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CASE REPORT

Curative endoscopic submucosal dissection for esophageal squamous cell carcinoma after chemoradiotherapy for pharyngeal cancer: A case report

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Abstract

BACKGROUND

Esophageal squamous cell carcinoma (ESCC) is often managed with surgery, which is the first-line treatment option for stage I–III lesions. However, definitive chemoradiotherapy (dCRT) is associated with a recurrence rate of 30% in stage I ESCC and higher rates in advanced-staged lesions. However, several patients prefer dCRT because their general condition is poor. Salvage therapies, including esophagectomy and endoscopic resection [endoscopic submucosal dissection (ESD)/endoscopic mucosal resection], are important for residual or recurrent tumors that develop after dCRT. Esophagectomy can have curative potential. However, it has high complication and mortality rates. Therefore, ESD is a safer alternative.

CASE SUMMARY

A Japanese man in his 70s was concurrently diagnosed with right hypopharyngeal cancer (T2N1M0, cStage III), left oropharyngeal cancer (T1N0M0, cStage I), and left hard palate cancer (T1N0M0, cStage I). Esophagogastroduodenoscopy (EGD) revealed a 20 mm reddish 0-Is+IIb lesion in the upper thoracic esophagus, with an invasion depth of SM2. The lesion was diagnosed as an esophageal moderately differentiated squamous cell carcinoma (T1bN0M0, cStage I). As the pharyngeal cancers were in advanced stages, chemoradiotherapy (docetaxel and cisplatin with a radiation dose of 66 Gy) was prioritized. Post-chemoradiotherapy

EGD showed that the lesion had flattened into a 0-IIb lesion, thereby indicating a reduced invasion depth (epithelium or lamina propria mucosa). ESD achieved *en bloc* and histologically confirmed curative resection. At 22 months after ESD, the patient did not present with signs of recurrence.

CONCLUSION
This case emphasizes that ESD can be successfully utilized as a salvage treatment for ESCC after chemoradiotherapy for otolaryngological cancers.

Key Words: Esophageal squamous cell carcinoma; Salvage therapy; Pharyngeal cancer; Otolaryngological cancer; Chemoradiotherapy; Case report

Core Tip: The current case highlights the successful application of endoscopic submucosal dissection (ESD) as a salvage therapy for esophageal squamous cell carcinoma after chemoradiotherapy for pharyngeal cancer. This case underscores the potential of ESD to achieve curative resection in patients with complex malignancies and emphasizes the importance of further research to validate its efficacy and safety in similar contexts.

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INTRODUCTION

Patients with stage I–III esophageal squamous cell carcinoma (ESCC) are candidates for surgery, which is the first-line treatment. However, several patients, even those with lesions in operable stages, avoid surgery because their general condition is poor. This then leads to the adoption of definitive chemoradiotherapy (dCRT). However, the prevalence rate of local residual recurrence after dCRT is approximately 30% in stage I lesions[1] and is higher in lesions in more advanced stages[2]. These details are considered important because the prognosis of patients with ESCC who exhibit local failure is poor.

Salvage therapies, such as esophagectomy and endoscopic resection [endoscopic submucosal dissection (ESD)/endoscopic mucosal resection (EMR)], are essential for treating local recurrence or residual tumors after dCRT in patients with ESCC. Esophagectomy has curative potential. However, it has high complication (65.1%) and mortality (7.9%) rates [3]. In contrast, ESD is less invasive and has favorable outcomes[4]. Recent studies support the feasibility of salvage ESD for local failure after dCRT. Based on this finding, salvage ESD has acceptable long-term outcomes and is a potentially safer, curative option in cautiously selected cases[5].

ESCC is associated with synchronous and metachronous malignancies[6]. The prevalence rate of squamous cell carcinoma of the head and neck is 6.7%[7]. In cases of ESCC concomitant with otolaryngological cancer, the treatment of otolaryngological cancer is often prioritized. However, several patients avoid surgery due to the abovementioned reason and receive nonsurgical therapies, such as radiation therapy and chemoradiotherapy (CRT). The contribution of CRT for concomitant primary cancers on the feasibility of salvage therapy in patients with ESCC remains unknown. There are no reports showing the achievement of complete resection *via* salvage endoscopic resection after CRT for otolaryngological cancer. Herein, we report a patient with ESCC who underwent ESD and achieved complete resection after CRT for otolaryngological cancer.

