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【 CASE REPORT 】

Salvage Endoscopic Submucosal Dissection for Local Recurrence of Superficial Esophageal Squamous Cell Cancer after Photodynamic Therapy

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Abstract:

Photodynamic therapy is useful as organ-preservation salvage therapy for residual recurrence of esophageal squamous cell carcinoma after chemoradiation therapy. However, the high residual recurrence rate of photodynamic therapy poses a problem. We herein report a patient who underwent photodynamic therapy for recurrence of superficial esophageal squamous cell carcinoma after chemoradiation therapy. The patient later exhibited another episode of recurrence of superficial esophageal squamous cell carcinoma, and R0 curative resection was obtained with endoscopic submucosal dissection. This suggests that endoscopic submucosal dissection may be an effective treatment option that can achieve R0 resection even for residual superficial cancer after salvage photodynamic therapy.

Key words: chemoradiation therapy, endoscopic submucosal dissection, esophageal squamous cell cancer, photodynamic therapy, salvage therapy

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Introduction

While salvage surgical resection is commonly performed for residual recurrence of esophageal squamous cell carcinoma (ESCC) after chemoradiation therapy (CRT), the procedure is highly invasive, and exist perioperative complications including mortality (1, 2). Recently, the usefulness of salvage photodynamic therapy (PDT) for treating residual recurrence of ESCC after CRT has been reported. In Japan, this procedure is now covered by insurance. Although PDT is considered relatively noninvasive and effective, it is associated with a high rate of residual recurrence after treatment (3, 4). Furthermore, there is no established treatment strategy for residual recurrence after PDT.

We herein report a case in which R0 resection was achieved by endoscopic submucosal dissection (ESD) for recurrence of superficial ESCC (SESCC) that occurred after PDT was performed for post-CRT cancer recurrence.

Case Report

The patient was an 80-year-old man who had been diagnosed with advanced cancer of the lower thoracic esophagus (cT2N0M0, cStage II) by his previous doctor (Fig. 1). Esophagogastroduodenoscopy (EGD) showed a 16-mm excavated lesion with marginal elevation (0-III). The lesion had a small ulcer with a white coat (arrowheads in Fig. 1). Since the patient refused surgical resection, radical CRT (50.4 Gy, 5-FU 1,000 mg/m^2+CDDP 75 mg/m^2: 2 cycles) was administered, and complete response (CR) was achieved.

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Eight years later, EGD showed a 20-mm excavated lesion in the lower thoracic esophagus. The lesion showed poor distensibility of the wall, wall thickening, and a Lugol voiding area. A histological analysis of the biopsy specimen revealed squamous cell carcinoma (SCC), and the patient was diagnosed with post-CRT recurrence of ESCC with estimated submucosal deep invasion (SM2) (Fig. 2a).

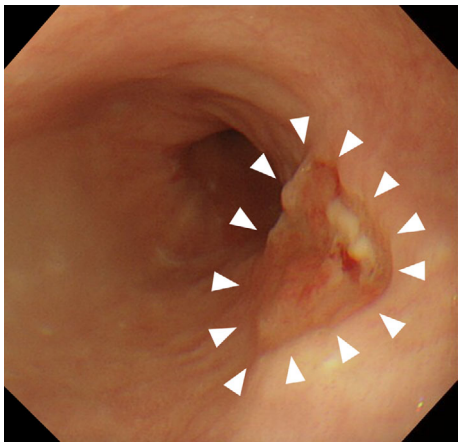

Figure 1. EGD showed a 16-mm 0-III lesion in the lower thoracic esophagus.

Contrast-enhanced computed tomography (CT) showed no obvious metastatic foci. Salvage surgical resection was considered highly challenging, as additional radiation was deemed impossible after radical CRT and due to the patient's advanced age. In addition, the excavated lesion was not indicated for ESD because the lesion was suspected of being submucosal cancer with deep SM invasion. Therefore, the patient was referred to our hospital.

