Multidisciplinary treatment of advanced cervical esophageal adenocarcinoma derived from a gastric inlet patch: A case report

KOICHI OKAMOTO[1,2], TAKAHISA YAMAGUCHI[3], TETSUYA ASAKAWA[4], DAISUKE KAIDA[1], TAKASHI MIYATA[1], TOMOYUKI HAYASHI[5], TOSHIHIKO OJIMA[6], HIDETO FUJITA[1], NORIYUKI INAKI[2], SHINICHI KINAMI[1], ITASU NINOMIYA[7] and HIROYUKI TAKAMURA[1]

[1]Department of General and Digestive Surgery, Kanazawa Medical University Hospital, Kahoku, Ishikawa 920-0293; [2]Department of Gastrointestinal Surgery, Kanazawa University, Kanazawa, Ishikawa 920-8641; [3]Department of Gastroenterological Surgery, Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa 920-8530; [4]Department of Surgery, Houju Memorial Hospital, Nomi, Ishikawa 923-1226; [5]Department of Gastroenterology, Kanazawa University, Kanazawa, Ishikawa 920-8641; [6]Department of Surgery, Toyama Nishi General Hospital, Toyama, Toyama 939-2716; [7]Department of Surgery, Fukui Prefectural Hospital, Fukui, Fukui 910-0846, Japan

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Abstract. A gastric inlet patch (GIP) is an ectopic gastric mucosal lesion usually arising at the cervical esophagus that may rarely cause esophageal adenocarcinoma (EAC). To the best of our knowledge, this is the first case of a GIP-derived EAC that was successfully treated using a multidisciplinary treatment approach. A 64-year-old man was referred to the Department of Gastrointestinal Surgery, Kanazawa University Hospital (Kanazawa, Japan) for surgical treatment of refractory recurrent cervical EAC derived from GIP who had previously been treated with induction chemotherapy, definitive chemoradiotherapy and photodynamic therapy (PDT). Esophagogastroduodenoscopy revealed a stenotic tumor at the GIP site in the cervical esophagus and submucosal tumors with suspected multiple intramural metastases in the anal side of the thoracic esophagus. The patient underwent robot-assisted thoracoscopic esophagectomy with laryngopharyngectomy and cervical lymphadenectomy as radical salvage surgery 4 months after the last PDT procedure. After postoperative adjuvant chemotherapy using oral administration of tegafur/gimeracil/oteracil (oral 5-fluorouracil prodrug) for 1 year; at present, the patient is alive without recurrence 3 years after the operation.

Correspondence to: Dr Koichi Okamoto, Department of General and Digestive Surgery, Kanazawa Medical University Hospital, 1-1 Daigaku, Uchinadamachi, Kahoku, Ishikawa 920-0293, Japan
E-mail: kokamoto@kanazawa-med.ac.jp

Abbreviations: GIP, gastric inlet patch; EAC, esophageal adenocarcinoma; PDT, photodynamic therapy; ESCC, esophageal squamous cell carcinoma; BE, Barrett's esophagus; CRT, chemoradiotherapy; EGD, esophagogastroduodenoscopy; CT, computed tomography; RAMIE, robot-assisted minimal invasive esophagectomy; GERD, gastroesophageal reflux disease; NAC, neoadjuvant chemotherapy; MIE, minimally invasive esophagectomy; GEJ, gastroesophageal junction

Key words: CRT, ectopic gastric mucosa, EAC, fluorouracil, GIP, lymphadenectomy, PDT

Introduction

Esophageal squamous cell carcinoma (ESCC) predominates in Asia and Africa, constituting ~90% of malignant esophageal tumors (1). However, esophageal adenocarcinoma (EAC) accounts for only 10% of the cases, but its incidence is increasing in Asia. EAC typically localizes to the distal third of the esophagus and is closely linked to chronic acid reflux, leading to the hallmark metaplasia commonly originating from Barrett's esophagus (BE). BE histopathology progresses from metaplasia to dysplasia and, without treatment, can progress to adenocarcinoma. People with BE have a ~0.2%-0.5% annual rate of developing EAC (2). In contrast, adenocarcinoma in the proximal third of the esophagus without BE is extremely rare and arises either from the focus of the ectopic gastric mucosa or submucosal glands (3).

