# Tumor location is a risk factor for lymph node metastasis in superficial Barrett's adenocarcinoma

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## ABSTRACT

**Background and study aims** Endoscopic treatment is indicated for superficial Barrett's adenocarcinoma (BA) with a negligible risk of lymph node metastasis (LNM). However, risk factors associated with LNM in superficial BA are still not well characterized. The aim of the current study was to clarify risk factors for LNM of superficial BA.

**Patients and methods** A retrospective study was conducted in 87 consecutive patients with BA that was resected at National Cancer Center Hospital, Tokyo, Japan between 1990 and 2013. We assessed tumor size, macroscopic type, histological type, tumor depth of invasion, lymphovascular invasion and tumor location to analyze factors associated with LNM. Tumor location was classified into following 2 groups according to Siewert classification: 1) BA of the esophagogastric junction (EGJ-BA) as those having their center within 1 cm proximal from the EGJ; and 2) Esophageal-BA as those having their center at 1 cm or more proximal to the EGJ. EGJ was defined as distal end of the palisade vessels.

**Results** LNM was detected in 10 (11 %) patients. Univariable analysis revealed that tumor size, tumor depth of invasion, histological type of mixed differentiated and undifferentiated-type adenocarcinoma, lymphovascular invasion and tumor location of esophageal-BA were significantly associated with LNM. Multivariable analysis revealed that tumor location of esophageal-BA [odds ratio 7.8 (95 %CI: 1.3 – 48.1)] was a potential risk factor for LNM.

**Conclusions** The current study demonstrated that tumor location is a potential risk factor for LNM in BA. Therefore, indications for endoscopic treatment of esophageal-BA and EGJ-BA could be different.

## Introduction

In Japan, Barrett's esophagus (BE) is rare compared to incidence in Western countries [1, 2]. However, the number of patients with BE could increase with the decline of *Helicobacter pylori* infection rates [3, 4].

Therapeutic endoscopy, including endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), radiofrequency ablation, photodynamic therapy and argon plasma coagulation, has been indicated for superficial Barrett's adenocarcinoma (BA) with a negligible risk of lymph node metastasis (LNM) [5, 6]. Therapeutic endoscopy is effective and safe as a

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curative intent, and organ preservation is a great benefit for patients [7, 8].

Tumor invasion through muscularis mucosae into the submucosa, lymphovascular invasion and poor differentiation of tumor are known risk factors for LNM in BA [9 – 13]. However, risk factors were determined from surgical series in Western countries. Furthermore, risk factors according to location of the tumor based on Siewert classification are unknown [14]. Our hypothesis was that differences in wall structure between the esophagus and the EGJ may affect LNM of BA. The current study aimed to identify risk factors for LNM in superficial BA.

## Patients and methods

Using a prospectively stored local histopathology database, the current study involved a total of 87 consecutive superficial BAs occurring among Japanese, which were resected at National Cancer Center Hospital, Tokyo, Japan, between 1990 and 2013. BA was defined as a tumor arising within or adjacent to an area of BE. BE was endoscopically defined as columnar-lined distal esophagus between the squamocolumnar junction and EGJ. EGJ was defined as distal end of the lower esophageal palisade vessels [15,16]. If the palisade vessels cannot be observed, EGJ was defined as upper ends of the gastric mucosal folds [17]. Maximum length of background BE was endoscopically measured between the estimated EGJ and proximal side of the squamocolumnar junction. Pathological report was also referred if the BE was long segment. This retrospective study was approved by the internal review board in our institution.

Of the cases, 50 were surgically resected between 1990 and 2013 and 37 cases were endoscopically resected between 1997 and 2011 with at least 3 years' follow-up observation. LNM of the surgically resected cases were evaluated in the resected specimens. LNM of the endoscopically resected cases was evaluated by annual computed tomography (CT) scans and/or endoscopic ultrasonography [18]. None of the patients received preoperative radiotherapy or chemotherapy. Of the 37 endoscopic resected cases, 2 underwent EMR and 35 underwent ESD.

Both surgically and endoscopically resected specimens were fixed in formalin spread out by pins. The surgically resected specimens were opened longitudinally and cut serially into 5-mm thick sections. The endoscopically resected specimens were sectioned serially at 2-mm intervals. The slices were embedded in paraffin and all the sections were stained with hematoxylin and eosin (HE).