CASE PRESENTATION

Chief complaints

A Japanese man in his 70s was referred to our institution due to pharyngeal discomfort lasting for 6 months.

History of present illness

He did not present with comorbidities.

History of past illness

He had no significant medical and personal or family history.

Table 1 The patient's serum tumor markers

Complete blood count			Biochemistry test			Blood urea nitrogen	12.2	mg/dL
White blood cell	6700	/μL	Total protein	7.3	g/dL	Creatinine	00.74	mg/dL
Red blood cell	396	× 10^4 /μL	Albumin	3.8	g/dL	Estimated glomerular filtration rate	80.3	
Hemoglobin	13.3	g/dL	Aspartate aminotransferase	35	U/L	Na	143	mEq/L
Mean corpuscular volume	99.7	fL	Alanine aminotransferase	14	U/L	K	4.0	mEq/L
Platelet	26.9	× 10^4 /μL	Lactate dehydrogenase	285	U/L	Cl	107	mEq/L
			Alkaline phosphatase	37	U/L	Ca	9.0	mg/dL
			γGTP	17	U/L			
Coagulation test			Total cholesterol	221	mg/dL	Tumor marker		
Prothrombin time-international normalized ratio	1.02		Triglyceride	77	mg/dL	Somatic cell count	1.3	ng/mL
Activated partial thromboplastin time	27.6	Second	C reactive protein	< 0.10	mg/dL	Cytokeratin fragment antigen	1.36	ng/mL

Personal and family history

He consumed 75 g of alcohol daily, and he had a Brinkman Index of 1260, which indicated heavy smoking and a high risk of smoking-related diseases.

Physical examination upon admission

Physical examination did not show any remarkable findings.

Laboratory examinations

The patient's serum tumor markers, including squamous cell carcinoma antigen and cytokeratin 19 fragment levels, were within the normal range (Table 1).

Imaging examinations

An otolaryngological examination was performed, and results revealed three types of otolaryngological cancers: (1) Right lower pharyngeal cancer (T2N1M0, cStage III); (2) Left middle pharyngeal cancer (T1N0M0, cStage I); and (3) Left hard palate cancer (T1N0M0, cStage I) (Figure 1). Gastroenterological examination was performed prior to chemoradiotherapy for otolaryngological cancers to screen for synchronous cancers in the gastrointestinal tract. Esophagogastroduodenoscopy (EGD) revealed a reddish 0-Is+IIb lesion, measuring 20 mm, in the upper thoracic esophagus (23 cm from the incisors) *via* white light imaging. Narrow-band imaging showed type B2 vessels in the elevated area. For further assessment, endoscopic ultrasonography was performed. Results revealed thinning of the submucosal layer (the fifth layer), which suggested an invasion depth of SM2. A biopsy specimen taken from the elevated lesion was examined, and the findings showed a moderately differentiated squamous cell carcinoma.

FINAL DIAGNOSIS

Based on the abovementioned findings, the esophageal lesion was diagnosed as ESCC (T1bN0M0, cStage I) (Figure 2). In this case, ESCC was concomitantly present with pharyngeal cancers, including stage III right lower pharyngeal cancer (T2N1M0), as well as stage I left middle pharyngeal cancer (T1N0M0) and stage I left hard palate cancer (T1N0M0).

TREATMENT

The treatment for advanced-stage pharyngeal cancers was prioritized after a discussion with the otolaryngology department (Figure 3). The patient received chemoradiotherapy in the otolaryngology department. The treatment included three cycles of docetaxel (DTX) and cisplatin (CDDP) (1st course: DTX 79 mg on day 1, CDDP 24 mg on days 2–5; 2nd and 3rd courses: DTX 78 mg on day 1 and CDDP 23 mg on days 2–5) and radiation therapy (with a dose of 66 Gy) to the neck area but excluding the thoracic area, which is where the esophageal cancer was located. Two months after completing the chemoradiotherapy, EGD revealed morphological changes in the esophageal lesion. The lesion initially comprised elevated and flat areas before the treatment. However, the elevated area had been flattened. Consequently, the lesion transformed into a 0-IIb lesion. Narrow-band imaging revealed the disappearance of type B2 vessels and only