A gastric inlet patch (GIP) is an ectopic gastric mucosal lesion usually found in the cervical esophagus and is considered an incidental finding, with a reported incidence of ~2.5% (3,4). Given the extreme rarity of GIP-derived EAC, its treatment strategy is notably complex due to its unique location, histology, and limited treatment precedents. To the authors' knowledge, no reported advanced GIP-derived EAC case exists within the cervical esophagus that was treated using a multidisciplinary treatment approach. This study described a GIP-derived EAC successfully treated with multidisciplinary treatment, including chemotherapy, definitive chemoradiotherapy (CRT), photodynamic therapy (PDT), and salvage surgery.

Case report

Present medical history. A 64-year-old Japanese man with hypertension, dyslipidemia, and chronic obstructive pulmonary disease with a chief complaint of swallowing discomfort visited his doctor. Subsequent esophagogastroduodenoscopy (EGD) identified an apparent elevated tumor at the ectopic gastric mucosal site of the cervical esophagus (Fig. 1A). Upon further examination, he received a diagnosis of advanced cervical EAC (CePh, 4.5 cm, tub2-por, cT2 N0 M0 IM0, cStage II) and was subsequently chosen for a multidisciplinary treatment approach. Later, he underwent induction chemotherapy using the DCF regimen (docetaxel, cisplatin, and fluorouracil), followed by CRT comprising cisplatin and fluorouracil, delivering 70 Gy over 35 sessions. This approach was in line with his strong preference for larynx preservation. Remarkably, he achieved complete response within 6 months after CRT completion (Fig. 1B). A year later, EGD identified a local EAC recurrence in the cervical esophagus (Fig. 1C). Therefore, he was referred to the Department of Gastroenterology at our hospital for endoscopic treatment using PDT. Nevertheless, a viable tumor persisted despite PDT procedures (Fig. 1D). After the second PDT procedure by gastroenterological physicians, a local recurrence with severe stenosis was identified in the cervical esophagus (Fig. 1E). As a result, he was referred to the Department of Gastrointestinal Surgery for salvage surgery aimed at treating the residual lesions. However, EGD revealed an elevated lesion at the cervical esophagus, 17 cm from the incisor, and severe stenosis (Fig. 1F). Endoscopy could be successfully conducted after balloon dilatation. During further EGD examination, multiple submucosal tumor-like lesions with vascular atypia were observed in the upper to middle esophagus, 22 to 28 cm from the incisor (Fig. 1G and H). Biopsy revealed that all lesions were adenocarcinomas with suspected multiple intramural metastases of the esophagus. Subsequent esophageal fluoroscopy revealed a 4.2 cm circumferential stricture from the entrance of the cervical esophagus (Fig. 2A). Computed tomography (CT) before treatment showed an apparent elevated tumor occupying the lumen of the cervical esophagus and no clear lymphadenopathy around the esophagus (Fig. 2B). Consequently, CT and positron emission tomography after PDT procedures showed a wall thickness with abnormal ^{18}F-fluorodeoxyglucose uptake remaining in the cervical esophagus (Fig. 2C and D). However, no obvious lymph node or distant metastasis was suspected. As a result, he was diagnosed with recurrent advanced cervical EAC (CePh, 4.5 cm, por, CRT-cT2 N0 M0 IM1, CRT-cStage II), and a radical operation was recommended as a necessary intervention. The surgery included esophagectomy with extensive mediastinal lymph node dissection and laryngopharyngectomy. Therefore, robot-assisted minimal invasive esophagectomy (RAMIE) with laryngopharyngectomy and cervical lymphadenectomy as radical salvage surgery were performed 4 months after the second PDT procedure.