Tumor depth of invasion, histological type and lymphovascular invasion (LVI) were histologically evaluated. Tumor depth of invasion was subclassified as mucosa (pM), superficial submucosa (pSM superficial, <500 μm into the SM) and deep SM (pSM deep, ≥500 μm). Histological type of the tumor was made by Japanese classification of gastric carcinoma and was classified as "differentiated-type" (tubular and papillary adenocarcinoma) and "mixed -type" (both differentiated- and undifferentiated-type within one lesion) [19]. Lymphovascular invasion was determined by HE staining, immunohistochemical a-

nalysis using D2 – 40 monoclonal antibody for lymphatic invasion and/or Elastica van Gieson staining for vascular invasion.

Tumor size, macroscopic type and tumor location were evaluated based on the endoscopic findings. We used Japanese classification of esophageal cancer for expression of the macroscopic type [20]. Tumor location was classified into 2 groups in accordance with Siewert classification: 1) BA of the esophagogastric junction (EGJ-BA) as those having their center within 1 cm proximal to the EGJ; and 2) esophageal-BA as those having their center at 1 cm or more proximal to the EGJ [14] (▶ Fig. 1).
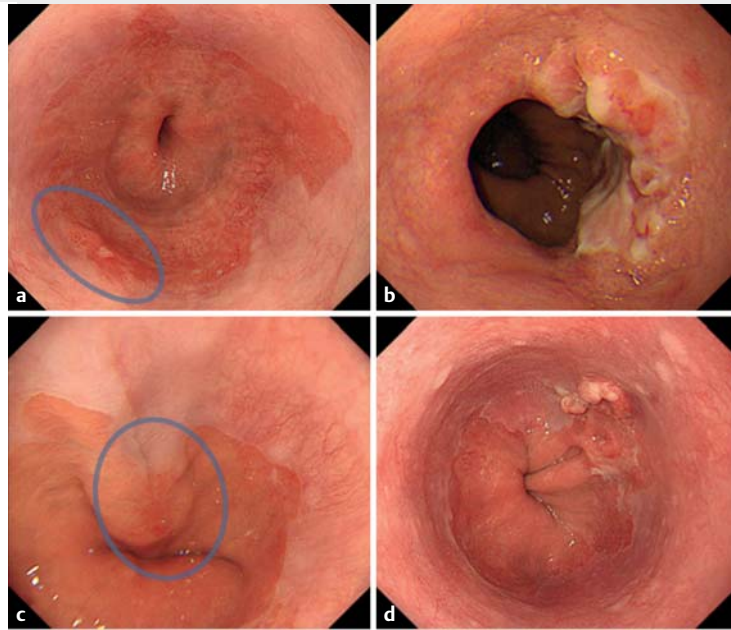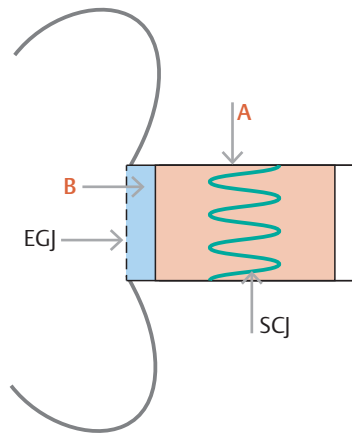
### Statistical analysis

A comparison of clinicopathological features, such as age, gender, tumor size, macroscopic type, histological type, depth of invasion, tumor location and present/absent of LVI, was made between LNM-positive and LNM-negative groups, and esophageal-BA and EGJ-BA groups.

For statistical analysis, exact test for categorical variables or Mann – Whitney U test for continuous variable was used to compare patient characteristics between esophageal-BA and EGJ-BA. Univariable odds ratios (ORs) with 95 % confidence intervals (CIs) were estimated. A logistic regression model was used to estimate ORs and 95 % CIs adjusted for potential confounders. The model included all variables with $P < 0.05$ in the univariable analyses, which were tumor size, depth of invasion, histological type and lymphovascular invasion, and tumor location. We used receiver operating characteristic curve to find the best cutoff point of tumor size that could separate LNM-positive patients from LNM-negative patients; and our data suggested the cutoff of 26 mm. Based on the result and the historical data [21], tumor size was divided into 2 categories with cutoff of 30 mm. All $P$ values were 2-sided and $P < 0.05$ was considered significant.

