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Original Research Article

# Predictive factors of recurrence in adenocarcinoma of the esophagogastric junction in the multimodal era

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ABSTRACT

*Introduction:* Adenocarcinoma of the esophagogastric junction (AEGJ) represents a poor prognostic tumor. We evaluated the recurrence pattern and risk factors associated with recurrence in patients undergoing surgical resection by AEJG.

*Methods:* Recurrences were categorized as locoregional, peritoneal, or distant. These three recurrence groups and a non-recurrence group were compared, and overall survival (OS) and disease-free survival (DFS) for each one was obtained.

*Results:* We analyzed 188 patients with curative surgical treatment. Recurrence was observed in 72 (38.3%) patients. Locoregional recurrence was observed in 17 (23.6%); 20 (27.8%) peritoneal recurrence and 35 (48.6%) distant metastasis. DFS was 9, 5, and 8 months, and OS was 21.8, 13.2, and 20.8, respectively. Tumors larger than 5 cm are risk factors for peritoneal recurrence (OR:2.88, $p = 0.012$). Positive lymph nodes were related to distant metastasis (OR:9.15, $p = 0.040$), and lymphatic invasion for locoregional recurrence (OR:3.81, $p = 0.028$).

*Conclusion:* AEGJ is associated with high rates of early recurrence.



## Introduction

Esophageal cancer is the eighth most common cancer worldwide and the sixth leading cause of cancer-related mortality. Unfortunately, in Brazil, over half of diagnosed cases are unresectable or metastatic, with a five-year survival rate lower than 3%.[1] Adenocarcinoma of the esophagogastric junction (AEGJ) represents a poor prognostic tumor with increasing prevalence over the last decades. It is estimated that only 30.4% of AEGJ were eligible for curative intent surgery.[2]

Currently, neoadjuvant therapy followed by surgical resection has improved the prognosis for locally advanced AEGJ, leading to tumor downstaging, increasing rates of curative resections, and decreasing chances of locoregional recurrence.[3] Patients who underwent neoadjuvant chemoradiation in the CROSS trial achieved a reduction in locoregional (38%–22%) and distant failure (48%–39%).[4] In the meantime, neoadjuvant chemotherapy has demonstrated a benefit with respect to recurrence rate (64%–55%), due mainly to an impact on distant relapse failure.[5]

However, some studies have still shown high rates of recurrence in gastroesophageal junction adenocarcinoma. After esophagectomy, recurrence is often within the first year; 90% of recurrences have been detected by two years after neoadjuvant therapy and three years after primary resection.[6]

In this sense, evaluation of recurrence patterns could provide important information for clinical practice and therapeutic decisions that contribute to a better prognosis and postoperative follow-up of patients with AEGJ. Thus, this study aimed to evaluate the recurrence pattern and risk factors associated with locoregional, peritoneal, and distant recurrence in patients undergoing surgical resection by AEGJ.

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## Methods

This is a retrospective study including patients with locally advanced AEGJ who were treated between 2010 and 2018 at the Instituto do Cancer do Estado de São Paulo (ICESP) – Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, a public hospital that provides tertiary health care service. The institutional ethics review board had approved the study protocol.

Patients who had undergone curative surgery for AEGJ were screened from the institutional database. They were considered eligible if they had histologically confirmed esophagogastric junction tumors with the adenocarcinoma subtype, regardless of age or performance status.

Exclusion criteria were I) Histological findings of positive margins or residual tumor (R1 or R2); II) Previous partial gastrectomy or any esophagus resection; III) Surgery involving total esophagogastrectomy; and IV) Presence of other active synchronous tumors during the pre-treatment period. Patient records and exams were analyzed. Clinical features, treatment, post-operative outcomes, pathological TNM staging, time of recurrence, and time of death were evaluated.

### *Surgical treatment*

According to the institutional protocol, patients with tumors located in the esophagus and/or esophagogastric junction underwent subtotal esophagectomy and proximal gastrectomy with cervical anastomosis plus standard lymphadenectomy. Transhiatal or transthoracic approaches using open, laparoscopic, or robot-assisted techniques were allowed, provided that they were performed with curative intention. Patients with advanced tumors located only in the proximal stomach underwent total gastrectomy with distal esophagectomy plus standard lymphadenectomy.