Surgical procedure. The surgical procedure was performed by a multidisciplinary team consisting of gastrointestinal surgeons and otorhinolaryngologists. First, thoracoscopic esophagectomy and mediastinal lymphadenectomy were performed with robot assistance as described previously (5). Second, to confirm whether the larynx can be preserved, the cervical esophagus on the anal side of the hypopharynx was cut by cervical manipulation, and the stump was submitted for intraoperative rapid pathological diagnosis. As a result, malignant cells were clearly detected in the oral-side stump, so it was judged that larynx preservation was impossible. Therefore, additional laryngopharyngectomy and cervical lymphadenectomy were performed by otorhinolaryngologists. Third, reconstruction of the digestive tract via the posterior mediastinal route by pharyngogastric anastomosis using gastric conduit was performed. Finally, a permanent tracheostomy was created and the cervical wound was closed. The overall intraoperative time and the amount of intraoperative bleeding were 650 min and 300 g, respectively.

Histological findings of the resected specimens. Macroscopically, the proximal side of the esophagus exhibited noticeable wall hardening and constriction. Furthermore, numerous submucosal tumors were noticed near the primary tumor (Fig. 3A). However, the laryngopharyngectomy specimens showed no evidence of tumor cells (Fig. 3B).

Histologically, viable adenocarcinoma cells remained with fibrosis and necrosis in the cervical esophagus, and multiple intramural metastases were distributed in the upper to middle esophagus (Figs. 3C and 4A). The deepest part of the cancer cells invaded the muscularis propria of the esophagus (Fig. 4B). Cancer cells were also observed in the proximal stump of the esophageal resection specimen (Fig. 4C). Adenocarcinoma cells were mainly moderate to poorly differentiated and distributed in the mucosa and lamina propria (Fig. 4D). However, multiple intramural metastases and vascular invasions were frequently observed in the anal side of the primary tumor (Fig. 4E). Multiple metastatic lymph node metastases were evident in mediastinal and intraabdominal lymph nodes (Fig. 4F). Finally, the pathological diagnosis was advanced cervical GIP-derived EAC [CePh, 4.5 cm, circ, moderately to poorly differentiated adenocarcinoma, INFc, ly3, v2, pIM1, pPM0, pDM0, pRM0, CRT-pT3, pN4 (10/44, #105x1, #106recLx2, #107x1, #110x1, #112aoAx4, #3ax1) M0, CRT-pStage IVA, D3, Cur B].

Postoperative clinical course. An anastomotic leakage on the 13th day after surgery was successfully resolved through conservative management. Subsequently, he was transferred to another hospital for rehabilitation on the 45th day after the operation. Given the substantial risk of recurrence, he underwent adjuvant chemotherapy with oral S-1 (a prodrug of 5-fluorouracil) for 1 year after the prescribed protocol for adjuvant chemotherapy in gastric cancer (6,7). Although the quality of life deteriorated due to the loss of vocal function, he has spent his daily life without significant deterioration in his general condition or body weight. Fortunately, the patient remained relapse-free with the assessment using EGD and CT, achieving a 3-year survival after the salvage surgery.

Discussion

This is a cervical EAC case that developed in the cervical ectopic gastric mucosa. EAC risk factors include gastroesophageal reflux disease (GERD), BE, obesity, and smoking. BE