## Results

Patient characteristics are summarized in ▶ **Table 1**. Maximum length of background BE was <1 cm in 34 cases (39 %), ≥1/<2 cm in 23 cases (26 %), ≥2/<3 cm in 13 cases (15 %) and ≥3 cm in 87 cases (20 %) [median 11 mm (range 2 – 120)]. Regarding macroscopic type, the present study included 3 cases of 0-Ip (3 %), 12 0-Is (14 %), 22 0-IIa (25 %), 2 0-IIb (2 %), 27 0-IIc (31 %) and 21 mixed type (24 %). The mixed type included 14 cases of 0-IIa + IIc (16 %), 1 IIc + IIb (1 %), 1 Ip + IIa (1 %), 2 Is + IIa (2 %), 1 Is + IIb (1 %), 1 Ip + IIc (1 %), 1 Is + IIc (1 %).

The 50 surgically resected cases [age 66 (39 – 85), male/female: 46/4] included 8 and 42 cases of pM and pSM superficial/deep, respectively. Mean tumor size was 17 mm (range 3 – 37). Among them, 9 cases were referred for additional surgery after non-curative ESD. In the remaining 41 cases resected by surgery only, the number of pM, pSM superficial and pSM deep were 8, 8, and 25 cases, respectively. In the 8 pSM superficial cases, 5 (63 %) were estimated pSM1, 2 (25 %) were pSM2, 1 (13 %) was pSM3. In contrast, in the 25 pSM deep cases, 11 (44 %) were estimated pSM2 and 14 (56 %) were pSM3, respectively. When compared pSM superficial/deep criteria in the current study and conventional criteria, most of the pSM superficial corre-

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▶ **Fig. 1** Tumor location classified into 2 subtypes: A esophageal-BA (**a, b**) and B EGJ-BA (**c, d**)

sponded to SM1 and pSM deep corresponded to SM2 or 3 in the conventional criteria [22]. The 37 endoscopically resected cases [age 67 (41 – 88), male/female: 33/4] included 31 and 6 cases of pM and pSM superficial/deep, respectively. Mean tumor size was 28 mm (range 12 – 107). No LNM or recurrences were discovered in the 37 endoscopically resected cases during a median follow-up period of 5.8 years (range 3.0 ~ 10.2).

Compaing esophageal-BA and EGJ-BA, median tumor size was significantly larger, rate of mixed histological type and presence of LVI was significantly higher in esophageal-BA patients (▶ **Table 1**).

Univariable analysis revealed that tumor size larger than 3 cm, pSM deep invasion, histological type of mixed-type adenocarcinoma, LVI and tumor location of esophageal-BA were significantly more likely to be associated with the LNM-positive group than with the LNM-negative group (▶ **Table 2**). Multivariable analysis revealed that esophageal-BA in tumor location was a potential risk factor for LNM. In the 13 cases of pSM superficial, there were no patients with LNM. In the 35 cases of pSM deep, 5 of 10 patients with esophageal-BA (50 %) had LNM, while 3 of 25 patients with EGJ-BA (12 %) had LNM ($P = 0.027$).

Stratified proportion of LNM in the EGJ-BA is summarized in ▶ **Table 3**. LNM was detected in 10 cases (11 %) that invaded into submucosal (SM) layer 1,000 μm or more except for 2 cases with muscularis mucosae (MM) invasion (▶ **Table 4**). Only 1 case exhibited LNM from intramucosal BA with differentiated type adenocarcinoma without LVI that invaded into muscularis mucosae [23].

## Discussion

Based on a systematic review, the proportion of LNM for intramucosal BA has been reported in 1.9 % (95 % confidence interval 1.2 – 2.7) and LNM from intramucosal BA have been analyzed in a few studies [13, 24 – 26]. However, there are no data assessing risk of LNM based on tumor location. The current study demonstrated that tumor location within the esophagus was a potential risk factor for LNM. Possible explanations for the difference between esophageal-BA and EGJ-BA can be divided into 2 factors, the host side and the tumor side. As for the host side, high densities of lymphatic and vascular channels in the lamina propria mucosa (LPM) of the esophageal wall may offer a possible explanation. Yajin et al. studied D2 – 40 immunohistochemical staining of human lymphatic epithelium in the esophagus and found that LPM contained abundant longitudinally running lymphatic vessels [27]. Hahn et al. studied CD31 and D2 – 40 immunohistochemical staining for BE and found that superficial and deep LPM in BE each had significantly higher blood vessel and lymphatic vessel densities compared with the submucosa [28]. Because of this difference in wall structure, esophageal location was considered to be a potential risk factor for LNM in the current study.

