Adenocarcinoma originating from long-segment Barrett’s esophagus over 15 cm: a series of 3 cases

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Abstract

Background: Barrett’s esophagus (BE) is characterized by presence of columnar epithelium in the lower esophageal mucosa, which originally comprises stratified squamous epithelium. Importantly, long-segment Barrett’s esophagus (LSBE) has a particularly high carcinogenic potential.

Case presentation: Herein, we report three cases of Barrett’s esophageal adenocarcinoma (BEAC) originating from LSBE larger than 15 cm. All three patients underwent surgery for the diagnosis of BEAC. A 66-year-old man with advanced esophageal cancer underwent neoadjuvant chemotherapy and subsequent subtotal esophagectomy. The postoperative pathological diagnosis was of poorly differentiated adenocarcinoma with lymph node metastasis (pT3 pN3 pM0 pStage III based on the Union for International Cancer Control TNM Classification 8th edition). Two years after the operation, the patient was diagnosed with recurrence around the celiac artery and underwent chemotherapy. An 83-year-old woman with advanced esophageal cancer underwent subtotal esophagectomy. The postoperative pathological diagnosis was of well-differentiated adenocarcinoma with supraclavicular lymph node metastasis (pT3 pN3 pM1 pStage IV). Two months after the operation, the patient was diagnosed with recurrence in the neck lymph nodes and underwent chemotherapy; however, she died. A 66-year-old man with early-stage esophageal cancer underwent subtotal esophagectomy. A superficial early cancerous lesion was seen over BE. The postoperative pathological diagnosis was of well-differentiated adenocarcinoma without lymph node metastasis (pT1a pN0 pM0 pStage 0). The patient was found to be alive and recurrence-free 3 months after the operation.

Conclusions: BEAC might show good prognosis if detected and treated early. Extremely LSBE is associated with a high incidence of BEAC; therefore, early detection and treatment with close surveillance is essential.

Keywords: Barrett’s esophagus, Adenocarcinoma, Surveillance

Background

Barrett’s esophagus (BE) is characterized by presence of columnar epithelium in the lower esophageal mucosa, which originally comprises stratified squamous epithelium. Importantly, long-segment Barrett’s esophagus (LSBE) has a particularly high carcinogenic potential. Here, we report three cases of Barrett’s esophageal adenocarcinoma (BEAC) originating from LSBE larger than 15 cm.

Case presentation

Case 1
A 66-year-old man with esophageal obstruction was admitted to a different hospital. He was referred to our institution following diagnosis of BEAC. Endoscopy revealed a squamocolumnar junction 24 cm from the...
incisor teeth and a type-3 circumferential tumor on the lower esophagus (Fig. 1). Mucosal biopsy revealed adenocarcinoma.

Computed tomography detected an enlarged lymph node but no other distant metastatic sites. Following diagnosis of cT3N1M0, subtotal esophagectomy with lymph node dissection was performed after three courses of S-1 + oxaliplatin therapy.

The postoperative pathological diagnosis was of poorly differentiated adenocarcinoma (T3 70 × 45 mm) with lymph node metastasis (N3) (pT3 pN3 pM0 pStage III; Fig. 1). Two years after the operation, the patient showed recurrence in the region of the celiac artery and is currently undergoing chemotherapy.

**Case 2**
An 83-year-old woman who had undergone upper gastrointestinal endoscopy for detailed examination of anemia was referred to our hospital with a diagnosis of BEAC.

Endoscopy revealed a squamocolumnar junction 15 cm from the incisor teeth and a type-2 semicircular tumor on the upper esophagus (Fig. 2). Mucosal biopsy showed adenocarcinoma.

Computed tomography detected enlarged cervical paraesophageal lymph nodes (#101) with no other distant metastatic sites. Following diagnosis of cT3N1M0, subtotal esophagectomy with lymph node and neck dissection were performed. The postoperative pathological diagnosis was of well-differentiated adenocarcinoma (60 × 52 mm) with supraclavicular lymph node metastasis (pT3 pN3 pM1 pStage IV; Fig. 2). Two months after the operation, the patient was diagnosed with recurrence in the neck lymph nodes, for which she underwent chemotherapy; however, she died.

**Case 3**
A 66-year-old man diagnosed with BEAC in a periodic medical check-up was referred to our institution.

Endoscopy revealed a squamocolumnar junction 20 cm from the incisor teeth and a type 0-IIb + IIc tumor with indistinct boundaries 30 cm from the incisor teeth (Fig. 3). Mucosal biopsy revealed adenocarcinoma.

Computed tomography detected no enlarged lymph nodes and no other distant metastatic sites. Following diagnosis of cT1aN0M0 based on the Union for International Cancer Control TNM Classification 8th edition, subtotal esophagectomy was performed with lymph node and neck dissection. The postoperative pathological
diagnosis was of well-differentiated adenocarcinoma (143 × 56 mm) with no lymph node metastasis (pT1a pN0 pM0 pStage 0 based on the Union for International Cancer Control TNM Classification 8th edition; Fig. 3). The patient was found to be alive and recurrence-free 3 months after the operation.

