT comprised external beam irradiation of 50 Gy or more, without concurrent chemotherapy.

The indication criteria for ESD were (1) no lymph-node or distant metastasis detected on computed tomography (CT); (2) lesion without deep ulceration; (3) endoscopy-based tumor staging indicating superficial invasion limited to slightly within the submucosal layer; and (4) written informed patient consent. When identifying a locally recurrent lesion during follow-up endoscopy after CRT, we evaluated tumor depth using imaging modalities such as conventional endoscopy (white light view and narrow-band imaging) and EUS, and lymph nodes and distant metastasis with CT. If we found it difficult to estimate tumor depth using conventional endoscopic observation, we used EUS. Esophagectomy, photodynamic therapy (PDT), or chemotherapy were considered when we judged that the recurrent lesion infiltrated the SM2 (200 μm from the muscularis mucosae or deeper), even if no lymph-node or distant metastasis was detected on CT. Tumor depth was evaluated according to the Japanese Classification of Esophageal Cancer.[16] We selected patients for inclusion in group B thus: (1) we examined the endoscopic records obtained before CRT and identified the primary lesion site to confirm that the recurrent lesion existed outside this area; (2) on endoscopic observation, the recurrent lesions were found outside the area of the scar of the lesion treated with CRT, (3) to the extent that the irradiated area could be identified, we could confirm that the recurrent lesions were within the irradiation field.

This study was approved by the Institutional Review Board of the National Cancer Center Japan (approval no. 2016-268) and carried out according to the Epidemiological Study Guideline issued by the Japan Ministry of Health, Labor, and Welfare.

Procedure for ESD

We performed ESD using a single accessory channel upper GI endoscope (GIF-H260Z, GIF-Q260J; Olympus, Tokyo, Japan) with a transparent cap (elastic touch, slit and hole, type F; Top, Tokyo, Japan). We used a high-frequency generator with an automatically controlled system (VIO-300D, ERBE Electromedicine, Tübingen, Germany) set to Endocast I mode, with Effect 2 for circumferential incision and swift coagulation, and with Effect 3 (40 W) for dissection of the submucosal layer. Before ESD, chromoendoscopy was performed after directly instilling iodine solution (2%) through the endoscope's biopsy channel. The tumor border was marked by making spots around the periphery of the lesion using a Dual-Knife (KD-650Q; Olympus). After a mixture of 0.4% sodium hyaluronate solution (Mucous; Johnson and Johnson Medical, Tokyo, Japan) diluted with epinephrine and some indigo carmine was injected into the submucosal layer around the tumor to lift the lesion, a circular incision of the mucosa was made with the Dual-Knife, and the submucosal layer was dissected. However, severe submucosal fibrosis and scarring induced by radiation were often present in patients indicated for salvage ESD, which made it difficult to create the submucosal fluid cushion and lift the lesion. In such cases, we approached the lesion as closely as possible using an endoscope with a transparent cap, and dissected the submucosal layer using high-voltage current emitted from the tip of the Dual-Knife. Because the tip of the transparent cap is thin, approaching the lesion is easy even in the presence of severe fibrosis and in narrow locations with reduced accessibility (Fig. 1). In patients who have undergone CRT for esophageal cancer, the esophageal wall is often thin. In conventional ESD, we usually dissect the middle of the submucosal layer. However, in salvage ESD, we try to dissect just under the mucosa using the Dual-Knife to reduce the perforation risk.