As deep submucosal invasion was suspected, ESD was not indicated, and he underwent salvage PDT. Talaporfin sodium (Meiji Seika Pharma, Tokyo, Japan) was injected intravenously at 4 mg/m^2, and the lesions were irradiated with PD-LASER (Meiji Seika Pharma) at 100 mW/m^2 for 11 minutes. An ulcer formed at the tumor site after salvage PDT, which showed scarring three months later, and EGD demonstrated a complete response by Lugol chromoendoscopy and magnified endoscopy with blue-laser imaging (BLI) (Fujifilm, Tokyo, Japan).

Eighteen months after salvage PDT, EGD revealed a 12-mm slightly depressed lesion with irregular margins at the PDT scar site in the lower thoracic esophagus (Fig. 2b). Most of the depressed lesion was covered with cloudy epithelium. Magnified endoscopy with BLI revealed the presence of abnormal blood vessels with loop-like formation in

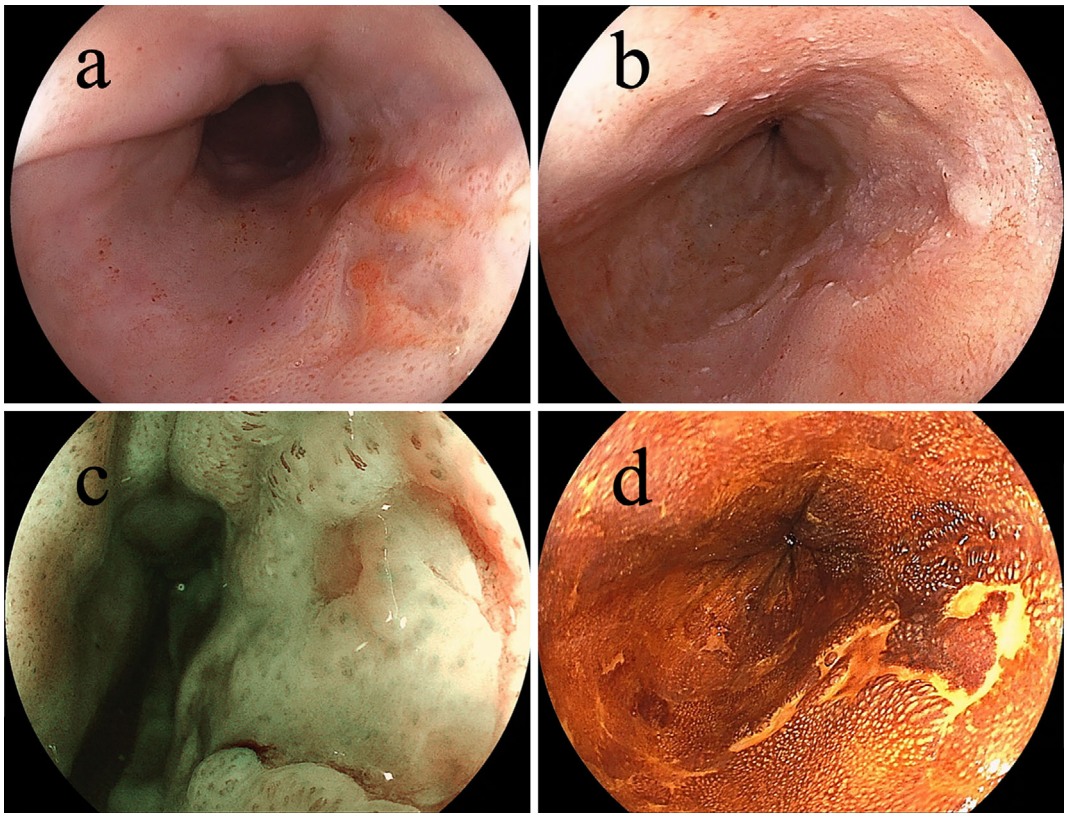

Figure 2. a: Before PDT, the lower thoracic esophagus exhibited an SM tumor-like protrusion with poor extension and wall thickening. b: Eighteen months after PDT, a 12-mm irregular depressed lesion was found at the same site. c: Magnified endoscopy with BLI showed a brownish area, but no vessels with severe irregularity were observed. d: Lugol staining showed an unstained area, suggesting SESCC. PDT: photodynamic therapy, BLI: blue-laser imaging, SESCC: superficial endoscopic squamous cell carcinoma, SM: submucosa