**Discussion**

BE was named after a British thoracic surgeon, Norman Rupert Barrett (1903–1979), who reported a patient showing presence of columnar epithelium covering the lower esophagus with an esophageal ulcer [1].

BE indicates the origin of adenocarcinoma. Especially in the United States of America, histologically, esophageal adenocarcinoma has overtaken esophageal squamous cell carcinoma since 1995, and in 2005, up to 70% of esophageal cancers were BEAC [2].

Gastroesophageal reflux disease (GERD) is well recognized as a major cause of BE and BEAC. Among the reflux contents, gastric acid and bile acid reflux are of critical importance [3].

One systematic review uncovered that the prevalence of GERD was 18–27% in North America, 8–25% in Europe, 2–7% in East Asia, and 23% in South America [4]. The prevalence of GERD has been increasing, especially in developed countries, and the associated BEAC is increasing in North America, Europe, and Australia [5].

In Japan, BE is classified according to its length; when it is 3 cm or larger, it is called LSBE, and when it is shorter than 3 cm, it is called short segment BE (SSBE) [6].

The detection frequency of LSBE larger than 13 cm is 1.27% (15/1175) [7], and it is conceivable that LSBE larger than 15 cm is a relatively uncommon condition. Until now, nine cases have been reported in the literature [8–15] (Table 1).

In these cases, including ours, 10 patients were men, and the average age was 65.5 years. The median length of BE was 17 cm (15–22 cm). The depth of invasion was T1a, T1b, T2, and T3 in 4, 5, 1, and 2 cases, respectively. Two of the three cases we encountered had advanced cancer with early recurrence. In one case, the enlarged lesion occupied almost the entire BE. Overall, 4 of 12 cases had superficial lesions (cases 7, 8, 9, 12). In some cases, the advanced cancer is associated with superficial, enlarged lesions, and preoperative diagnosis of the resection area is important. In such cases, marginal resection is required, and total resection of BE may be preferable owing to the heterogeneity of BEAC derived from LSBE.
The treatment policy for BEAC depends on the depth of invasion and the stage of the disease as in the case of esophageal cancer. We performed surgery after three courses of SOX therapy in case 1. The effectiveness of preoperative chemotherapy for esophageal cancer has been reported, and the National Comprehensive Cancer Network guideline also recommends preoperative chemotherapy as an option for esophageal adenocarcinoma with lymph node metastases deeper than T2 [16, 17]. A clinical trial of preoperative SOX therapy for esophageal adenocarcinoma of Siewert type I or II with esophageal invasion larger than 3 cm with lymph node metastasis regardless of T3/T4a or T factor is ongoing in Japan.

Overall, long-term recurrence-free survival is achieved, except in patients with advanced cancer and in case 4, early curative resection may improve the prognosis of BE cancer. Based on these findings, residual BE surveillance and prevention of BEAC are critical.

Heartburn and esophageal reflux were observed in 8 of the 12 cases. Gashi et al. [18] reported that BE shortened the maximum length and total circumference when proton pump inhibitors (PPIs) were administered for 2 years. As such, PPIs may be effective in patients with reflux esophagitis and GERD.

There were two cases of BE after total gastrectomy. In an animal model, Miwa et al. [19] reported that the presence of bile acids and gastric juice was important for the development of BE and adenocarcinoma. It is suggested that bile acid reflux influences the occurrence of BEAC in two cases after total gastrectomy. Shirvani et al. [20] reported that stimulation of the BE mucosa with bile acid increased the expression of cyclooxygenase 2 (COX2); it is considered to suppress apoptosis via prostaglandin E2 by expression of COX2. COX2-selective inhibitors and aspirin may increase apoptosis, suppress growth of esophageal adenocarcinoma, and shorten BE [21–23].

LSBE surveillance is another important consideration for future research. Annual surveillance of all BE cases is financially inefficient, and it is important to identify BE with a high carcinogenic risk and apply an efficient method for narrowing the cases that require close surveillance.

In 2014, the British Gastroenterological Society recommended surveillance every 2–3 and 3–5 years for LSBE 3 cm or larger and SSBE shorter than 3 cm, respectively [24].

Rajeswari et al. reported that BE length may be a risk for BEAC. The annual risk of BEAC stratified by length is 0.31%/year (3 cm or shorter), 0.97%/year (4 to 6 cm),
Table 1 Characteristics of patients with LSBE larger than 15 cm

