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The controversy of esophageal carcinosarcoma

A case report and brief review of literature

Xiaoyang Xu, MD[a,*], Yan Xu, MD[b], Jiang Wang, MD[a], Can Zhao, MD[c], Chang Liu, MD[c], Bin Wu, MD[c], Lei Gao, MD[c], Guangquan Dai, MD[c], Dongqiu Dai, MD[d]

Abstract

Rationale: Esophageal carcinosarcoma (ECS) is defined as a relatively rare malignant neoplasm with both epithelial carcinomatous and sarcomatous components. Besides, there were so many various controversies in ECS. This article describes a case of ECS that was effectively treated with radical esophagectomy and adjuvant chemotherapy. Also, we discuss the presentation, differential diagnosis, treatment, and prognosis of ECS.

Patient concerns: A 58-year-old man presented with a history of progressive dysphagia and precordial pain after swallowing for 1 month.

Diagnosis: Esophagogastroduodenoscopy (EGD) revealed a large polypoid neoplasm that occupied the esophageal lumen 30 to 34 cm from the incisors. On the characteristic morphology, clinical symptom and biopsy findings, the ECS was the primary considerated. Computed tomography (CT) examination demonstrated no radiological evidence of metastatic disease.

Interventions: The patient underwent an Ivor Lewis esophagectomy, coupled with adequate lymph node dissection (2-field lymphadenectomy). ECS was confirmed by pathology report of postoperative. Then, the patient underwent adjuvant chemotherapy with docetaxel, oxaliplatin, and capecitabine.

Outcomes: The patient remained alive without tumor recurrence at 24 months after multidisciplinary therapy.

Lessons: It is generally treated by surgery, radiotherapy, and chemotherapy according to the protocols used for other esophageal cancers (EC). However, there is no recommended clinical treatment for ECS because of the rarity of the disease. Esophagectomy with extended lymphadenectomy followed by adjuvant chemotherapy with docetaxel, oxaliplatin, and capecitabine may be recommended treatment for ECS. Chemotherapy regimen with docetaxel, oxaliplatin, and capecitabine may be a suitable adjuvant therapy for ECS.

Abbreviations: CR = complete remission, CT = computed tomography, EAC = esophageal adenocarcinoma, EC = esophageal cancer, EGD = esophagogastroduodenoscopy, EMR = endoscopic mucosal resection, ESCC = esophageal squamous cell carcinoma, ESD = endoscopic submucosal dissection, EUS = esophageal ultrasound, IHC = immunohistochemical, OS = overall survival, PR = partial remission.

Keywords: adjuvant chemotherapy, carcinosarcoma, docetaxel, esophagus, multidisciplinary therapy

Editor: N/A.

The Ethics Committee of our hospital approved the study and provided permission to publish the results

This case report was written following the CARE guidelines. Informed consent was obtained from the patient for publication of this case report and accompanying images.

The authors declare that they have no conflict of interest.

[a] Department of Surgery, Fushun Mining Bureau General Hospital of Liaoning Health Industry Group (The Seventh Affiliated Hospital of China Medical University), Fushun, [b] The First Department of Radiotherapy, Fushun Fourth Hospital, [c] Department of Thoracic Surgery, Fushun Mining Bureau General Hospital of Liaoning Health Industry Group (The Seventh Affiliated Hospital of China Medical University), Fushun, [d] Cancer Center, The Fourth Affiliated Hospital, China Medical University, Shenyang, China.

[*] Correspondence: Xiaoyang Xu, Department of Surgery, Fushun Mining Bureau General Hospital of Liaoning Health Industry Group (the Seventh Affiliated Hospital of China Medical University), No. 24 Central Street, 113008, Fushun, China (e-mail: yangyu198713@163.com).