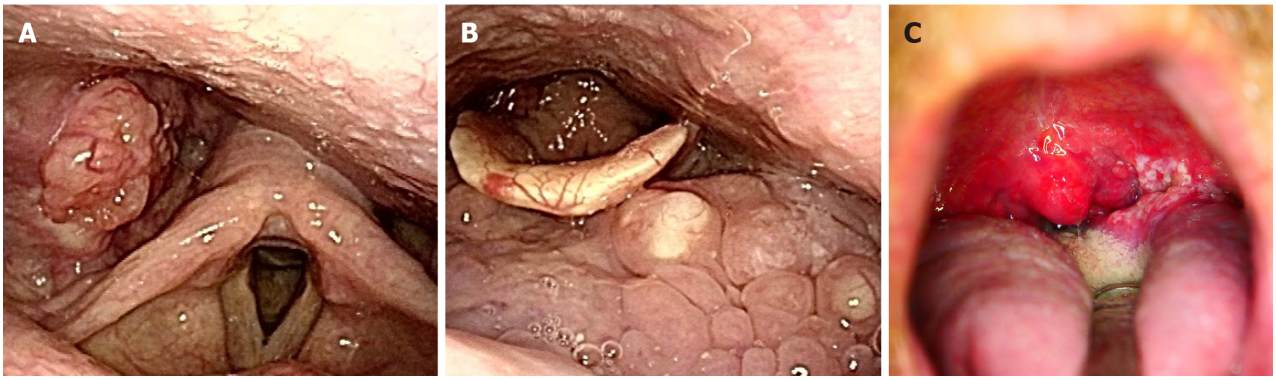

Figure 1 Endoscopic and macroscopic examination. A: Right lower pharyngeal cancer; B: Left middle pharyngeal cancer; C: Left hard palate cancer.

