Clinicopathological Features of Early-Stage Esophageal Carcinosarcoma

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Abstract
Esophageal carcinosarcoma (EC) is a rare malignant tumor, accounting for 0.5–2.8% of esophageal cancers. Most are advanced cancers that are detected as polypoid lesions and are treated with multidisciplinary therapy with a focus on surgery. However, endoscopic findings, pathological findings, and long-term outcomes of early-stage EC are often unclear because there are very few reported cases. This paper reports three cases of EC confined to the mucosal layer. The macroscopic type of all tumors was polypoid lesion with a slightly depressed lesion. All cases were clinically diagnosed as invasive cancer before treatment. Pathological diagnosis of tumor depth showed that one case had invaded the lamina propria mucosae, and two cases had invaded the muscularis mucosae (MM). One case of diagnosed MM had lymphoid invasion and lymph node metastasis to the upper mediastinum. After 1 year, although adjuvant treatment had been administered, there was lymph node recurrence in the left upper clavicle, and thus chemoradiation therapy was performed. Two other cases survived without recurrence. Early-stage EC is characterized by polypoid lesions with a slightly depressed lesion, and it is challenging to predict the histology on biopsy. Furthermore, it is difficult to determine the depth of invasion in the MM and submucosal layer in squamous cell carcinoma by endoscopy alone, and hence depth diagnosis by multiple modalities should be considered.
Introduction

According to the World Health Organization, esophageal carcinosarcoma (EC) is classified as a spindle cell squamous cell carcinoma that has a biphasic pattern of neoplastic squamous epithelium and spindle cells [1]. EC is extremely rare, accounting for 0.5–2.8% of esophageal cancers [2]. EC is characterized by the detection of polypoid lesions on endoscopy, and multidisciplinary treatment is performed, focusing on esophagectomy with lymph node dissection, but a standard treatment has not yet been established. In addition, EC is often found to invade deeper than the submucosal layer (SM), and the frequency of lymph node metastasis is not much different from that of squamous cell carcinoma (SCC), with some reports suggesting that its prognosis is better than that of SCC [3, 4]. However, there are very few reports of early-stage EC confined to the mucosal layer [5]. Therefore, the endoscopic findings, pathological findings, and long-term outcomes of early EC are unclear. The present report describes three surgical cases with pathological depth reaching the lamina propria mucosae (LPM) and muscularis mucosae (MM).

Case Reports

The clinicopathological characteristics of 3 patients are shown in Table 1.

Case 1
A 51-year-old man underwent upper gastrointestinal endoscopy for screening after treatment for acute pancreatitis, which revealed a 30-mm-sized, slightly depressed lesion with polypoid growth (type 0-IIc + Ip) in the lower esophagus (Fig. 1a). The anal side of the polypoid lesion was irregular, and thus the tumor was determined to be SM-invasive. Biopsies from the elevated and depressed areas both revealed SCC. However, the biopsy from the polypoid lesion also showed proliferation of spindle-shaped cells with prominent pleomorphism, indicative of EC. Thoracoscopic esophagectomy with three-field lymphadenectomy was performed 2 months after the initial consultation (Fig. 1b, c). There were no postoperative complications. The pathological diagnosis was EC with LPM invasion. The invasive front of this tumor was the SCC component. No lymph node metastasis, lymphatic invasion, or venous invasion was observed (Fig. 1d). The spindle cell component is shown in blue and the SCC component is shown in pink (Fig. 1e). Magnification of sarcoma component and vimentin staining results are shown (Fig. 1f, g), and magnification of SCC component and p40 staining results are shown (Fig. 1h, i). The patient was recurrence-free for 8 months after surgery.

Case 2
A 72-year-old man underwent an upper gastrointestinal endoscopy during a physical examination, which revealed a 15-mm-sized polypoid lesion protruding into the esophageal lumen (type 1) in the middle thoracic esophagus (Fig. 2a). The depth was determined to be muscularis propria because this polypoid growth lesion was irregular and tall. Biopsy from the polypoid lesion showed proliferation of short, spindle-shaped cells with fibrosis, which resulted in the diagnosis of carcinosarcoma. Thoracoscopic esophagectomy with three-field lymphadenectomy was performed 1 month after the initial consultation (Fig. 2b, c). There were no postoperative complications. Pathological diagnosis revealed EC and SCC as another lesion. The depth of the EC was MM, and no lymph node metastasis, lymphatic invasion, or venous invasion was observed (Fig. 2d). The spindle cell component is shown in blue and the SCC component is shown in pink (Fig. 2e). Magnification of sarcoma component and vimentin
staining results are shown (Fig. 2f, g), and magnification of SCC component and p40 staining results are shown (Fig. 2h, i). The patient was recurrence-free for 86 months after surgery.