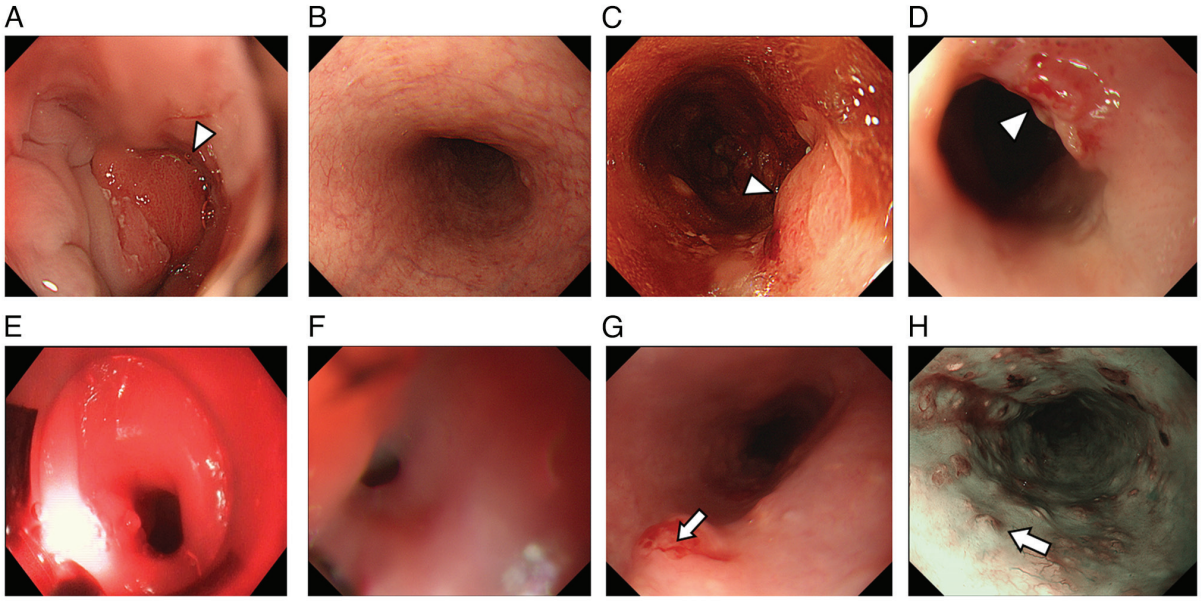

Figure 1. Changes in the endoscopic findings of cervical EAC in the overall clinical course. (A) Pretreatment findings in EGD. An apparent elevated tumor in the ectopic gastric mucosa was observed at the cervical esophagus (white arrowhead). (B) Cervical EAC completely diminished without esophageal stenosis 6 months after CRT completion. (C) Local recurrence at the cervical esophagus was revealed 1 year after CRT completion (white arrowhead). (D) A viable tumor remained after the first PDT procedure for the recurrent lesion (white arrowhead). (E) The second PDT procedure was performed to treat local recurrence in the cervical esophagus. (F) EGD indicated an apparent elevated lesion with severe stenosis of the cervical esophagus. (G) Some submucosal tumor-like lesions with a depression at the top of the tumor were observed in the anal esophagus (white arrow). (H) Multiple submucosal tumor-like lesions with vascular atypia were observed in the upper to middle esophagus (white arrow). CRT, chemoradiotherapy; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; PDT, photodynamic therapy.

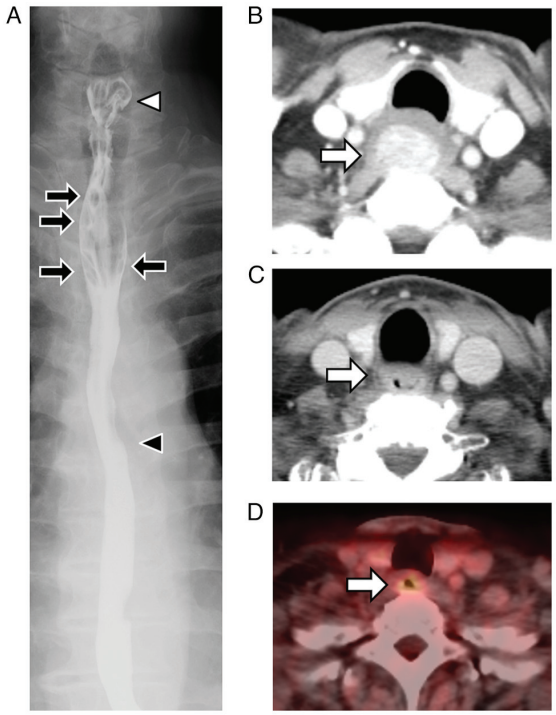

Figure 2. Preoperative imaging findings. (A) Esophagography revealed a 4.2-cm circumferential stricture from the entrance of the cervical esophagus (white arrowhead). Multiple submucosal tumors were observed on the anal side of the main lesion (black arrows), and the intramural metastatic lesion of the most anal side was located in the middle thoracic esophagus (black arrowhead). (B) Computed tomography before treatment revealed an apparent elevated tumor occupying the lumen of the cervical esophagus (white arrow). (C) After the two photodynamic therapy procedures, the relapsed cervical esophageal tumor shrunk but the wall thickening remained (white arrow). (D) The residual tumor showed abnormal ^{18}F-fluorodeoxyglucose uptake remaining in positron-emission tomography (white arrow).