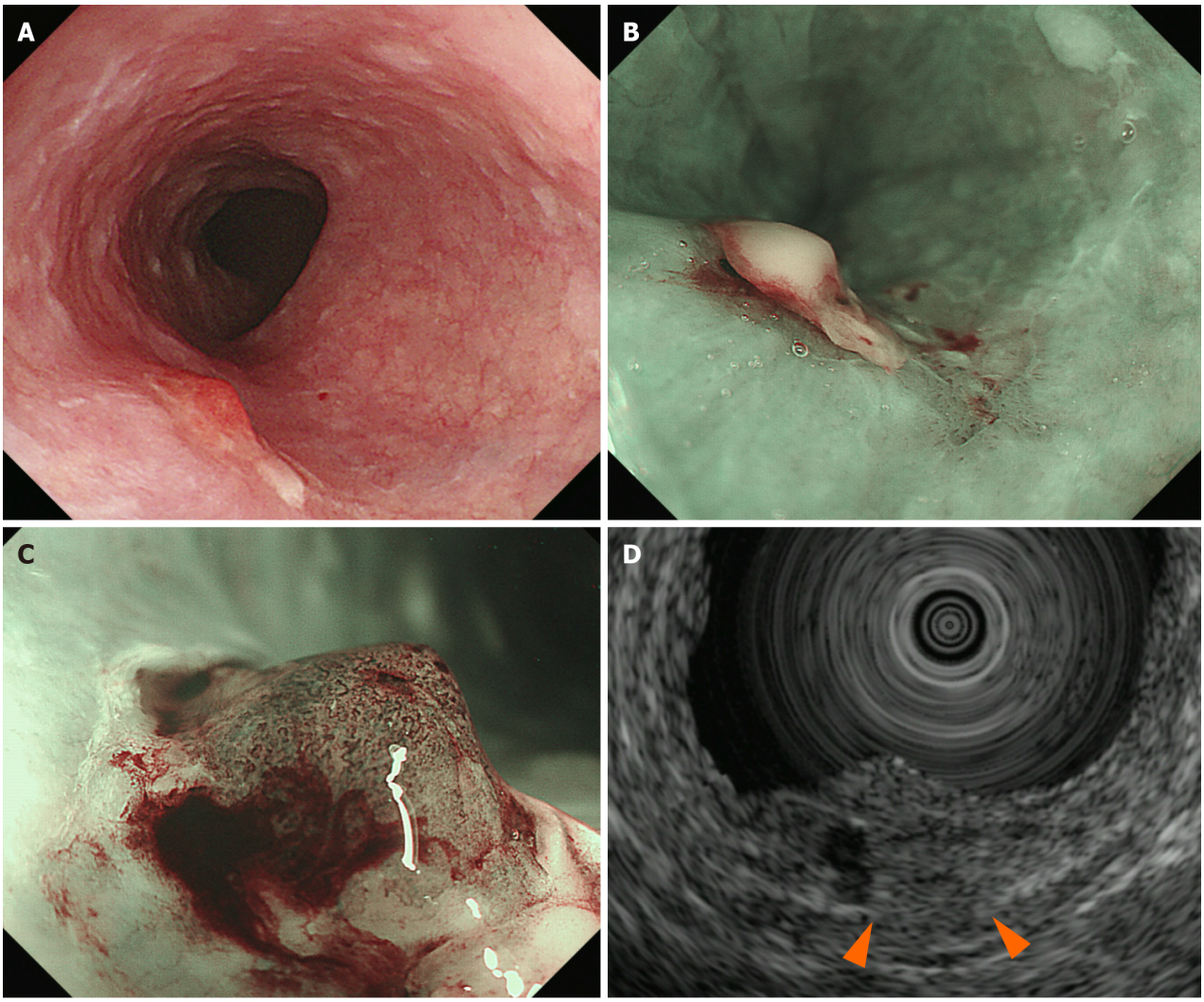

Figure 2 Endoscopic examination. A: White light endoscopy; B: Narrow band imaging (NBI) endoscopy; C: NBI endoscopy showed type B2 vessels in prominent elevated area; D: Endoscopic ultrasonography revealed submucosal layer thinning (the fifth layer) (UM-3R 20MHz). Esophageal cancer was observed at the upper thoracic esophagus (23 cm from the incisors).

detected type B1 vessels and a small avascular area, indicating the possibility of shallowing the invasion depth to epithelium or lamina propria mucosa (LPM). Endocytoscopy showed complete loss of cellular structure with a significant increase in cellular density (classified as EC3) (Figure 4). Computed tomography scan did not reveal the presence of lymph nodes or distant metastases. Based on the abovementioned findings, the esophageal lesion was diagnosed as ESCC (T1aN0M0, cStage I). In addition, as the lesion was outside the radiation field, it was not affected by fibrosis caused by radiotherapy. Thus, curative resection was achievable *via* ESD. After obtaining informed consent, ESD was performed to resect the esophageal lesion (Figure 3). Fibrosis was not observed in the submucosal layer during the procedure, and the