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1. Introduction

Esophageal cancer (EC), mainly includes esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC), is the most common cancer in sixth place with a high incidence rate and is the third most common gastrointestinal cancer (one of the most fatal types of digestive tract malignant tumour as well.).[1] Carcinosarcoma usually occurs in such diverse locations as the uterus, breast, thyroid, lung, and upper gastrointestinal system.[2] Esophageal carcinosarcoma (ECS) is a relatively rare malignant neoplasm composed of both epithelial carcinomatous and mesenchymal sarcomatous elements,[3] which makes up 0.5 to 2.8% of all esophageal malignancies.[4] Due to the rarity of the disease, there are so many various controversies in esophageal carcinosarcoma. We herein report a case of esophageal carcinosarcoma treated with esophagectomy and docetaxel, capecitabine, and oxaliplatin as postoperative chemotherapy. We also discuss the pertinent literature.

2. Case report

A 58-year-old man presented with a history of progressive dysphagia and precordial pain after swallowing for 1 month, with weight loss of 5 kg. The symptom did not accompany

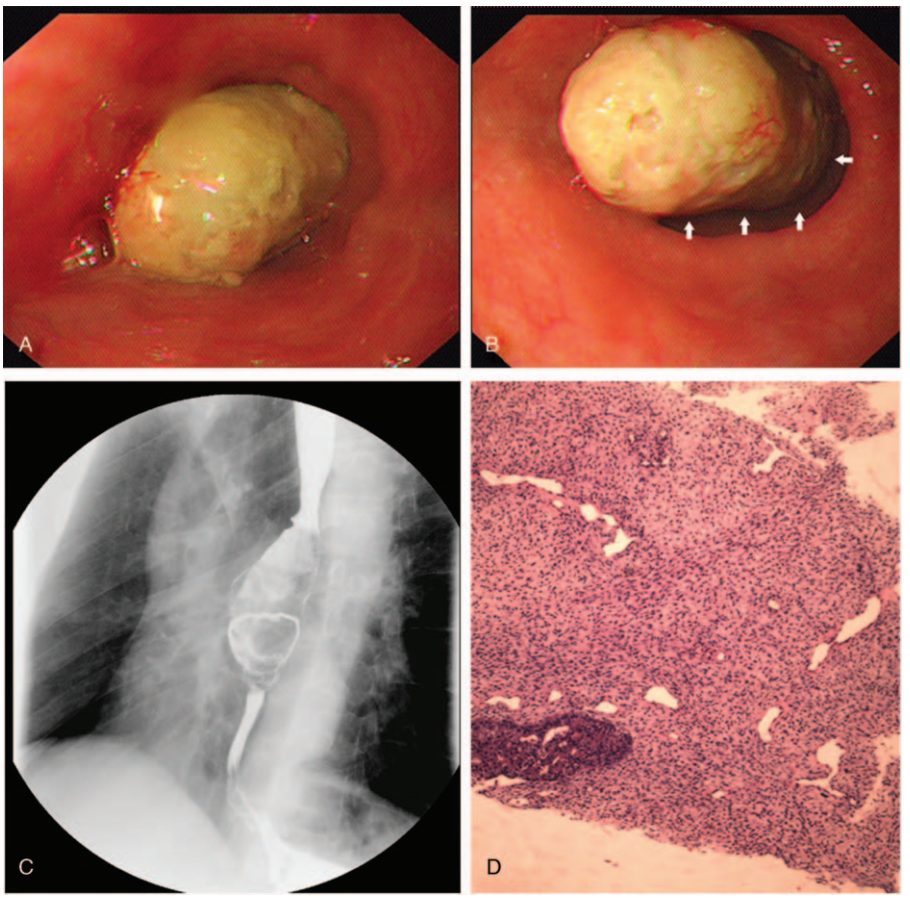

Figure 1. (A) The EGD showed a huge mass with a relatively smooth occupying the esophageal lumen. (B) The tumor was partially covered with normal esophageal mucosa (arrows). (C) Barium esophagography showed a lobulated polypoid lesion with a relatively smooth surface, central superficial irregularity and depression in the lower esophagus. (D) Pathology of the biopsy specimen showed esophageal malignant tumour. EGD = esophagogastroduodenoscopy.

melena and bloody vomit. Neither his medical nor family history included any relevant disease. At around 20 years old, he experienced a left leg fracture. For the past 30 years, he had drunk 250 mL per day of white wine and smoked 20 cigarettes per day.