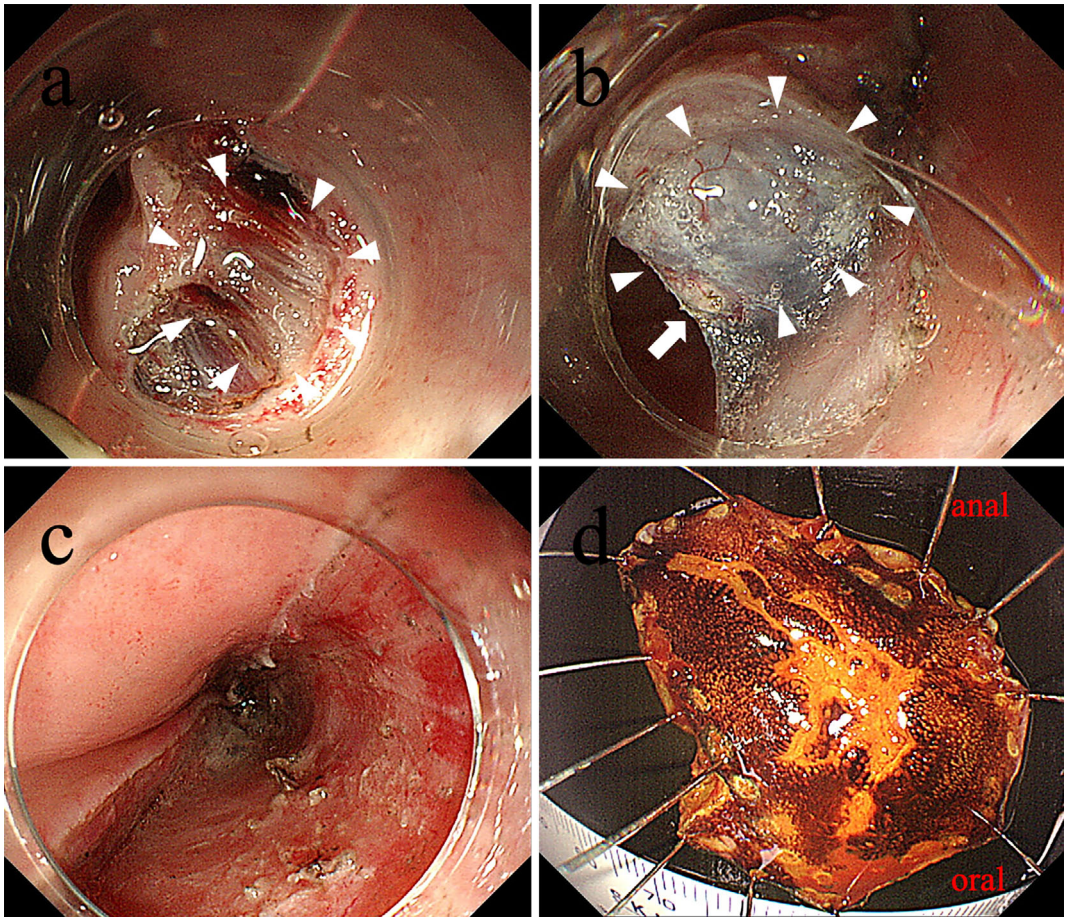

Figure 3. **a: Moderate fibrosis was observed in part of the submucosal layer during the peripheral incision (arrowhead: tissue thought to be fibrosis). b: Severe fibrosis was not observed. Cloudy submucosa (arrowheads) with an esophageal gland proper (arrow) were seen during submucosal dissection. C: ESD was completed safely with no damage to the muscle layer. d: ESD specimen: En bloc resection including the marking was possible.**

the subepithelial layer (Fig. 2b, c). Most of the lesion showed a Lugol voiding area, and SCC was diagnosed by a biopsy (Fig. 2d). In addition, part of the biopsy specimen indicated SM invasion by SCC. Based on a comprehensive evaluation of these clinicopathological findings, we suspected that the tumor was SESCC that had invaded the submucosa slightly.