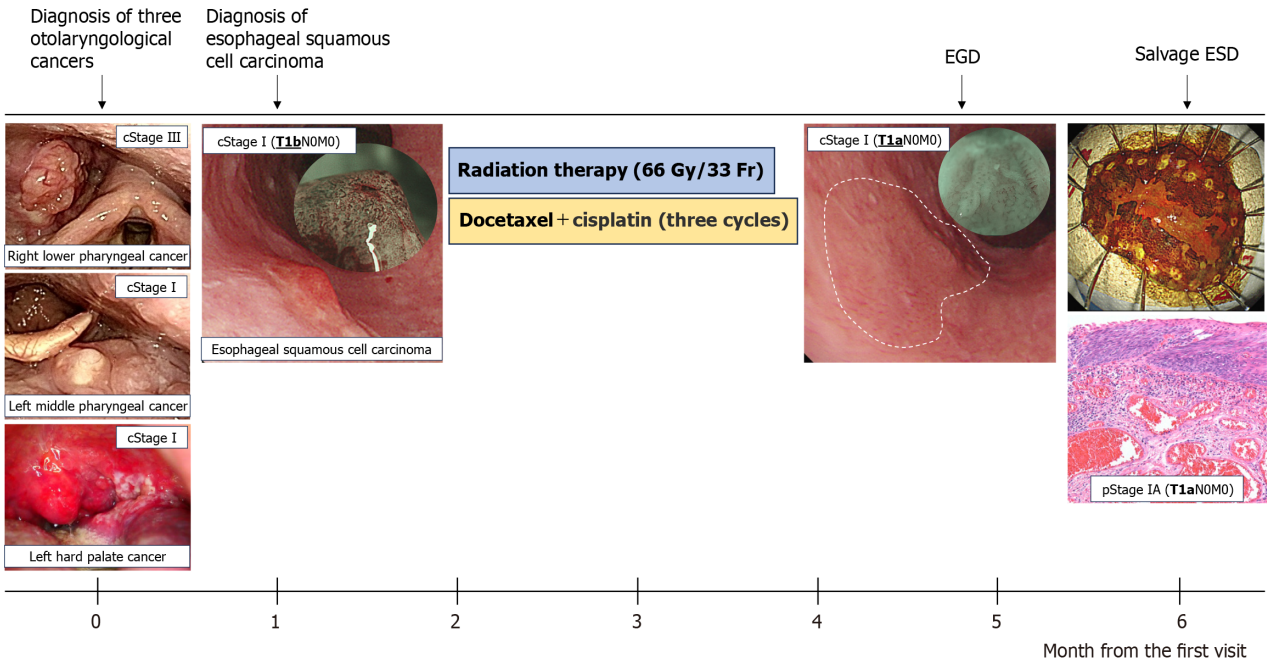

Figure 3 Summary of the treatment timeline and clinical course of this case. EGD: Esophagogastroduodenoscopy; ESD: Endoscopic submucosal dissection.

lesion was completely resected without significant complications (Figure 5). Pathological analysis revealed a moderately differentiated squamous cell carcinoma, and the invasion depth of the cancer was limited to the LPM. Both vertical and horizontal margins were negative, and there was no lymphovascular invasion (Figure 5). These findings completely met the criteria for curative resection, which include invasion depth limited to the LPM, margin negativity, and absence of lymphovascular invasion. The final diagnosis was confirmed as pStage IA ESCC (T1aN0M0).

OUTCOME AND FOLLOW-UP

At 22 months post-ESD, there were no signs of pharyngeal cancer, hard palate cancer, or esophageal cancer recurrence.

DISCUSSION

Unique aspects of the current case

To the best of our knowledge, this is the first case involving a patient with ESCC who successfully underwent salvage ESD after chemoradiotherapy for otolaryngological cancer. ESCC is frequently associated with multiple primary cancers. Based on a previous study on patients with ESCC who developed second primary malignancies, 35% presented with head and neck cancers, 20% with gastric cancers, and 14% with lung cancers[8]. This finding indicated that these cancers are common in patients with ESCC. The factors affecting the successful endoscopic treatment for esophageal cancer after dCRT for otolaryngological cancer in the current case still remain unclear. However, several possible reasons should be considered.

Field cancerization and treatment implications

In otolaryngological cancers, the histological type is commonly squamous cell carcinoma. These cancers, along with ESCC, are examples of field cancerization[9]. Field cancerization is the concept that multiple primary cancers occur either simultaneously or metachronously in the head and neck region and the esophagus, with a high incidence in patients with similar backgrounds and risk factors. Consequently, the same drugs, such as CDDP, 5-fluorouracil, and DTX, were administered as standard chemotherapeutic agents in patients with otolaryngological cancers or ESCC. Thus, chemotherapy for otolaryngological cancers may also be effective against ESCC. Further, when combined with radiation therapy, the abscopal effect[10] might be expected. The abscopal effect refers to a phenomenon in which localized radiation therapy not only decreases the targeted tumor but also induces the regression of distant, untreated tumors *via* systemic immune responses. Thus far, the abscopal effect is commonly observed in renal cell carcinoma, melanoma, and lymphoma. These diseases are conventionally considered immunogenic. There are extremely few reports on the abscopal effect in ESCC[11]. However, the efficacy of immunotherapy for ESCC is well-known, and immunotherapy is a promising treatment option[12]. Hence, ESCC might have immunogenic aspects. Recently, chemoradiotherapy has been found to