### *Neoadjuvant treatment (NAT)*

Standard neoadjuvant chemoradiotherapy (a platinum-based doublet plus a radiotherapy dose of $\geq$41.4 Gy) was performed for patients with advanced tumors located in the esophageal and/or esophagogastric junction. The interval between NAT completion and surgery was approximately 12 weeks. Patients with advanced tumors located only in the stomach could receive perioperative or adjuvant chemotherapy.

### *Follow-up and recurrence*

Patients were evaluated with a clinical examination every three months during the first two years, every six months thereafter until the fifth year, and then once a year. When indicated, serum biochemistry was performed. CT scans were performed every six months during the first three years; other imaging studies, such as PET-CT, could be obtained according to clinical indication. Flexible upper GI endoscopy was performed once a year. We evaluated the pattern of recurrence considering medical records and exam reports. Recurrences were categorized as locoregional, peritoneal, or distant. Locoregional recurrence included mediastinal or abdominal lymph nodes, masses in the esophageal or gastric bed, or anastomotic recurrence. Distant recurrence includes metastases in solid organs. Peritoneal recurrence was documented by ascitic-fluid and convincing peritoneal nodules in the CT scan or positive cytology in ascitic fluid. These three recurrence groups and the non-recurrence group were compared, and overall survival (OS) and disease-free survival (DFS) for each was obtained. In addition, relevant prognostic factors were identified.

### *Statistical analysis*

Data were reported as number (%) or mean (standard deviation, SD). Categorical variables were compared using Pearson's chi-squared test and continuous variables were compared using the ANOVA test. The association of clinical and pathological characteristics with recurrence according to the sites (locoregional, peritoneal, and distant) was analyzed by binary logistic regression analysis, and odds ratios (ORs) with a 95% confidence interval (95% CI) were calculated. Variables with $p < 0.100$ in the univariate analysis were included in the multivariate model. Receiver operating characteristic (ROC) curves were used to assess whether tumor size could predict disease recurrence, and the accuracy of this prediction was judged based on the area under the ROC curve (AUC). The optimal cut-off value was also identified based on the ROC curve.

Survival outcomes were estimated using the Kaplan–Meier method, and the log-rank test was used to analyze the difference between the curves. Differences were considered statistically significant at p-values of <0.05, and all analyses were performed using IBM SPSS software (version 20. IBM Corp. Armonk, NY).

## Results

In this study, we analyzed 188 patients. The overall median age was 64.9 years (SD: 10.3) and 86% were male. (supplementary table). Esophagectomy was performed in 140 patients and total gastrectomy in 48 patients. Neoadjuvant treatment (NAT) was performed in 81 patients (43%) and the mean of resected lymph nodes was 27.9. The mean tumor size was 4.1 cm (SD: 2.4 cm), and the optimal cut-off value of 5 cm provided 68% accuracy in predicting disease recurrence (AUC: 0.68, 95% CI 0.60–0.75).

Among the 188 patients, recurrence was observed in 72 (38.3%) patients. Patients were stratified according to the site of recurrence (Table 1) – 17 (23.6%) had locoregional, 20 (27.8%) had peritoneal recurrence, and 35 (48.6%) had distant metastasis. Distant metastasis was observed in the liver in 21 cases (60%), in the lung in 12 cases (34.3%), and in the bone in two cases (5.7%).

There was no statistical difference among the groups in terms of clinical features such as age, sex, BMI, and any comorbidities. Neoadjuvant treatment was similar among the groups.

As expected, patients with earlier stages (I/II) were more common in the non-recurrence group, as well in low-grade tumors (Table 1).

### *Risk factors for recurrence*

An analysis of potential risk factors for locoregional, distant, and peritoneal recurrence is shown in Table 2.

### *Locoregional recurrence*

Lymphatic invasion represents an Odds Ratio (OR) of 3.81 (CI 1.16–12.51, $p = 0.028$) with a significant *p* value in both univariate and multivariate analysis. Tumors located in the esophagogastric junction (EGJ) have less locoregional recurrence than those located in the distal esophagus or cardia (proximal stomach), with significance in the multivariate analysis OR: 0.32 (CI 0.11–0.97, $p = 0.044$).