histopathology progresses from metaplasia to dysplasia and, without treatment, can progress to adenocarcinoma. People with BE have a ~0.2%-0.5% annual rate of developing EAC. Although alcohol consumption is not associated with EAC risk, other exposures, such as physical activity, nutrition, and medication use, require further studies. Genetic variants are also associated with EAC risk, but their overall contribution is low (2). Additionally, he did not drink alcohol and had a heavy smoking history. There was also a family history of gastric cancer, but the presence of *Helicobacter pylori* was not investigated in detail. Generally, the prognosis in EAC has been reported to be poor because of the late presentation of symptoms and the aggressiveness of the tumor; appropriate treatment strategy, screening, and surveillance trials of high-risk individuals are needed (1,2).

The previously reported prevalence of GIP in the proximal esophagus ranges from 0.18 to 14% in endoscopic studies (8-11). However, adenocarcinoma incidence among patients with cervical ectopic gastric mucosa is 0-1.56% (12). Orosey *et al* (13) reported only 5 (1.3%) patients with ectopic gastric mucosa among 398 EAC diagnosed over 14 years, and only 3 (0.8%) patients had ectopic gastric mucosa within the proximal esophagus. Only 58 EAC and ectopic gastric mucosa were reported between 1950 and 2015 worldwide, and most were from Japan.

The pathogenesis of adenocarcinoma within an ectopic gastric mucosa might comprise a metaplastic-dysplastic pathway, leading to intestinal metaplasia and an intestinal-type adenocarcinoma or the development of adenocarcinoma within gastric/foveolar cells in an ectopic gastric mucosa (3). Tang *et al* (14) reported that GERD and BE are significantly more common in cervical ectopic gastric mucosa, suggesting