Contrast-enhanced CT showed no obvious metastatic lesions. As the patient did not desire salvage surgical resection or a second salvage PDT procedure, ESD was performed. The intraoperative findings showed white cloudiness of submucosal tissue on the oral side of the lesion, which was suspected to be mild fibrosis (Fig. 3a, b). Despite the presence of submucosal fibrosis, local injection into the SM layer created sufficient swelling that enabled en bloc resection of the lesion without any difficulty (Fig. 3c, d).

Histology of the ESD specimens showed that the horizontal tumor extent corresponded to the Lugol voiding area, and the tumor cells had invaded the shallow layer of the SM (T1b-SM2 350 μm). There was no vascular invasion, and the vertical and horizontal margins were negative (R0 resection) (pT1bN0M0, pStage I, Fig. 4a). Elastica van Gieson (EVG) staining showed thickening of the muscularis mucosa and moderate fibrosis from the lamina propria to the submucosa (Fig. 4b). In addition, a mixture of relatively sparse collagen fibers and elastic fibers was found in the SM fibrotic tissue. The patient did not receive any additional treatment, and we performed close surveillance every four months using EGD and CT. He is currently alive without recurrence 24 months after ESD.

Discussion

We identified two important clinical issues. First, we experienced a rare case of local recurrence of SESCC after salvage PDT. Second, this case suggests that ESD may be an effective option to enable less-invasive R0 resection for recurrent tumor lesions after salvage PDT.

Salvage surgical resection is usually performed for local residual recurrence of ESCC following CRT (1, 2). Long-term outcomes (3- to 5-year postoperative survival rates) are poor, at around 30%, the incidence of surgery-related complications is high, and the in-hospital mortality rate is 10-15% (5). Given the invasiveness of surgical resection, CRT

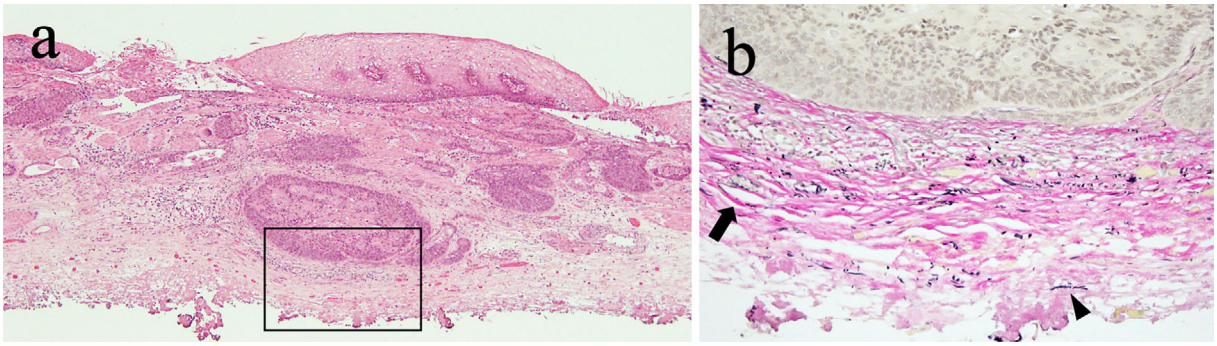

Figure 4. **a: Hematoxylin and Eosin staining: Intraepithelial carcinoma that corresponded to the Lugol voiding area with a thickened and intertwined muscularis mucosa was observed. The invasion depth was T1b (350 μm from the muscularis mucosa), lymphatic and venous involvement was negative, and the horizontal and vertical stumps were negative. b: Elastica van Gieson staining: A mixture of collagen and elastic fibers with loose connective tissue was observed near the specimen's vertical stump. Arrowhead: elastic fibers (black), arrow: collagen fiber (pink)**

is often selected when patients are unable to tolerate surgery due to advanced age or co-morbidities, as in the present case, where the patient refused surgery.