### *Distant recurrence*

*Positive lymph nodes* was the factor associated with distant recurrence in both univariate OR: 10.55 (CI 2.43–141.76, $p = 0.005$) and multivariate analysis OR: 9.15 (CI 1.11–75.81, $p = 0.040$). Although non-independent in multivariate analysis, univariate analyses showed the following risk factors for distant recurrence:

**Table 1**
Clinicopathological characteristics and outcomes of AEGJ patients according to the site of recurrence.

| Variables | non-recurrence | Locoregional | Peritoneal | Distant | *p* |
|---|---|---|---|---|---|
| | n = 116 (%) | n = 17 (%) | n = 20 (%) | n = 35 (%) | |
| **Age (years)** | | | | | 0.134 |
| Mean (±SD) | 66.2 (10) | 63.7 (8.3) | 62 (12) | 62.6 (10.5) | |
| **Sex** | | | | | 0.709 |
| Female | 16 (13.8) | 1 (5.9) | 2 (10) | 6 (17.1) | |
| Male | 100 (86.2) | 16 (94.1) | 18 (90) | 29 (82.9) | |
| **BMI (Kg/m$^2$)** | | | | | 0.686 |
| Mean (±SD) | 23.3 (3.7) | 23.2 (4.7) | 22.4 (2.6) | 22.8 (3.2) | |
| **Presence of Comorbities** | | | | | 0.625 |
| No | 44 (37.9) | 5 (29.4) | 10 (50) | 13 (37.1) | |
| Yes | 72 (62.1) | 12 (70.6) | 10 (50) | 22 (62.9) | |
| **Type of resection** | | | | | **0.025** |
| Esophagectomy | 80 (69) | 12 (70.6) | 15 (75) | 33 (94.3) | |
| Gastrectomy | 36 (31) | 5 (29.4) | 5 (25) | 2 (5.7) | |
| **Neoadjuvante treatment** | | | | | 0.930 |
| No | 67 (57.8) | 10 (58.8) | 10 (50) | 20 (57.1) | |
| Yes | 49 (42.2) | 7 (41.2) | 10 (50) | 15 (42.9) | |
| **Extension to Esophagus** | | | | | 0.558 |
| No | 88 (75.9) | 13 (76.5) | 13 (65) | 23 (65.7) | |
| Yes | 28 (24.1) | 4 (23.5) | 7 (35) | 12 (34.3) | |
| **Extension to Stomach** | | | | | 0.127 |
| No | 70 (60.3) | 7 (41.2) | 8 (40) | 23 (65.7) | |
| Yes | 46 (39.7) | 10 (58.8) | 12 (60) | 12 (34.3) | |
| **Centered on EGJ** | | | | | **0.027** |
| No | 25 (21.6) | 6 (35.3) | 4 (20) | 1 (2.9) | |
| Yes | 91 (78.4) | 11 (64.7) | 16 (80) | 34 (97.1) | |
| **Tumor size (cm)** | | | | | **0.001** |
| Mean (±SD) | 3.5 (2.3) | 4.5 (1.9) | 5.2 (2.4) | 5.0 (2.3) | |
| **Histologic grade differentiation** | | | | | **0.013** |
| Well/moderate | 89 (76.7) | 9 (52.9) | 10 (50) | 20 (57.1) | |
| Poorly | 27 (23.3) | 8 (47.1) | 10 (50) | 15 (42.5) | |
| **Lymphatic invasion** | | | | | **<0.001** |
| absent | 69 (59.5) | 4 (23.5) | 4 (20) | 13 (37.1) | |
| present | 47 (40.5) | 13 (76.5) | 16 (80) | 22 (62.9) | |
| **Venous Invasion** | | | | | **0.006** |
| absent | 80 (69) | 7 (41.2) | 7 (35) | 18 (51.4) | |
| present | 36 (31) | 10 (58.8) | 13 (65) | 17 (48.6) | |
| **Perineural invasion** | | | | | **0.007** |
| absent | 55 (47.4) | 6 (35.3) | 2 (10) | 10 (28.6) | |
| present | 61 (52.6) | 11 (64.7) | 18 (90) | 25 (71.4) | |
| **Tumor invasion** | | | | | **0.001** |
| T0/T1/T2 | 55 (47.4) | 4 (23.5) | 1 (5) | 10 (28.6) | |
| T3/T4 | 61 (52.6) | 13 (76.5) | 19 (95) | 25 (71.4) | |
| **No of Lymph nodes** | | | | | **0.039** |
| Mean (±SD) | 30.5 (19.2) | 24.5 (8.2) | 27.2 (18.1) | 21.1 (14.0) | |
| **pN status** | | | | | **<0.001** |
| pN negative | 66 (56.9) | 6 (35.3) | 1 (50) | 11 (31.4) | |
| pN positive | 50 (43.1) | 11 (64.7) | 19 (95) | 24 (68.6) | |
| **pTNM stage** | | | | | **<0.001** |
| 0/I/II | 75 (64.7) | 5 (29.4) | 4 (20) | 14 (40) | |
| III/IV | 41 (35.3) | 12 (70.6) | 16 (80) | 21 (60) | |
| **Mortality-30 days** | | | | | 0.092 |
| No | 108 (93.1) | 13 (76.5) | 19 (95) | 33 (94.3) | |
| Yes | 8 (6.9) | 4 (23.5) | 1 (5) | 2 (5.7) | |
| **Mortality-90 days** | | | | | **0.014** |
| No | 104 (89.7) | 11 (64.7) | 19 (95) | 32 (91.4) | |
| Yes | 12 (10.3) | 6 (35.3) | 1 (5) | 3 (8.6) | |
| **Death** | | | | | na |
| No | 95 (81.9) | 4 (23.5) | 1 (5) | 11 (31.4) | |
| Yes | 21 (18.1) | 13 (76.5) | 19 (95) | 24 (68.6) | |