When he was referred to our hospital for further examination, his physical findings were normal. He ingested only liquids. All laboratory data and serum tumor markers, including carcinoembryonic antigen (CEA) and SCC antigen were within the normal limits. EGD revealed a large polypoid neoplasm that occupied the esophageal lumen 30 to 34 cm from the incisors. The tumor surface was relatively smooth (Fig. 1A) and part of the surface comprised normal esophageal epithelial mucosa (Fig. 1B). However, due to the size of the tumor the basal part could not be totally visualized by EGD. A barium swallow esophagogram showed a lobulated polypoid tumor in the lower esophagus (Fig. 1C). Endoscopic biopsy revealed esophageal malignant tumour (Fig. 1D). Both differentiation between epithelium and mesenchyma were performed by immunohistochemical (IHC) analysis. However, the insufficient amount of tissue confined to further immunohistochemical analysis. On the characteristic morphology, clinical symptom and biopsy findings, the ECS was the primary considerated. CT examination demonstrated a heterogenous tumorous formation obturating the esophageal lumen without enlarged lymph nodes in the thoracic and egigastric region and invaded to the adjacent organs (Fig. 2A and B). No metastatic regions were found in distant organs, including the lungs and liver. An esophageal ultrasound (EUS) was difficult to perform on this patient due to the huge mass.

The patient underwent an Ivor Lewis esophagectomy, coupled with adequate lymph node dissection (2-field lymphadenectomy). On a resected specimen showed a polypoidal growth, measuring 73 mm × 32 mm × 31 mm in size, including a short stalk (Fig. 2C). H&E staining (Fig. 2D) and IHC analysis (Fig. 2D) were both performed. According to pathology report, the tumor had invaded the muscular layer of the esophagus, and without metastasized to several dissected regional lymph nodes (according to 7th International Union Against Cancer TNM staging system:T2,N0,M0). The report of IHC analysis was S100 (–), CK (focal+), Vim (+), EMA (+), DOG1 (–), SMA (focal+), CD65 (+), CD117(–), CD34 (–), P40 (–) and P63 (–). Approximately 45% of the cells were positive for Ki67. The IHC analysis supported the diagnosis of esophageal carcinosarcoma.

The patient had a smooth recovery. He was discharged after 12 days of postoperative stay. He had no complaint except for esophagostenosis after 1 month surgery (Fig. 3A and B), which esophagectasis treatment was given twice interval 1 month (Fig. 3C and D). The chemotherapy therapy, which consisted of intravenous docetaxel (60 mg/m^2, day 1), oxaliplatin (130 mg/m^2, day 1), and capecitabine (625 mg/m^2, days 1–21), was administered 4 courses at an interval of 3 weeks, as adjuvant therapy. There was no evidence of recurrence or metastasis in the 24 months follow-up (Fig. 4).