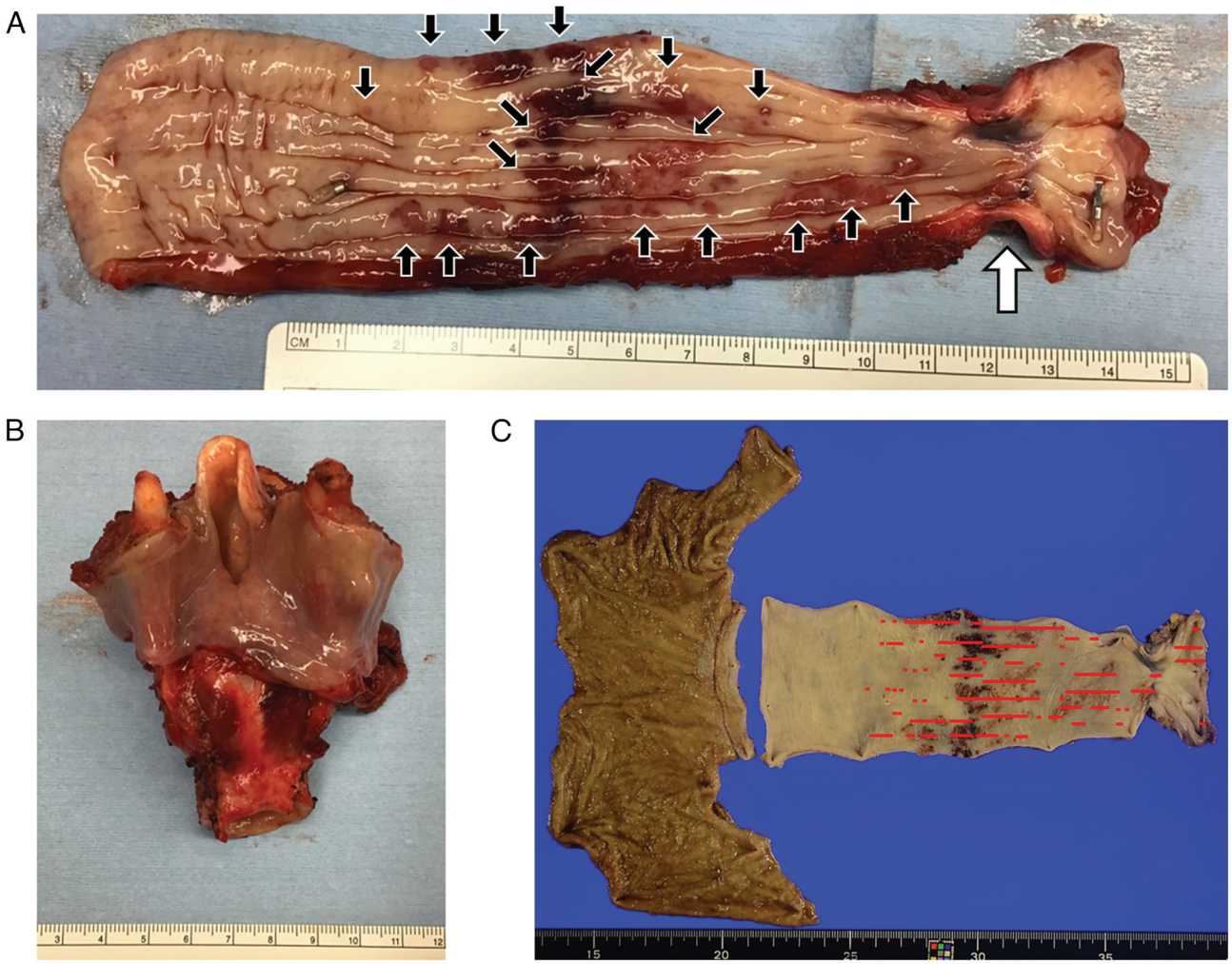

Figure 3. Histopathological findings of the macroscopic image of the resected specimens. (A) Esophagectomy specimen with a stenotic cancer lesion length of 4.5 cm (white arrow). Submucosal tumors with suspected multiple intramural metastases were observed in the upper to middle esophagus (black arrows). (B) Tumor cells were not evident in the laryngopharyngectomy specimen. (C) Red lines showing the distribution of cancer lesions in the resected esophagus.

that acid reflux is involved in their development (14-16). This case was not associated with BE and had no history of GERD treatment.

Several case reports of EAC derived from ectopic gastric mucosa have been reported (17-23). Kitasaki *et al* (17) reported a case of repeated local recurrence at the same site despite multiple radical endoscopic resections. Ito *et al* (18) reported that ESD-pT1a (MM) EAC derived from ectopic gastric mucosa in the neck developed lymph node recurrence. In our case, although the primary tumor was relatively mild, lymphatic and vascular invasion was significant, there were more lymph node metastases than preoperatively diagnosed, and there were widespread intramural esophageal metastases. These results suggested that EAC in the cervical or upper thoracic esophagus, rich in lymphatic chains and vascular networks, may be difficult to treat and have a poor prognosis (23). The basic treatment strategy for EAC is local control through resection, and some reports have shown that endoscopic resection can be expected to treat cervical esophageal lesions in early-stage cancers (19-22). Tanaka *et al* (22) reported a case in which complete resection was achieved with larynx-preserving surgery, indicating that larynx-preserving surgery is possible for localized lesions that do not extend to the hypopharynx as long as negative margins are ensured. In contrast, von Rahden *et al* (24) reported a treated case of EAC derived from the heterotopic gastric mucosa by definitive CRT. Surgery after neoadjuvant chemotherapy (NAC) and CRT for esophageal cancer is frequently performed in Europe and the United States (25-27). This study first selected induction DCF therapy and subsequent definitive CRT as a radical treatment strategy because the patient strongly desired to preserve the larynx.