Tumor size, tumor depth of invasion, histological type and LVI might affect LNM, although only tumor location was statistically significant by multivariable analysis [9]. According to results of the current study, the differences between EGJ-BA and esophageal-BA were larger size, higher proportion of mixed histological type, and LVI in esophageal-BA. There is a possibility that esophageal BA is already large and invasive on detection. An easily missed lesion or one that is rapidly growing is consid-

| | Esophageal-BA | EGJ-BA | Total | P value[1] |
|---|---|---|---|---|
| | n = 17 | n = 70 | n = 87 | |
| Age (yr)[2] | 68 (52 – 81) | 64 (39 – 88) | 66 (39 – 88) | 0.17 |
| Gender (Male) | 15 (88 %) | 64 (91 %) | 79 (91 %) | 0.64 |
| Tumor size (mm)[2] | 41 (5 – 107) | 22 (3 – 60) | 23 (3 – 107) | <0.01 |
| Macroscopic type[3] | | | | |
| ▪ Flat | 6 (35 %) | 45 (64 %) | 51 (59 %) | 0.095 |
| ▪ Protruded and mixed | 11 (65 %) | 25 (16 %) | 36 (41 %) | |
| Treatment strategy | | | | |
| ▪ Endoscopy only | 4 (24 %) | 33 (48 %) | 37 (43 %) | 0.30 |
| ▪ Endoscopy + Surgery | 0 | 9 (13 %) | 9 (10 %) | |
| ▪ Surgery only | 13 (76 %) | 28 (39 %) | 41 (47 %) | |
| Tumor depth of invasion | | | | |
| ▪ pM | 4 (24 %) | 35 (49 %) | 39 (45 %) | 0.13 |
| ▪ pSM superficial | 3 (18 %) | 10 (14 %) | 13 (15 %) | |
| ▪ pSM deep | 10 (59 %) | 25 (36 %) | 35 (40 %) | |
| Histological type | | | | |
| ▪ Differentiated | 9 (53 %) | 55 (79 %) | 64 (74 %) | 0.028 |
| ▪ Mixed | 8 (47 %) | 15 (21 %) | 23 (26 %) | |
| Lymphovascular invasion | | | | |
| ▪ Absent | 8 (47 %) | 57 (81 %) | 65 (75 %) | <0.01 |
| ▪ Present | 9 (53 %) | 13 (19 %) | 22 (25 %) | |
| LNM | 6 (38 %) | 4 (6 %) | 10 (11 %) | <0.01 |

EGJ, esophagogastric junction; BA, Barrett's adenocarcinoma; M/F, Male/Female; M, intramucosal carcinoma; SM, submucosal invasive cancer; superficial, <500 μm invasion; deep, ≥500 μm invasion; Mixed, both differentiated- and undifferentiated-type within one lesion; LNM, lymph node metastasis.
[1] Comparison between Esophageal-BA and EGJ-BA
[2] Data were expressed as median and range.
[3] "Protruded" type includes 0-Ip or Is, "Flat" type includes 0-IIa, IIb or IIc, and "Mixed" type included 0-IIa + IIc, IIc + IIb, Ip + IIa, Is + IIa, Is + IIb, Ip + IIc, Is + IIc.

ered as a possible characteristic of esophageal-BA that is mostly related to long-segment BE.

We tried to find patients with a low risk of LNM. In the EGJ-BA group, while the upper limit of the 95 % confidence intervals was still high, none of the 34 cases with pM or 10 cases of pSM superficial without LVI had LNM (95 % confidence intervals, 0 – 10.2 and 0 – 28, respectively). Therefore, these criteria may indicate patients who are good candidates for endoscopic treatment. Indeed, in our previous study about long-term clinical outcomes of 53 superficial adenocarcinomas of the EGJ resected by ESD, superficial adenocarcinoma of the EGJ was well controlled by ESD when curative resection was achieved [29]. Given these differences in risk of LNM, we considered that indications for endoscopic treatment should be considered separately for esophageal-BA and EGJ-BA.