BMI, body mass index; EJG, esophagogastric junction; SD, standard deviation. *P*-values in bold are statistically significant.

more invasive tumors (pT3/T4), with an expressive OR: 13.24 [CI 1.73–101.25, p = 0.013]; tumor size larger than 5 cm (OR: 3.03 [CI 1.18–7.78, p = 0.021]); and lymphatic invasion (OR: 4.19 [CI 1.35–13.07, p = 0.013]);

*Peritoneal recurrence*

*Tumor size larger than* 5 cm was associated with peritoneal recurrence in univariate (OR: 2.52 [CI 1.20–5.27, p = 0.014]) and multivariate analysis (OR: 2.88 [CI 1.27–6.54, p = 0.012]). Positive lymph nodes, number of dissected lymph nodes less than 25, tumors located in EGJ, and tumors resected by esophagectomy (instead of gastrectomy) were risk factors associated with significance only in a univariate analysis.

*Overall survival and disease-free survival*

In a mean follow-up of 30.8 months, 77 patients died. The

**Table 2**
Risk factors for the occurrence of relapse according to the recurrence sites: locoregional, distant and peritoneal.

| Locoregional Recurrence | Univariate analysis | | *p* | Multivariate analysis | | *p* |
|---|---|---|---|---|---|---|
| Variables | Odds Ratio | 95% CI | | Odds Ratio | 95%CI | |
| Male (vs Female) | 2.61 | 0.33–20.62 | 0.362 | – | – | – |
| Age > 65 (vs < 65 years) | 1.48 | 0.54–4.07 | 0.448 | – | – | – |
| Neoadjuvant treatment (vs absence) | 1.09 | 0.40–3.00 | 0.869 | – | – | – |
| Esophagectomy (vs Gastrectomy) | 0.81 | 0.27–2.42 | 0.701 | – | – | – |
| Poorly differentiated (vs others) | 2.03 | 0.74–5.57 | 0.167 | – | – | – |
| Centered on EJG (vs non-EJG) | 0.39 | 0.13–1.14 | 0.085 | 0.32 | 0.11–0.97 | **0.044** |
| Tumor size ≥ 5 cm (vs < 5 cm) | 2.07 | 0.76–5.68 | 0.156 | – | – | – |
| Lymphatic invasion (vs absent) | 3.29 | 1.03–10.49 | **0.044** | 3.81 | 1.16–12.51 | **0.028** |
| pT3/pT4 status (vs pT0/T1/pT2) | 2.04 | 0.64–6.53 | 0.228 | – | – | – |
| pN+ (vs pN0) | 1.54 | 0.54–4.35 | 0.417 | – | – | – |
| <25 LNs (vs > 25LNs) | 1.09 | 0.44–2.50 | 0.871 | – | – | – |
| **Distant recurrence** | **Univariate analysis** | | ***p*** | **Multivariate analysis** | | ***p*** |
| **Variables** | **Odds Ratio** | **95% CI** | | **Odds Ratio** | **95%CI** | |
| Male (vs Female) | 1.43 | 0.31–6.56 | 0.647 | – | – | – |
| Age > 65 (vs < 65 years) | 0.64 | 0.25–1.63 | 0.347 | – | – | – |
| Neoadjuvant treatment (vs absence) | 0.72 | 0.29–1.85 | 0.510 | – | – | – |
| Esophagectomy (vs Gastrectomy) | 1.03 | 0.35–3.01 | 0.954 | – | – | – |