In a lesion extending to the pharynx, combined resection of the pharynx and laryngopharynx is unavoidable, resulting in the loss of vocalization and swallowing functions. In our case, the primary lesion not only extended to the pharynx but was also accompanied by extensive multiple intramural metastases in the anal esophagus and the necessity of mediastinal lymph node dissection. Finally, laryngopharyngectomy was unavoidable for radical resection without residual tumor. Indeed, in superior aerodigestive airway cancer with rare histology like EAC or sarcoma, the protocols have to be individualized and made by a multidisciplinary team to obtain a better prognosis (28). In the present cases, a multidisciplinary treatment was subsequently performed by a multidisciplinary team consisting of gastroenterological physicians, radiologists,

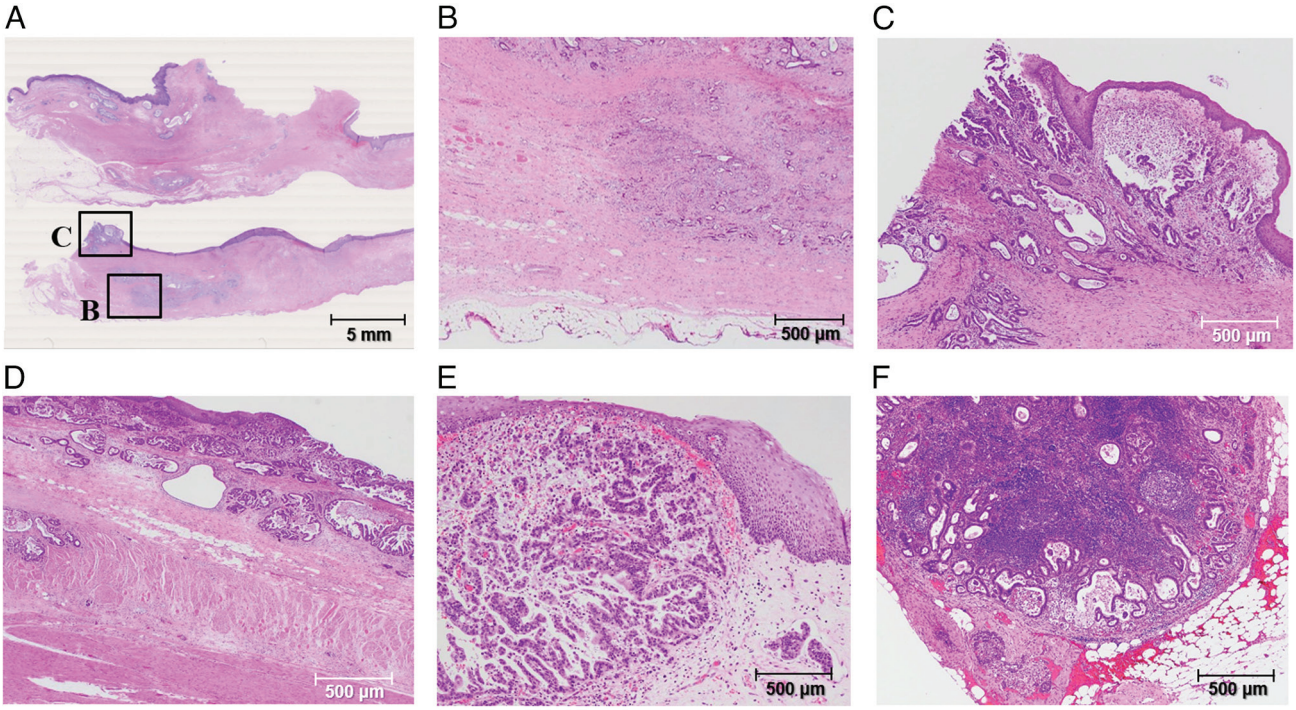

Figure 4. Pathological findings of the resected specimens. (A) Loupe view of the resected esophagus. The oral resection margin of the cervical esophagus was macroscopically positive. (B) Macroscopically, viable adenocarcinoma cells remained with fibrosis, necrosis and the infiltration of inflammatory cells in the cervical esophagus. The deepest part of the cancer invaded the muscularis propria of the esophagus. (C) The viable adenocarcinoma cells were proven to remain in the oral edge of the resected esophagus. No residual ectopic gastric mucosal tissue was evident around the primary tumor. (D) Moderate to poorly differentiated adenocarcinoma cells were mainly distributed in the mucosa and lamina propria, and cancer infiltration was also observed in the muscularis propria. (E) Multiple intramural metastases were observed in the anal side of the main tumor, and some venous and lymphatic invasions were observed. (F) Viable adenocarcinoma cells were pathologically observed in some mediastinal and intraabdominal lymph nodes. Scale bar, (A) 5 mm or (B-F) 500 μm.