The esophageal-BA group had a higher risk of LNM even in the intramucosal BA. Based on the pSM deep subgroup, the proportion of LNM was significantly higher in the esophageal-BA group than in the EGJ-BA group. However, because postoperative mortality for esophagectomy has been reported as 2 % to 5 % and can be associated with significant morbidity [11, 30 – 32], some studies noted the possibility of endoscopic treatment for esophageal-BA with submucosal superficial invasion [33 – 36]. Particularly when submucosal superficial invasion is confined to the upper one-third of the submucosal layer, these patients might be considered low risk for LNM if the tumor is histological grade G1 or G2 and LVI is absent. Indeed, Manner et al. studied long-term clinical outcome of 72 patients with pT1b esophageal adenocarcinoma who underwent endoscopic resection with EUS follow-up or radical esophageal resection with LN dissection. Because LNM was detected in only 1 patient (2 %) in the low-risk group during the median 5-year follow-up period, they concluded that endoscopic therapy may be chosen as an alternative to esophageal resection in low-risk patients [34]. Patients with esophageal-BA should re-

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▶ **Table 2** Risk factors for lymph node metastasis.

| | Total | LNM (%) | | Univariable | Multivariable |
|---|---|---|---|---|---|
| | No. | Positive | Negative | OR (95 %CI) | OR (95 %CI) |
| | **87** | **10** | **77** | | |
| **Age (yrs)** | | | | | |
| ▪ <65 | 39 | 3 (30) | 36 (47) | ref | |
| ▪ ≥65 | 48 | 7 (70) | 41 (53) | 2.04 (0.49 – 8.52) | |
| **Gender** | | | | | |
| ▪ Male | 79 | 9 (90) | 70 (91) | ref | |
| ▪ Female | 8 | 1 (10) | 7 (9) | 1.11 (0.12 – 10.1) | |
| **Tumor size** | | | | | |
| ▪ <3 cm | 60 | 4 (40) | 56 (73) | ref | ref |
| ▪ ≥3 cm | 27 | 6 (60) | 21 (27) | 4.00 (1.03 – 15.6) | 0.72 (0.11 – 4.74) |
| **Macroscopic type[1]** | | | | | |
| ▪ Flat | 51 | 3 (30) | 48 (62) | ref | |
| ▪ Protruded and mixed | 36 | 7 (70) | 29 (38) | 3.86 (0.93 – 16.1) | |
| **Tumor depth of invasion** | | | | | |
| ▪ pM | 39 | 2 (20) | 37 (48) | ref | ref |
| ▪ pSM superficial | 13 | 0 (0) | 13 (17) | | |
| ▪ pSM deep | 35 | 8 (80) | 27 (35) | 5.48 (1.08 – 27.9) | 4.38 (0.58 – 33.2) |
| **Histological type** | | | | | |
| ▪ Differentiated | 64 | 4 (40) | 60 (78) | ref | ref |
| ▪ Mixed | 23 | 6 (60) | 17 (22) | 5.29 (1.34 – 20.9) | 2.25 (0.47 – 10.8) |
| **Lymphovascular invasion** | | | | | |
| ▪ Present | 65 | 4 (40) | 61 (79) | ref | ref |
| ▪ Absent | 22 | 6 (60) | 16 (21) | 5.72 (1.44 – 22.7) | 1.41 (0.24 – 8.26) |
| **Tumor location** | | | | | |
| ▪ EGJ | 70 | 4 (40) | 66 (86) | ref | ref |
| ▪ Esophagus | 17 | 6 (60) | 11 (14) | 9.0 (2.18 – 37.1) | 7.78 (1.26 – 48.1) |

OR, odds ratio; CI, confidence intervals; LNM, lymph node metastasis; M, intramucosal carcinoma; SM, submucosal invasive cancer; superficial, <500 µm invasion; deep, ≥500 µm invasion; Mixed, both differentiated- and undifferentiated-type within one lesion; EGJ, esophagogastric junction
[1] "Flat" type includes 0-IIa, IIb and IIc, and "protruded" type includes 0-Ip and Is, and "Mixed" type included 0-IIa+IIc, IIc+IIb, Ip+IIa, Is+IIa, Is+IIb, Ip+IIc, Is+IIc.