**Case 3**

A 71-year-old man underwent upper gastrointestinal endoscopy to investigate epigastric discomfort and was diagnosed with a 50-mm-sized protuberance surrounded by a slightly depressed lesion (type 0-IIc + Is) in the middle thoracic esophagus (Fig. 3a). Endoscopic ultrasonography (EUS) showed irregularity in the epithelium and thickening in the LPM, and the SM was intact, thus the diagnosis of tumor depth was MM. Biopsy results from the polypoid and surrounding lesions all revealed SCC. Endoscopic submucosal dissection (ESD) was performed. The pathological diagnosis was EC and the depth of the tumor was MM with lymphatic invasion (Fig. 3b–d). Lymphatic invasion was vimentin negative and p40 positive, which indicates an SCC component (Fig. 4a–c). The spindle cell component is shown in blue and the SCC component is shown in pink (Fig. 3e). The invasive front of this tumor was the SCC component, and the volume of the SCC component was larger than in the other cases. Magnification of sarcoma component and vimentin staining results are shown (Fig. 3f, g), and magnification of SCC component and p40 staining results are shown (Fig. 3h, i). Thoracoscopic esophagectomy with three-field lymphadenectomy was performed as an additional treatment after non-curative ESD. There were no postoperative complications. Pathological diagnosis revealed no residual tumor in the esophagus, but SCC metastasis was observed in the left tracheobronchial lymph node (106tbL) (Fig. 4d). The sarcoma component was not observed in the lymph nodes. Although a 5-FU + CDDP regimen was performed as adjuvant chemotherapy, recurrence in the left cervical lymph node was observed 13 months after surgery, and a lymphadenectomy was performed. Pathological diagnosis was the metastasis of SCC.

### Table 1. Patients’ characteristics

|                      | Case 1 | Case 2 | Case 3 |
|----------------------|--------|--------|--------|
| **Age**              | 51     | 72     | 71     |
| **Sex**              | Male   | Male   | Male   |
| **Tumor location**   | Lt     | Mt     | Mt     |
| **Tumor length, mm** | 32     | 15     | 55     |
| **Macroscopic type** | IIc+Ip | 1      | IIc+Is |
| **Biopsy**           | SCC    | Carcinosarcoma | SCC |
| **Clinical depth**   | SM     | MP     | MM     |
| **ESD**              | No     | No     | Yes    |
| **Pathological depth** | LPM   | MM     | MM     |
| **Pathological N factor** | 0  | 0      | 1 (#106tbL) |
| ly/v                 | 0/0    | 0/0    | 1/0    |
| **Recurrence**       | no     | no     | yes    |
| **Outcome (month)**  | Alive (8) | Alive (86) | Alive (21) |

ESD, endoscopic submucosal dissection; LPM, lamina propria mucosae; Lt, lower thoracic esophagus; ly, lymphatic invasion; Mt, middle thoracic esophagus; SCC, squamous cell carcinoma; SM, submucosal layer; MM, muscularis mucosae; MP, muscularis propria; v, venous invasion.
The patient was subsequently treated with chemoradiation therapy and is alive 21 months after esophagectomy.

**Discussion**

EC is a rare disease, accounting for 0.5–2.8% of all esophageal cancers [2]. Moreover, endoscopic and pathological findings and long-term outcomes of early-stage EC are often unclear because there are very few reported cases [5]. In terms of depth, EC is often detected at depths below the SM [3]. The frequency of early-stage EC in our institution is as low as 10% among surgical specimens diagnosed as EC. Also, in terms of public ratio, the exact number is unknown because they are extremely rare. Generally, EC is composed of spindle cells and an SCC component [1, 6]. The appearance of EC is characterized by polypoid lesions mainly composed of spindle cells. In addition, SCC in the form of a slightly depressed type is often detected around polypoid lesions [7]. This finding was consistent in our cases. Macroscopic type 0-IIc + Is is probably characteristic of early-stage EC. While the frequency of lymph node metastasis of EC is not different from that of SCC, some reports suggest that the prognosis is better than that of SCC [4], and other reports suggest that there is no significant difference in 5-year survival because of the high recurrence rate in the late period [8]. Multidisciplinary
treatment, focusing on esophagectomy with lymph node dissection, has been performed in patients, but no standard treatment has been established. In this study, 2 patients were treated by surgery alone, and 1 patient underwent additional treatment because of lymphatic invasion detected by ESD. In the case of additional treatment, lymph node metastasis was observed. Despite subsequent adjuvant therapy, left cervical lymph node recurrence occurred. Therefore, it is necessary to keep in mind that lymph node metastasis, as well as SCC, is possible in early-stage EC when the tumor depth is MM.