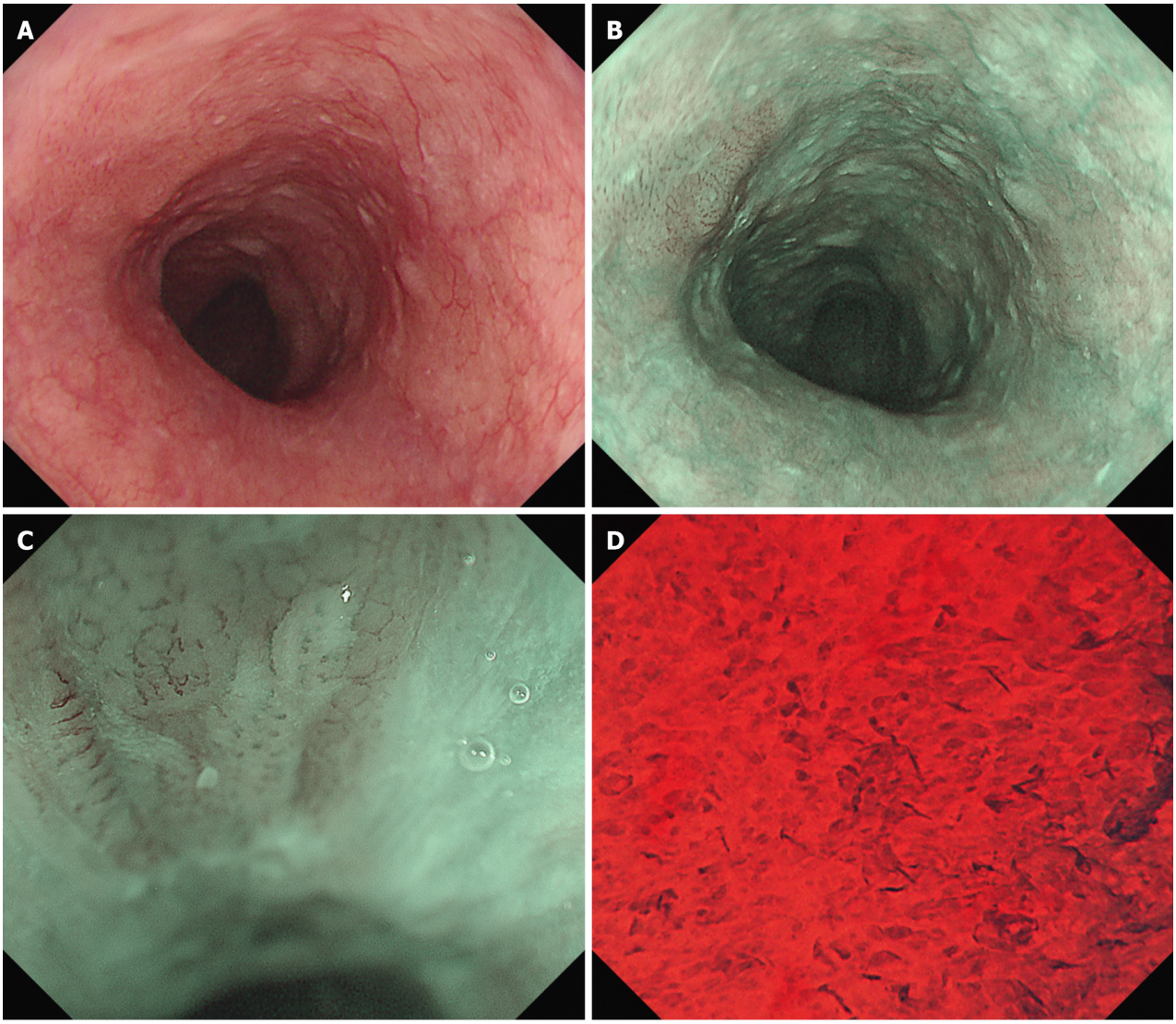

Figure 4 Endoscopic examination (after undergoing chemoradiotherapy to the neck area). A: White light endoscopy; B: Narrow band imaging (NBI) endoscopy; C: NBI endoscopy showed type B1 vessels and small avascular area; D: Endocytoscopy showed complete loss of cellular structure with a significant increase in cellular density (EC classification: EC3). Esophagogastroduodenoscopy revealed the previously prominent elevated area had flattened and transformed into a 0-IIb lesion.

enhance the immunogenicity of ESCC, potentially increasing its sensitivity to immune checkpoint inhibitors[13]. Thus, the combination of radiation therapy and immunotherapy could induce the abscopal effect and improve the response to treatment synergistically[14].