| Poorly differentiated (vs others) | 2.36 | 0.93–60.2 | 0.072 | 1.26 | 0.43–3.67 | 0.675 |
| TEG (vs non-TEG) | 0.94 | 0.30–3.01 | 0.919 | – | – | – |
| Tumor size ≥ 5 cm (vs < 5 cm) | 3.03 | 1.18–7.78 | **0.021** | 1.56 | 0.55–4.43 | 0.404 |
| Lymphatic invasion (vs absent) | 4.19 | 1.35–13.07 | **0.013** | 1.38 | 0.38–5.05 | 0.624 |
| pT3/pT4 status (vs pT0/T1/pT2) | 13.24 | 1.73–101.25 | **0.013** | 4.47 | 0.51–38.93 | 0.175 |
| pN+ (vs pN0) | 10.55 | 2,43–141.76 | **0.005** | 9.15 | 1.11–75.81 | **0.040** |
| <25 LNs (vs > 25LNs) | 1.05 | 0.38–2.41 | 0.920 | – | – | – |
| **Peritoneal recurrence** | **Univariate analysis** | | ***p*** | **Multivariate analysis** | | ***p*** |
| **Variables** | **Odds Ratio** | **95% CI** | | **Odds Ratio** | **95%CI** | |
| Male (vs Female) | 0.56 | 0.27–2.02 | 0.744 | – | – | – |
| Age > 65 (vs < 65 years) | 0.54 | 0.26–1.30 | 0.102 | – | – | – |
| Neoadjuvant treatment (vs absence) | 0.99 | 0.48–2.05 | 0.986 | – | – | – |
| Esophagectomy (vs Gastrectomy) | 4.81 | 1.41–16.48 | **0.012** | 2.04 | 0.32–12.81 | 0.449 |
| Centered on EJG (vs non-EJG) | 5.08 | 1.16–22.23 | **0.031** | 2.86 | 0.32–25.81 | 0.384 |
| Poorly differentiated (vs others) | 1.61 | 0.76–3.38 | 0.211 | – | – | – |
| Tumor size ≥ 5 cm (vs < 5 cm) | 2.52 | 1.20–5.27 | **0.014** | 2.88 | 1.27–6.54 | **0.012** |
| Lymphatic invasion (vs absent) | 1.92 | 0.91–4.05 | 0.087 | 1.20 | 0.51–2.85 | 0.679 |
| pT3/pT4 status (vs pT0/T1/pT2) | 1.78 | 0.80–3.94 | 0.155 | – | – | – |
| pN+ (vs pN0) | 2.21 | 1.02–4.80 | **0.044** | 1.61 | 0.66–3.94 | 0.300 |
| <25 LNs (vs > 25LNs) | 2.35 | 1.10–5.01 | **0.028** | 2.07 | 0.90–4.73 | 0.085 |

CI, confidence interval; OR, odds ratio; EJG, esophagogastric junction; LN, lymph node. *P-values less than 0.100 in univariate analysis were included in the multivariate model. P-values in bold are statistically significant.

median OS survival for all patients was 41.5 months and the DFS rate was 51.7%.

According to the pattern of recurrence, the median DFS for patients who had locoregional, peritoneal, and distant recurrence was nine, five, and eight months, respectively (p = 0.732).

Considering the OS, patients with peritoneal recurrence had worse survival (median of 13.2 months). The median OS survival was 21.8 and 20.8 months for patients with locoregional and distant recurrence, respectively (p = 0.242). As expected, OS in patients without recurrence was better compared to that of other groups (p < 0.001). (Fig. 1).