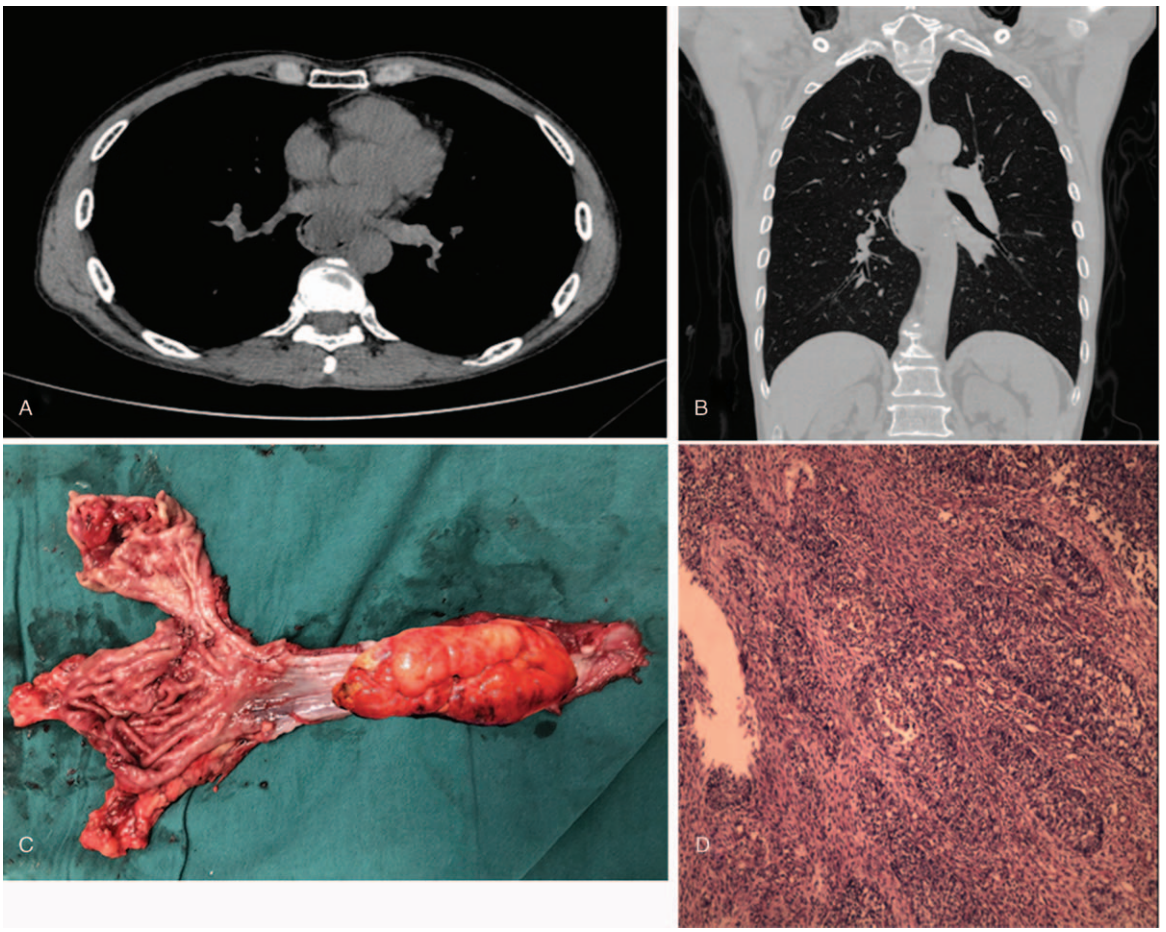

Figure 2. (A, B) Computed tomography (CT) showed a large, heterogeneous tumorous formation obturating the esophageal lumen without enlarged lymph nodes and invasion to the adjacent organs. (C) Macroscopic findings of the resected specimen showed a lobulated polypoid tumor that was 73 mm × 32 mm × 31 mm in diameter in the lower esophagus. (D) Pathological findings of the resected specimen showed both carcinomatous and sarcomatous components. CT = computed tomography.

3. Discussion

Virchow in 1864 investigated a tumor with tumorous proliferation of both epithelial and nonepithelial components within a single tumor.[5] Von Hansemann first reported the esophageal carcinosarcoma in 1904.[6] The etiology and oncogenesis of carcinosarcoma remains unclear. Three major theories have been proposed for the pathogenesis of carcinosarcoma. The first theory is that the spindle cell component develops in reaction to the carcinosarcoma (pseudosarcoma). The second theory, the collision theory, postulates that 2 individual stem cells independently or simultaneously transform into malignant cells, progressing thereafter into separate tumors (true carcinosarcoma). The third theory, the metaplastic theory, points to that the individual components are derived from the same malignant stem cell (so-called carcinosarcoma).[7] The last theory is that the sarcomatous component is derived from differentiation of the carcinomatous component.[8,9]