Salvage treatment options

To cure patients, several salvage therapies, including esophagectomy, lymphadenectomy, metastasectomy, endoscopic resection, and photodynamic therapy, were administered[15] because recurrence or residual tumors after dCRT are complex. Previous studies have shown that the incidence rate of local failure after dCRT in patients with ESCC patients is 19%–34%[16-19]. The prognosis of patients with local failure is poor. Among these salvage therapies, esophagectomy is a curative approach. However, 59% of the patients who underwent salvage esophagectomy developed postoperative complications, and the prevalence rates of pulmonary complications and anastomotic leakage were 30% and 37%, respectively. The mortality rate in these patients was 7.4%, indicating that salvage esophagectomy carries a high surgical risk[20].

Endoscopic resection as a salvage treatment for patients with local recurrence or residual ESCC has been found to be effective. The JCOG 9906 phase II trial evaluated the safety of dCRT for patients with stage II/III ESCC[18]. Of 76 patients who enrolled in the study, 26 presented with residual disease or locoregional recurrence without distant metastasis after dCRT. In total, 14 of 26 patients, including 11 patients who underwent esophagectomy and 3 patients who received endoscopic treatment, had salvage therapy. The details of the three patients who underwent endoscopic treatment are as follows: (1) One patient received argon plasma coagulation but later developed mediastinal lymph node metastasis; (2) Another patient died of an otolaryngological surgery-related complication after EMR; and (3) The third patient survived for > 5 years. Yano *et al*[16] reported that they performed salvage EMR on 21 patients with ESCC and 10 patients without