Considering sites of distant relapse (liver, lung, and bone), patients with pulmonary recurrence had better DFS and OS rates compared to the liver (10 vs. 6 months, p = 0.030 and 32.9 vs. 14.4 months, p = 0.125, respectively).

## Discussion

AEGJ is associated with a high recurrence rate, ranging from 38% to 54.7% in single center's casuistic.[7,8] In accordance, we found a recurrence rate of 38.3%. Parallelly, differences in the recurrence of AEGJ were documented over time. Studies from the beginning of NAT observed an earlier recurrence for those patients who had received neoadjuvant treatment; instead, the pattern of recurrence was similar and higher recurrence rates in the first two years for those who receive NAT.[6,7] After that, NAT protocols have been improving, such as chemoradiation in CROSS[4] and perioperative chemotherapy in FLOT[9] trials. Neoadjuvant treatment was performed in 43% of all 188 patients, and we did not find differences among the recurrence groups (p = 0.930).

Regarding the patterns of recurrence and their predictors, lymphatic invasion was the most important factor related to locoregional recurrence, with OR: 3.81 [CI 1.16–12.51, p = 0.028]. Previous studies have shown lymphatic invasion as a significant and independent prognostic factor in AEGJ.[10,11]

Distant recurrence was associated with more advanced tumors, following the parameters of TNM classification. The presence of a metastatic lymph node was the only independent risk factor for distant recurrence, with significance in both univariate and multivariate analysis, with an expressive OR: 9.15 (CI 1.11–75.81, p = 0.040).

For peritoneal recurrence, a tumor size larger than 5 cm was the only risk factor in both univariate and multivariate analysis (OR: 2.88 [CI 1.27–6.54, p = 0.012]). Indeed, our findings indicate that larger tumors represent a potentially larger area in which to spread.[12] Furthermore, peritoneal recurrence is associated with

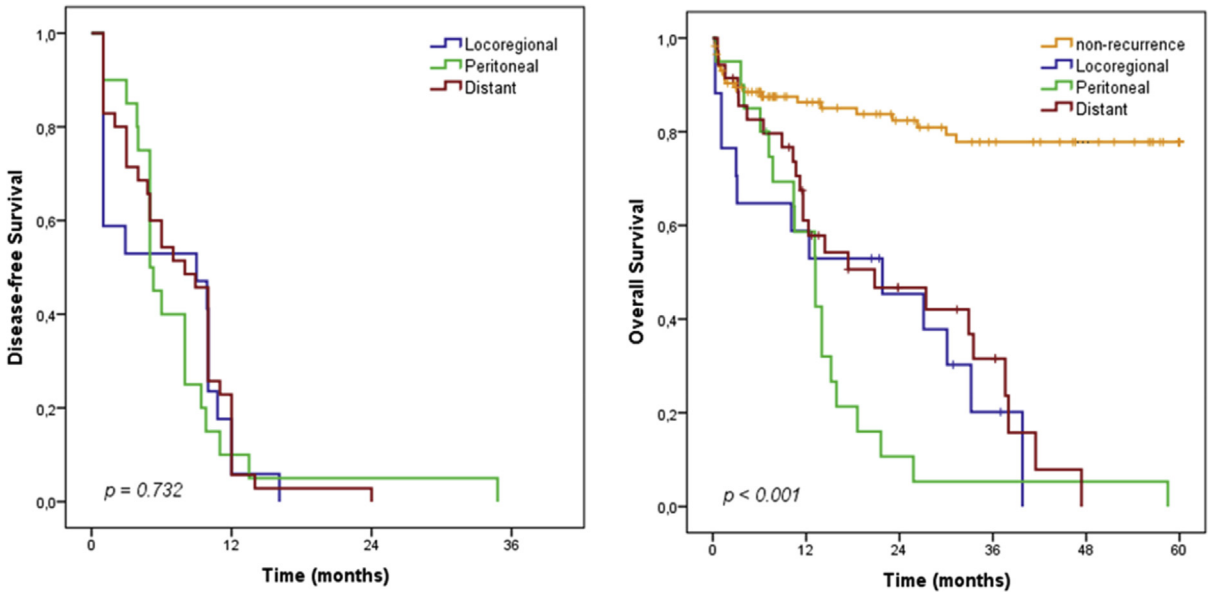


**Fig. 1.** Disease-free survival and overall survival according to the groups for each recurrence site.

earlier recurrence and death (DFS: 5 months; OS:13.2 months). Those findings might indicate an individualized strategy, such as, for example, tumors larger than 5 cm in AEGJ should be discussed for diagnostic laparoscopy before NAT or pN + should be considered as a complementary treatment.