Salvage PDT has been reported to be a useful and minimally invasive therapy for residual recurrence of ESCC following CRT. The criteria for application are (a) no lymph node metastasis after CRT; (b) residual recurrence after CRT no deeper than the superficial muscularis propria; (c) no desire by the patient to undergo or no ability of the patient to tolerate surgical resection due to comorbidities; and (d) endoscopic resection not possible due to the presence of ulcers or fibrosis inside the lesion (3). With regard to the therapeutic outcomes of PDT for residual recurrent cancer after CRT, a CR rate of 59.5% and a 5-year progression-free and overall survival rate of 20.7% have been reported (3).

The residual recurrence rate after salvage PDT is high, and local control is often poor, but there have been few reports concerning residual recurrent lesions after salvage PDT. To our knowledge, no case reports exist describing the endoscopic images and treatments for early or superficial recurrent tumors. We therefore believe that the present case will be significant because we detected a recurrent tumor of superficial cancer following salvage PDT and achieved R0 resection by performing ESD without surgical resection.

One indication for salvage PDT for ESCC is when endoscopic resection is deemed impossible due to ulcer scarring or fibrosis inside the lesion. A previous report on ESD for SESCC after CRT indicated that while there was thickening of the muscularis mucosa, severe fibrosis in the SM was uncommon (6). In the present case, although PDT was performed in addition to CRT, potentially leading to an extremely high degree of SM white fibrosis, and cloudiness of the SM tissue was observed during ESD, the fibrosis was not severe. Furthermore, a local injection created sufficient swelling of the SM layer that enabled dissection of the SM tissue (Fig. 3a, b). There were no ESD-related complications, and the ESD was completed safely.

Histologically, the SM layer of the resected specimen showed uniform fibrosis of the SM layer (Fig. 4a), and instead of dense connective tissue composed of thick collagen fibers, we found loose connective tissue composed of thin entangled collagen and elastic fibers (Fig. 4b, arrow and arrowhead, respectively). We surmise that one reason why the SM layer could be dissected was the lack of dense connective tissue and presence of loose connective tissue in the SM layer of the lesion site. In the esophagus, endoscopic resection causes severe fibrosis. This fibrosis can make repeated R0 endoscopic resection difficult to achieve and significantly increase the risk of perforation (7, 8). However, the level of fibrosis in the surrounding tissues caused by PDT is unclear (9). Unlike surgery or endoscopic resection, CRT and PDT are treatments that do not directly damage tissue but rather induce necrosis in tumor cells. Hence, the mechanism may induce the organization of loose connective tissue. If a "complete scar" is a regular scar with a large amount of collagen fibers, in the present case, ESD may have been successful due to the formation of an "incomplete scar" that had a mixture of collagen fibers and elastic fibers.

Although there have been a few cases in which salvage surgical resection was performed for residual recurrent tumor after salvage PDT (3), patients with a history of having undergone CRT or PDT, as in the present case, are often unable to tolerate surgery or else refuse the surgery (3). Furthermore, although additional PDT would be minimally invasive, it does not ensure success in cases with residual recurrence after the same PDT treatment. In the present case, the SM fibrosis after salvage PDT was not severe, and R0 resection of SESCC was possible with ESD. This suggests that ESD may be an effective treatment option for residual recurrence of superficial tumors lesions after salvage PDT (1-3).

While there have been many reports on the relationship between morphological changes of microvessels and tumor invasion depth (10-13), these studies excluded patients who had undergone chemotherapy or radiation therapy, as their superficial vessels had been deformed by the therapies.

Thus, how the microvascular morphology relates to the invasion depth in SESCC after CRT, such as in the present case, is unclear. In fact, in the present case, it was not possible to make detailed observations of superficial microvessels at the lesion site with preoperative magnifying observation. It was thus believed to be difficult to accurately predict the depth of SESCC after CRT even using magnifying endoscopy. ESD has a considerable advantage over PDT in that it can confirm histological staging of the invasive depth using resected specimens.

We encountered a rare case of residual recurrence of SESCC following PDT in which R0 resection was achieved safely with ESD. Although further case studies are needed, this case suggests that ESD may be an effective treatment option to enable less-invasive R0 resection for residual recurrence of SESCC after salvage PDT.

The authors state that they have no Conflict of Interest (COI).

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