The clinical features of ECS is similar to that of ESCC with dysphagia as the most prominent and frequent symptom,[10,11] and sometimes with chest pain and weight loss. More than 80% of ECS are located in the middle and/or lower esophagus.[12] Macroscopically, ECS was 75% polypoid type and 15% ulcerative type.[12] In additional, infiltrative type of ECS was 33.8%.[11] Whereas, ESCC was 8.3% polypoid type and 91.7% infiltrative type.[11] When sarcomatous components are predominant, gross type is polypoid because of the few stromal ingredients. Likewise, when carcinomatous components are predominant, ulcerative type is usual.[13] In our case, the patient presented progressive dysphagia and precordial pain after swallowing, and the esophageal tumor was polypoid type that located in the lower esophagus. Endoscopic biopsy was inconclusive, because of the presence of necrosis and the insufficient amount of tissue required for immunohistochemical analysis, as well the biopsy samples taken in insufficient size and depth might miss one of the cellular components and led to a misdiagnosis. However, clinical features of ECS are different with ESCC in some degree. Thus, we diagnosed ECS based on characteristic morphology and pathology report of preoperative.

Due to the rare incidence of ECS, there are several controversies mainly focused on therapy and prognosis. Despite the huge size of the tumor, it does not invade as deeply as ESCC. More than 80% of tumors are limited to the submucosa or muscularis propria at presentation.[14] Zhang et al[11] reported the percentage of T1/2 lesions was higher in the ECS group than in the ESCC group (67.6% vs 29.7%, $P < .001$), which was similar to Liang Wang reported (20/33, 60.6%).[4] Therefore,