| Case no. | Author       | Year | Age | Gender | Length of Barrett's esophagus | Size of carcinoma (cm) | Location of the tumor | Histology | Depth of invasion | N | Iy | V | Background disease | Prognosis |
|----------|--------------|------|-----|--------|--------------------------------|------------------------|----------------------|------------|------------------|----|----|---|------------------|-----------|
| 1        | Kato         | 2002 | 45  | M      | 15                             | 2.7 × 23               | Lt                   | tub2       | SM               | 0  | 0  | 0 | Hiatus hernia     | 2Y9M alive |
| 2        | Fujimura     | 2006 | 67  | F      | 18                             | 5                      | Ut Mt                | tub1       | SM               | 0  | 2  | 0 | Kyphosis, hiatus hernia | 4Y8M alive |
| 3        | Fujimura     | 2006 | 57  | M      | 22                             | 2                      | Lt                   | tub1       | M                | 0  | 0  | 0 | Post-total gastrectomy (R-Y, 29 years ago) | 2Y alive |
| 4        | Stefan Hartl | 2008 | 58  | M      | 15                             | 3                      | Lt                   | tub1       | M                | 0  | –  | – | –                | 1M EMR, 4M additional operation |
| 5        | Shimada      | 2013 | 74  | M      | 20                             | 2.0 × 30               | Ut Mt                | tub1       | M                | 0  | –  | – | Post-total gastrectomy (R-Y, 44 years ago) | 1Y10M alive |
| 6        | Morita       | 2013 | 74  | M      | 17                             | 2.5 × 19               | Ae                   | tub1       | SM               | 0  | 0  | 0 | Hiatus hernia     | 3Y alive |
| 7        | Kikuchi      | 2016 | 63  | M      | 18                             | 18 × 4                 | Mt Lt                | tub1, pap > tub2, por | MP          | 0  | 0  | 0 | Hiatus hernia     | 1Y6M alive |
| 8        | Zaiki        | 2016 | 65  | M      | 15                             | 12                     | Lt Mt Ae             | tub1       | M                | 0  | 0  | 0 | Hiatus hernia     | 1Y6M alive |
| 9        | Miyazaki     | 2016 | 68  | M      | 17                             | 11.6 × 49              | Lt Mt Ae             | tub2 > tub1 > por | SM           | 0  | 1  | 0 | Hiatus hernia     | 2Y5M died |
| 10       | Our case     | 2020 | 66  | M      | 16                             | 7 × 45                 | Lt Ae                | por > sig   | AD             | N3 | 1  | 2 | Hiatus hernia     | 2Y lymph node recurrence, alive |
| 11       | Our case     | 2020 | 66  | M      | 18                             | 6.0 × 5.2              | Ut                   | tub1, tub1 | AD             | N3 | 2  | 2 | Hiatus hernia     | 2M lymph node recurrence, died |
| 12       | Our case     | 2020 | 66  | F      | 18                             | 14.3 × 5.6             | Ut Mt Lt Ae G        | tub1       | SM             | 0  | 0  | 0 | Hiatus hernia     | 3M alive |

tub1 well-differentiated tubular adenocarcinoma, tub2 moderately differentiated tubular adenocarcinoma, pap papillary adenocarcinoma, por poorly differentiated adenocarcinoma, M mucosal layer, SM submucosal layer, MP muscularis propria, AD adventitia, EMR endoscopic mucosal resection
1.26%/year (7 to 9 cm), 1.64%/year (10 to 12 cm), and 2.41%/year (13 cm or larger). Patients with carcinogen- 
essis within a year have significantly longer BE length, 
and a 28% increase in annual risk of BEAC was seen 
for every 1 cm of BE length increase. Ultra-long BE is 
a risk factor for carcinogenesis, and for LSBE > 15 cm, 
short-term follow-up within at least 1 year is consid- 
ered necessary.

Random biopsy is recommended for surveillance of 
BEAC in Europe and America; magnifying endoscopy 
is not recommended. For early lesions, the general strategy is to perform radiofrequency ablation (RFA) on the 
remaining BE after removal by endoscopic mucosal resection.

However, although RFA is an option for LSBE treat- 
ment and prevention of cancer development, it is not 
particularly common in Asian countries. Further reporting 
and accumulation of therapeutic results is necessary for 
its dissemination. The patient in case 6 underwent 
endoscopic submucosal dissection. Narrow-band im- 
ing (NBI) allowed accurate recognition of the lesion 
position and curative resection, and 3-year recurrence-
free survival was achieved. Sharma et al. and Curvers 
et al. [25, 26] reported that biopsy using NBI was useful; 
however, further work remains to be done as NBI was 
expected to be efficient for future surveillance.

Conclusions

BEAC might show good prognosis if detected and treated 
early. Extremely LSBE is associated with a high incidence 
of BEAC; therefore, early detection and treatment with 
close surveillance is essential. Further case accumula-
tion is warranted for prevention and establishment of 
surveillance.

Abbreviations

BE: Barrett's esophagus; BEAC: Barrett's esophageal adenocarcinoma; COX2: 
Cyclooxygenase 2; ESD: Endoscopic submucosal dissection; GERD: Gas-
troesophageal reflux disease; LSBE: Long-segment Barrett’s esophagus; NBI: 
Narrow-band imaging; PPI: Proton pump inhibitor; RFA: Radiofrequency 
ablation.

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Authors’ contributions

IH made substantial contributions to the concept and design of the case 
report. NK, IH, HG, NT, and YN envisioned the study, participated in its design 
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