gastrointestinal surgeons, and otorhinolaryngologists. In recent years, thoracoscopic and robot-assisted surgeries have become increasingly popular for minimally invasive esophagectomy (MIE). The same applies to EAC treatment. Warner *et al* (29) reported that MIE is an acceptable surgical therapy for advanced-stage esophageal malignancies after neoadjuvant CRT without evidence for increased morbidity or mortality. Tagkalos *et al* (30) reported the usefulness of RAMIE vs. conventional MIE for EAC. Therefore, this study elected RAMIE for thorough and less invasive mediastinal lymph node dissection and esophagectomy.

DCF therapy as induction chemotherapy has been positioned as a standard treatment for NAC for advanced ESCC after the results of the JCOG1109 trial due to its potency (31). The usefulness of DCF therapy as NAC for adenocarcinoma cases has not been sufficiently demonstrated (32). In contrast, several reports on the usefulness of NAC for gastroesophageal adenocarcinoma have been recently reported (33-37). However, which neoadjuvant treatment is best for patients with gastroesophageal junction (GEJ) tumors remains controversial. The FLOT4 trial showed a significant overall survival benefit of the perioperative triplet regimen (fluorouracil + leucovorin, oxaliplatin, and docetaxel) plus surgery compared to the ECF/ECX-MAGIC regimen (fluorouracil or capecitabine + cisplatin and epirubicin) for resectable gastric or GEJ adenocarcinoma (38). In Europe and the United States, preoperative CRT has better results than NAC and has become the standard treatment for advanced GEJ adenocarcinoma. In the CROSS study, long-term follow-up results of neoadjuvant CRT combined with surgery compared to surgery alone demonstrated more profound survival benefits in patients with squamous cell carcinoma than in those with GEJ adenocarcinoma (35). Unfortunately, cure by induction DCF therapy and subsequent definitive CRT was not obtained in our case, and salvage surgery was unavoidable.

PDT is an effective treatment for postradiotherapy residual tumors and local recurrence, but it is not originally indicated for cervical lesions due to the risk of esophageal stricture, injury, and perforation (39). Conversely, Hayashi *et al* (40) reported that PDT is also effective for cervical lesions and is a treatment expected to expand its indications in the future. In this case, the cause of stenosis remains unclear whether it was caused by cauterization by PDT or CRT. Moreover, PDT is the approved curative treatment for high-grade dysplasia and EAC in BE by the U.S. Food and Drug Administration and provides favorable and comparable long-term outcomes to esophagectomy (41,42). Because this patient was resistant to various anticancer treatments, such as chemotherapy, CRT, and PDT, and multiple intramural metastases later appeared, it was considered that salvage surgery was inevitable for a radical cure. However, no remaining columnar epithelial components were observed around the cervical EAC of the resected specimen. Although cervical ectopic gastric mucosa indeed existed before treatment, it was thought that it had been cauterized by the effects of CRT or PDT during the clinical course of the treatment for cervical EAC.

In summary, this is a rare multidisciplinary treatment approach for advanced cervical GIP-derived EAC of the

cervical esophagus, which was resistant to chemotherapy, CRT, and PDT and radically resected by salvage surgery. For refractory EAC, a long-term prognosis can be expected by aiming to eradicate the tumor through multimodal treatment tailored to the disease state.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

KO, NI and IN designed the study and drafted the manuscript. KO, TY, TA and IN performed the surgery and therapeutic management of the patient. TH performed the endoscopic treatment of the patient. TO performed the postoperative management and managed adjuvant chemotherapy. KO, TY, TA, TH, TO and NI obtained medical images. DK, TM, TH, HF, NI, SK, IN and HT contributed to analysis of the patient's data and the editing of the report. KO and NI confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Authors' information

KO, NI and IN are specialists and instructors of the Japanese Society of Gastroenterological Surgery and the Japanese Esophageal Society, and serve as councilors of the Japanese Esophageal Society.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

Competing interests

The authors declare that they have no competing interests.

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