There are several methods of diagnosing tumor depth by endoscopy. Especially, EUS can provide a more detailed diagnosis of depth. If the tumor is limited to the epithelium or LPM, endoscopic treatment such as ESD can be considered. Macroscopic type with 0-IIc + Is is common for both early-stage EC and submucosally invaded EC. In the endoscopic diagnosis of SCC, the depth of type 0-I with a polypoid growth lesion is diagnosed as SM. Therefore, early-stage EC with protuberance is likely to be diagnosed at a deeper depth. Thus, if the biopsy reveals carcinosarcoma, it should be kept in mind that it may be over-diagnosis, and a careful depth diagnosis using various modalities. In two of the three cases in this study, the pre-operative diagnosis of invasion depth was overestimated. Preoperative and postoperative diagnoses were consistent in one case, in which EUS was performed; superficial lesions that reveal macroscopic type 0-IIc + Is should be considered for EUS or diagnostic ESD because it may be early-stage EC that has invaded within the mucosal layer.

Fig. 2. a Endoscopy revealed elevated lesions with irregular surfaces. b, c The surgical specimen shows a polypoid lesion protruding into the lumen and slightly depressed lesion with unstained iodine staining on the oral side. d Panoramic view of the lesion. e The spindle cell lesion is marked in blue and the SCC lesion is marked in pink. f, g Spindle cells proliferate in the polypoid lesion, and vimentin is positive for spindle cells. h, i SCC is found in the epithelium of the polypoid lesion, and p40 is positive for SCC.
Histological diagnosis often cannot be determined by biopsy alone, and thus, if a polypoid growth lesion is detected, the possibility of EC should be considered, and it is necessary to consider taking biopsies not only from the protuberance area but also from the surrounding area. If spindle cells and SCC components are observed in a single specimen, EC is suspected, and endoscopic findings are also helpful in the pathological diagnosis. Then, we can identify the spindle cells and SCC components by adding vimentin and p40 staining. Histological results showed that the invasive SCC components were more widely proliferative in case 3 than in the other two cases. In addition, it was diagnosed as lymphatic invasion because of the presence of SCC in the lymphatic duct. Furthermore, 106thL metastasis and cervical lymph node metastasis also consisted of the SCC component, which was characteristic. Lymphatic invasion and lymph node metastasis are often SCC [9]. This is consistent with the present case. SCC components are more likely to develop lymph node metastasis than spindle cell components because of a more invasive tendency. In addition, we perform non-surgical treatment according to SCC in advanced cases.

In conclusion, the features of the macroscopic type of early-stage EC are polypoid growth with a surrounding slightly depressed lesion. When a polypoid lesion is detected, EC should be considered, and the biopsy site should be determined. Because type 0-I EC may be confined to the mucosal layer, ESD can be performed to complete the resection. Therefore, a detailed depth diagnosis is essential, such as by EUS. Then, if an invasive SCC component is present and
the tumor depth is MM, the possibility of lymphatic invasion and lymph node metastasis should be considered.

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**Statement of Ethics**

Written informed consent was obtained from every patient for publication of the details of their medical case and any accompanying images. This retrospective review of patient data was approved by the Review Board of the National Cancer Center Hospital (Approval No. NCC 2017-061).

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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Author Contributions

Kentaro Kubo, Junya Oguma, and Hiroyuki Daiko reported the cases and wrote the manuscript. Daichi Utsunomiya, Kyohei Kanematsu, Yusuke Fujii, Daisuke Kurita, and Koshiro Ishiyama helped in drafting the manuscript. Seiichiro Abe and Shigeki Sekine participated in revising the manuscript critically. All the authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Any further query may be addressed to the corresponding author.

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