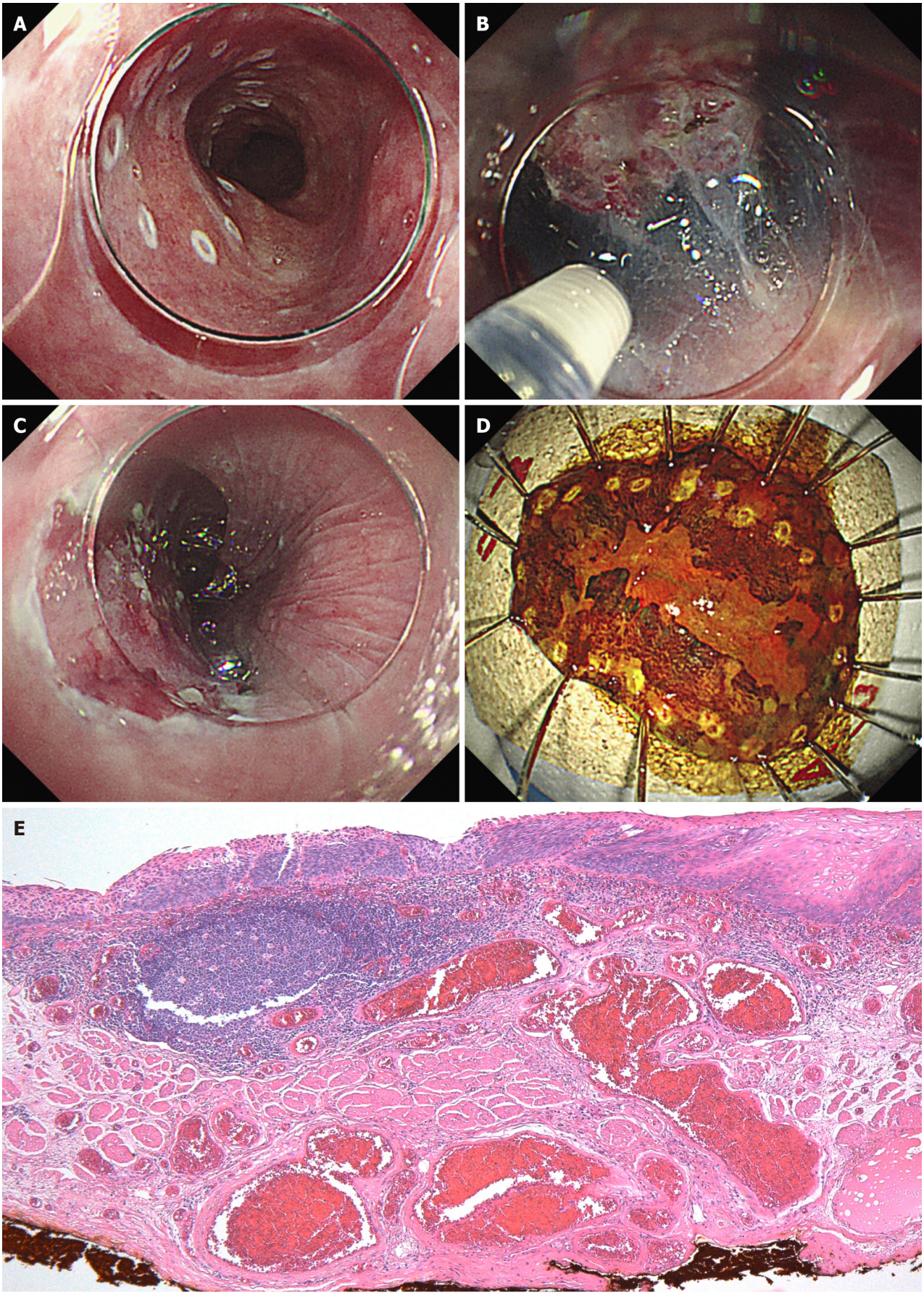

Figure 5 Endoscopic submucosal dissection. A: Marking was performed around the lesion; B: No fibrosis was observed in the submucosal layer during endoscopic submucosal dissection; C: The lesion was completely resected without significant complications; D: Lugol's iodine staining of the lesion revealed to be removed *en bloc*; E: Pathological analysis revealed moderately differentiated squamous cell carcinoma and the invasion depth of the cancer was limited to lamina

propria mucosa with negative vertical and horizontal margins, without lymphovascular invasion.

recurrence. The median overall survival time was 46 months, and the 5-year survival rate was 49.1%. None of the patients developed severe complications associated with EMR. Another study[21] investigated the efficacy of salvage EMR in 11 patients with ESCC who received dCRT. Results showed that salvage EMR could be performed safely, and 6 of 11 patients did not present with recurrence. The median overall survival time was 38.9 months, and the 5-year survival rate was 41.6%. Al-Kaabi *et al*[22] summarized nine previous reports (eight reports regarding ESCC and one about esophageal adenocarcinoma) in which salvage endoscopic treatment was implemented after dCRT. The baseline characteristics of ESCC are as follows: (1) The total number of patients with ESCC was 225; and (2) The clinical stages were stage I (n = 111), stage II (n = 54), stage III (n = 33), and stage IV (n = 27). The number of each clinical T, N, and M stages were as follows: (1) T1/T2/T3/T4; (2) 112/27/52/17; (3) N0/N1/N2/N3; (4) 113/59/4/0; and (5) M0/M1, 68/4, respectively. However, not all papers provided detailed data. The prevalence rate of stage I or II cancer was > 70%. The recurrence rate, 3-year overall survival rate, and 5-year overall survival rate were 16%–59%, 56%–74%, and 30%–53%, respectively. In one of the eight reports regarding ESCC, the prevalence rate of adverse events, such as bleeding and stricture, was 18.9%. However, seven reports showed no major adverse events. Salvage endoscopic resection is a safe, minimally invasive, and promising option for patients with ESCC who received dCRT. In recent years, the data regarding salvage endoscopic treatment has been accumulated, and they are gradually raising awareness about its efficacy.

Limitations

This study was based on a single case, thereby making it difficult to generalize the results. In addition, data on immune changes and the underlying mechanisms after chemoradiotherapy remain insufficient.

CONCLUSION

This case represents a unique example in which ESCC was unintentionally downgraded after chemoradiotherapy for otolaryngological cancers, resulting in the successful implementation of salvage ESD. The outcome is promising. Nevertheless, further research should be performed to validate the study findings in larger patient populations. Expanding studies on the efficacy, safety, and underlying mechanisms, including potential immunogenic responses and the abscopal effect, can help establish evidence-based guidelines and improve treatment strategies in similar cases.

FOOTNOTES

Author contributions: Tachibana S and Moriichi K drafted the manuscript; Tachibana S, Moriichi K, Takahashi K, Sato M, Kobayashi Y, Sugiyama Y, Sasaki T, Sakatani A, Ando K, Ueno N, Kashima S, and Tanabe H were involved in the clinical management and treatment of the patient; Moriichi K and Fujiya M reviewed and revised the manuscript; all authors have read and approved the final manuscript.

Informed consent statement: Informed consent was obtained from the patient for publication of this case report.

Conflict-of-interest statement: Fujiya M received lecture fees from Olympus Corporation.

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