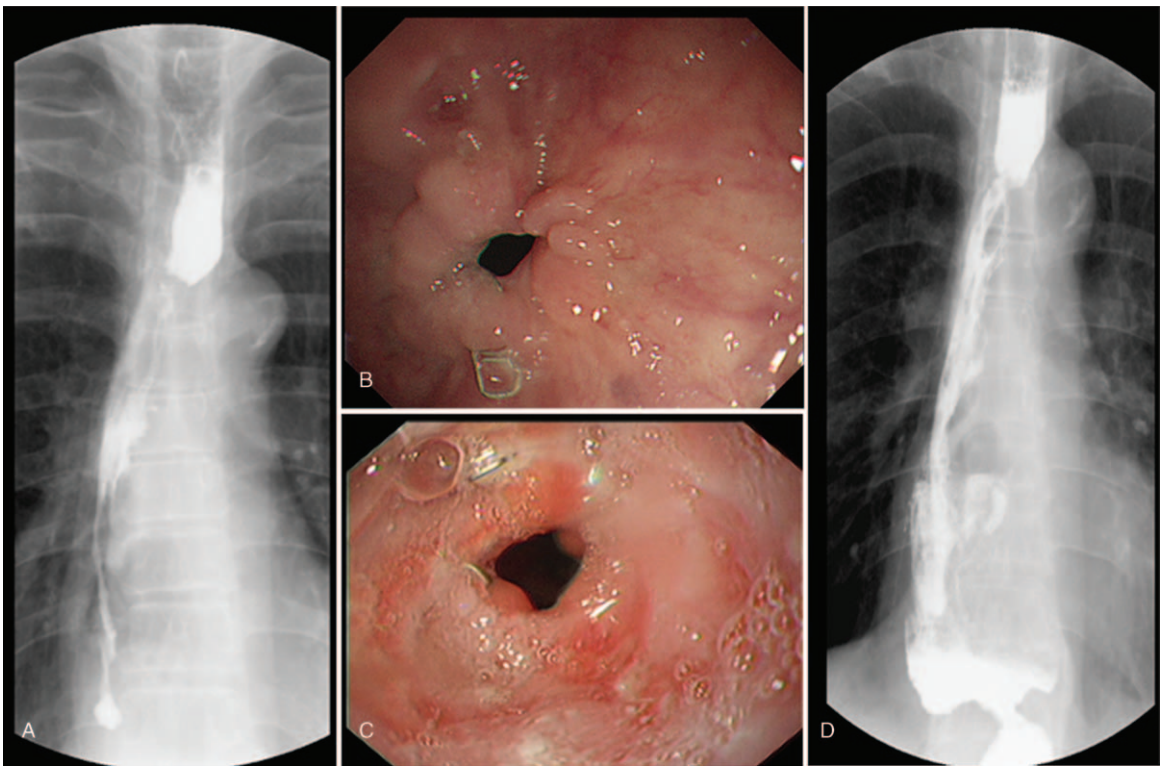

Figure 3. (A, B) Barium esophagography and EGD showed esophagostenosis after 1 months surgery. (C, D) Barium esophagography and EGD showed the esophageal lumen was enlarged by esophagectasis. EGD = esophagogastroduodenoscopy.

some investigations supported therapeutic endoscopy, including endoscopic polypectomy, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), which may represent an alternative to esophagectomy for superficial esophageal carcinosarcoma[15] and are more tolerable, less invasive, less expensive, notably, it enables the esophagus to be preserved, compared with traditional esophagectomy. Ji et al[14] reported 1 patient underwent endoscopic polypectomy without recurrence 17 months after operation. Nevertheless, we performed an Ivor Lewis esophagectomy, coupled with adequate lymph node dissection (2-field lymphadenectomy) for several reasons. Firstly, the rate exactly diagnosis of preoperative is low, which was reported by 14.1%,[11] whereas surgery could help make a definitive diagnosis and guide treatment of postoperative. Secondly, the rate of lymph node metastasis in ECS is about 50% to 67%, which is comparable to that of ESCC.[12] In other studies, the rate of lymph node metastasis was 45.1%,[11] 45.5%,[4] 52.6%,[16] 63.6%,[17] respectively, suggesting the highly biological behavior of metastasis. Thirdly, high-grade hyperplasia or carcinoma in situ was found in adjacent esophageal mucosa at a certain distance from the tumor body,[18] furthermore, Pesenti et al[15] found remnant tumor in area of

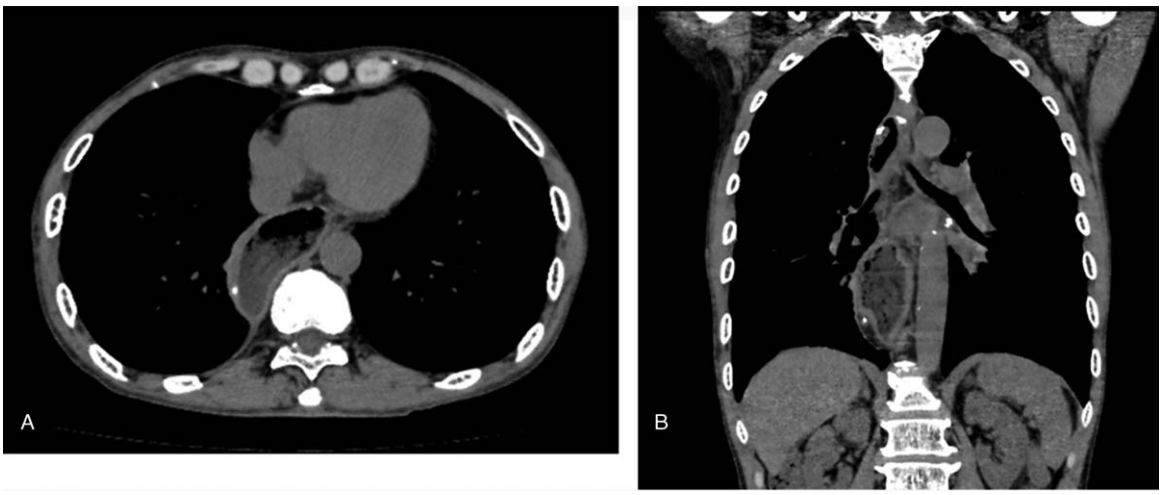

Figure 4. Computed tomography (CT) performed without evidence of recurrence or metastasis in the 24 months follow-up. CT = computed tomography.

previous ECS after EMR. Although long-term survivals may be achieved in single cases that underwent endoscopic resection. These ideas support radical esophagectomy and a wide lymphadenectomy.