▶ **Table 3** Proportions of lymph node metastasis stratified by tumor depth.

| | Number | 95 % CI |
|---|---|---|
| **EGJ-BA** | | |
| ▪ pM, ly0, v0 | 0/34 (0 %) | 0 – 10.2 |
| ▪ pSM superficial, ly0, v0 | 0/10 (0 %) | 0 – 28 |

EGJ, esophagogastric junction; BA, Barrett's adenocarcinoma; CI, confidence interval; M, intramucosal carcinoma; SM superficial, submucosal invasive cancer (<500 µm).

ceive appropriate individualized treatment based on both risk of LNM and surgical risks.

The current study has several limitations. First, due to the relatively rare incidence of BA in Japan, the number of cases was small. Our findings should be confirmed in further independent studies. In addition, the number of patients with esophageal-BA, in particular, was low compared to those who had EGJ-BA. Length of background Japanese BE is frequently shorter than 10 mm [37]. Indeed, most of the background BE was maximally shorter than 3 cm in the current study. Therefore, the number of patients with esophageal-BA was considered to be low. However, we considered tumor location an important risk factor for

**▶ Table 4** Clinicopathological features of lymph node metastasis-positive cases.

| No. | Age | Sex | Location | Size (mm) | Macro. | Invasion depth | Histology | LVI |
|-----|-----|-----|----------|-----------|--------|----------------|-----------|-----|
| 1 | 67 | M | Esophagus | 80 | Is | MM | Diff. | ly 0, v 0 |
| 2 | 57 | M | EGJ | 16 | IIc | MM | Mixed | ly 1, v 1 |
| 3 | 66 | M | Esophagus | 30 | IIc | SM 1000 µm | Mixed | ly 0, v 0 |
| 4 | 79 | F | Esophagus | 60 | IIc | SM 1000 µm | Diff. | ly 0, v 0 |
| 5 | 59 | M | EGJ | 20 | Is + IIc | SM 1500 µm | Diff. | ly 1, v 0 |
| 6 | 67 | M | EGJ | 28 | IIa + IIc | SM 2400 µm | Mixed | ly 0, v 0 |
| 7 | 66 | M | Esophagus | 45 | Is + IIb | SM 2875 µm | Diff. | ly 0, v 1 |
| 8 | 68 | M | Esophagus | 45 | IIa | SM 3000 µm | Mixed | ly 1, v 0 |
| 9 | 50 | M | EGJ | 25 | Is | SM 4700 µm | Mixed | ly 0, v 1 |
| 10 | 81 | M | Esophagus | 107 | Is + IIa | SM 2350 µm | Mixed | ly 1, v 1 |

M, male; F, female; Size, tumor size; Macro, macroscopic type; MM, muscularis mucosae; SM, submucosal; Diff., differentiated type adenocarcinoma; Mixed, both differentiated- and undifferentiated-type within one lesion; LVI, lymphovascular invasion; ly, lymphatic invasion; v, vascular invasion.

LNM based on the results with and different wall structures between esophagus and EGJ. Second, pathological evaluation differed between endoscopically and surgically resected specimens. However, the number of pM lesions was very small in surgically resected specimens and it caused selection bias if we used only surgically resected specimens. Therefore, the current study involved both endoscopically and surgically resected specimens. Third, LNM of the endoscopically resected group was judged at 3 years and the follow-up schedule was not decided. Based on the oncological reports, the relapse-free survival curve for patients with pStage I esophageal squamous cell carcinoma decreased within 3 years [38]. Most LNMs after esophagectomy were diagnosed within 2 years based on the surgical series [26]. Therefore, it is considered reasonable to judge LNM at 3 years. Improvement in technology and technique during study periods is another limitation. However, we studied consecutive cases to minimize sampling bias. Therefore patient selection was done independent of technology and technique. Finally, tumor depth of pM could not be analyzed using subclassification of LPM, superficial MM and deep MM due to the small number of patients in the study. Confirmation of the results of the current study by a multicenter validation study is needed.

## Conclusions

The current study demonstrated that tumor location within the esophagus is a potential risk factor for LNM. Therefore, indications for endoscopic treatment of esophageal-BA and EGJ-BA could be different and further studies are needed.

## Acknowledgements

## Competing interests

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