Based on the tumor location of AEGJ, lesions placed in EGJ, compared to the distal esophagus or proximal stomach sites, were identified as being of "less risk" in regard to lymph node recurrence in multivariate analysis. This might represent a statistical finding which doesn't mean less aggressive tumors. On the other hand, most cases with distant or peritoneal recurrence were located in EGJ.

Differences in the locations of distant recurrence and their behavior may play an important role in clinical practice regarding palliative treatment. In our study, pulmonary recurrence was associated with a statistically significantly longer disease-free survival as compared to liver recurrence. Although non-statistically significant, overall survival is longer for pulmonary recurrence, too.

The AIO-FLOT3 (Arbeitsgemeinschaft Internistische Onkologie-fluorouracil, leucovorin, oxaliplatin, and docetaxel) trial was a prospective phase 2 trial that demonstrated a median OS of 22.9 months in patients with limited metastatic spread (non-regional lymph node, metastasis in one organ) who underwent resection compared to 10.7 in those patients who received only systemic treatment.[13] Currently, a phase 3 trial, RENAISSANCE (AIO-FLOT5), is randomizing patients with limited metastatic spread to chemotherapy alone or chemotherapy followed by surgical resection. If this strategy were to reveal a survival benefit, follow-up strategies should be reconsidered.[14]

In our study, the non-statistical significance among disease-free survival and overall survival for different patterns could be due to the small number of patients in our sample. A statistically significant longer survival for pulmonary recurrence leads us to think about how to be more aggressive for isolated pulmonary recurrence. Certainly, all potentially resectable metastases should be discussed in a multidisciplinary tumor board, such as for colorectal tumors, pulmonary metastasectomy is a widely accepted practice for selected cases with curative intention.[15] Another study of recurrence after esophagectomy and salvage therapies demonstrates that prolonged survival can be obtained in well-selected patients in both isolated locoregional and single distant (solid organs) recurrence, especially if surgery (with or without systemic therapy) can be offered.[16]

Regimens of palliative chemotherapy for metastatic esophageal disease and AEGJ were studied in our institution in 2019.[1] The AEGJ group had OS of 15 months (CI 13.4–16.6). Those results are similar to our findings as, peritoneal recurrence (OS:13.2 months), hepatic recurrence (OS: 14.4 months), and bone recurrence (OS:11.6 months). These early periods might indicate a pre-treatment understaging process in advanced AEGJ tumors, refractory to NAT. In this way, cases with associated risk factors for recurrence should be discussed individually to perform a complementary preoperative exam, such as laparoscopy or magnetic resonance.

Our findings could identify a subgroup in AEGJ of high-risk recurrence patient. Nowadays, some authors are questioning the benefits of surveillance for recurrence.[17,18] Some authors support frequent early follow-up, as 90% of recurrence will occur within three years after surgery and survival after recurrence is improved with therapy.[6,7] They suggest that the best test for identifying both systemic and locoregional recurrence is a contrast-enhanced CT scan of the chest and abdomen.

Some limitations of this study should be noted. First, this is a retrospective study with a small sample size, which is reflected in the large confidence intervals and, mainly, for the analysis of subgroups in distant recurrence. We did not consider treatment after recurrence in our analysis; patients with good performance were selected to receive palliative chemotherapy. Yet, this represents the "real world" in a single-center experience, with curative surgeries performed with a standard lymphadenectomy, in which a satisfactory number of resected lymph nodes could explain that a positive lymph node status did not mean a risk factor for locoregional recurrence.

## Conclusion

Adenocarcinoma of the esophagogastric junction is associated with high rates of early recurrence. A tumor larger than 5 cm was an independent risk factor for peritoneal recurrence. The presence of positive lymph nodes in a pathological evaluation represents a risk for distant metastasis, while lymphatic invasion is associated with locoregional recurrence.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2020.07.031.

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