It is well known that radiotherapy and chemotherapy are important in malignant tumor treatment. The chemoradiotherapy includes preoperative and postoperative. Kobayashi et al[19] considered chemotherapy with 5-fluorouracil plus cisplatin seemed to be partially effective in ECS, and that patient who underwent neoadjuvant chemotherapy remained disease free for 5 years after surgery. Some studies considered that chemoradiotherapy was active against carcinosarcoma and could be considered as a therapeutic option whenever surgery was not feasible, the clinical response of these cases were PR (partial remission), CR (complete remission), or downstage in these reports;[15,20,21] nevertheless recurrences sometimes occurred hematogenous metastasis or outside the field of radiation. Due to the effective of chemoradiotherapy, the chemoradiotherapy seemed useful in carcinosarcoma of cervical esophagus to preserve the laryngeal function, while that alone could not be considered because of the tumoral volume and dysphagia.[15] Thus, we recommend chemoradiotherapy associated with therapeutic endoscopy which could improve food intake is an interesting alternative to surgery for a patient with a large pedunculated esophageal tumor whenever surgery is not feasible. In previous studies,[20,21] the chemotherapy regimen mainly was 5-FU and CDDP, S-1, and 5-FU. In Wang's study,[4] the DP (docetaxel +cisplatin) regimen represented outstanding in not only neoadjuvant chemotherapy, but also recurrent treatment; especially in 1 case, the patient with supraclavicular lymph nodes metastasis (T3N1M1, stage IV) attained PR after concurrent chemoradiotherapy which was radiotherapy of 60 Gy and accompanied weekly docetaxel of 60 mg; then, 4 cycles of XELOX regimen (capecitabine + oxaliplatin) was given and the patient had CR, which lasted for 16.1 months; after tumor recurrence, CR was regained after the salvage treatment with 4 cycles of DP (docetaxel + cisplatin) regimen, which indicated that ECS may be partially sensitive to docetaxel combined with 5-fluorouracil or platinum-based chemotherapy. Additionally, Yoshimoto et al[22] reported the sarcomatous element had completely disappeared, and the carcinomatous element was only observed in situ after neoadjuvant chemotherapy of DCF regimen. To date, docetaxel is an anticancer agent used to treat sarcomas in several fields.[23] The efficacy of docetaxel for soft tissue sarcomas has been proven, mainly in combination regimens with gemcitabine.[24] Meanwhile, Yoshimoto et al[22] considered docetaxel may also be effective for the sarcomatous element. For patients who did not tolerate the prolonged hospitalization needed for fractionated delivery of intravenous 5-FU, the drug was replaced by capecitabine, an oral derivative of 5-FU that is known to be active against ESCC.[25] Thus, we selected docetaxel, capecitabine, and oxaliplatin as adjuvant therapy in the present case. However, Sanada et al[26] reported 1 patient underwent chemotherapy (docetaxel + 5FU) and radiation therapy (66 Gy) for 2 months, although the primary lesion became smaller, abdominal computed tomography found liver metastasis immediately. What is more, autopsy examination revealed liver metastasis, peritoneal dissemination, and intramural metastasis. Besides, Iwaya et al[27] reported the ECS recurrence was observed in the thorax; despite radiotherapy, tumor growth could not be controlled and the patient died 3 months later. This is the other debate whether the effective of chemoradiotherapy in ESC. Hence, Sano et al[28] investigated particularly MET and EGFR were overexpressed in ECSs. It suggested that molecular-targeted therapies directed to MET, EGFR, or other RTKs may be effective in inhibiting the growth or progression of the epithelial and/or mesenchymal component of ECS.[28] This is further to study to demonstrate the effective of molecular-targeted therapy. The immunohistochemical report was negative for CD34, and therefore, we did not consider the use of imatinib mesylate for medication in the present case.

The more main controversy is prognosis in ECS compared to ESCC. Some investigators reported that ECS had low-grade malignant potential and that its intraluminal growth contributed to early detection of the disease, leading to a comparatively good prognosis.[10] What is more, ECS is more resectable and lower invasion to adjacent organs than ESCC.[4] In Wang's study,[4] the 1-year, 3-year, and 5-year OS rates of ECS were 74%, 57%, and 48%, respectively, better than that of ESCC treated in their center,[29] in which the overall 1-year, 3-year, and 5-year survival rates were 82.9%, 44.3%, and 34.2%, respectively. Also, Zhang et al[11] reported the 5-year OS of ECS were 43 months and 44.8%, respectively, which was higher than 37.5 months and 38.3%, respectively, for ESCC ($P = .044$). Thus, these investigators considered the prognosis of ECS is better than ESCC. But there was other voice about that. The concept of better prognosis was not agreed with Iyomasa et al,[12] who reported that although the 3-year survival rate was higher for ECS (62.8%) than for ESCC (28.1%), there was no significant difference in 5-year survival between the 2 groups (26.7% vs. 22.4%), likely due to high recurrence rate in the late period of disease course. The prognosis is not as favorable as previously believed, due to the high possibility of hematogenous metastasis in the late period. Moreover, Iyomasa et al[12] reported that recurrence due to hematogenous metastasis was more frequent in ECS than ESCC. That was agreed with Ogasawara et al,[30] who reported 1 case died 16 months later due to lung metastasis caused by late hematogenous metastasis. As well as, Sanada et al[26] have reported that liver metastasis and peritoneal dissemination typically accompany sarcomatous components. Not only the squamous cell component, but also the sarcomatous cell component can metastasize or mixed. The rapidly growing ECS metastasized to regional lymph nodes and was mostly composed of sarcomatous elements,[31] which was also found in liver metastases and peritoneal dissemination.[26] While these sarcomatous cells might be more resistant to standard chemo- and/or radiotherapy than ESCC cells. In the other words, Sasajima and colleagues[32] reported the doubling time of their case to be 2.2 months, whereas that of ordinary ESCC was 5 months. The rapid growth of the tumor and sarcomatous elements are the reasons of poor prognosis in ECS. So it is reported that an even lower survival in ECS T1 patients than in ESCC T1 patients, and only 18.2% were alive "free of disease" at 2 years after surgery which did not support the better prognosis concept of ECS. Therefore, the prognosis of ECS remains to be elucidated further. The biological behavior of ECS is required to further investigate. However, how to identify the patients with high risk of tumor recurrence and poor prognosis who may benefit from adjuvant treatment is critical for improving treatment efficacy and survival outcome. We approved the TNM stage was identified as an independent prognostic factor in ECS.[11] In our case, we performed chemoradiation to provide local control and suppress hematogenous metastasis for patients with ECS.

In summary, we have described a case of ECS that was effectively treated with radical esophagectomy with adequate

lymph node dissection followed by adjuvant chemotherapy. Chemotherapy regimen with docetaxel, oxaliplatin, and capecitabine may be an potential and novel option for ECS. In additional, the molecular-targeted therapy is needed to further study.

Author contributions

Data curation: Can Zhao.
Formal analysis: Guangquan Dai.
Investigation: Yan Xu, Chang Liu.
Project administration: Jiang Wang, Dongqiu Dai.
Resources: Lei Gao.
Software: Bin Wu.
Writing – original draft: Xiaoyang Xu.
Writing – review & editing: Xiaoyang Xu.

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