Original Article

Role of the Capillary Invasion Index: A Prognostic Indicator for Adenocarcinoma of the Esophagogastric Junction

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ABSTRACT

Introduction: Adenocarcinoma which occurs in the esophagogastric junction (EGJ) does not have a clear answer with regards to surgical procedures and the prognosis. In the present study, prognostic evaluation factors, including patient characteristics and results of pathological examination were evaluated.

Methods: The present study included 29 patients with adenocarcinoma of the EGJ who underwent R0 surgery at our department between January 2007 and December 2016. Univariate and multivariate analysis were conducted to examine the associations of age, sex, tumor size, histopathological type, depth of tumor invasion, lymph node metastasis, pathological disease stage, neoadjuvant and adjuvant chemotherapy, and lymphatic and vascular invasion index or "LV Index" as prognostic factors for survival. The log-rank test was used to determine differences in survival between groups for each factor.

Results: On pathological examination, the median maximum tumor size was 33 mm (range: 11-113 mm), and the median location of the center of the tumor relative to the EGJ was 13 mm distal to the EGJ (range: 7 mm proximal to the EGJ to 20 mm distal to the EGJ). For the LV Index, the hazard ratio was 0.136 (95% confidence interval (CI)), (0.016-1.171; $P = 0.069$) on univariate analysis, and 0.102 (95% CI, 0.009-1.115; $P = 0.061$) on multivariate analysis. Survival rate was significantly different between the high and low LV Index groups ($P = 0.033$, log-rank test).

Conclusions: Evaluation of prognosis in patients who underwent R0 resection for adenocarcinoma of EGJ at our hospital showed that the LV Index based on the lymphatic and vascular invasion contributes to survival as a prognostic factor.

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KEYWORDS: adenocarcinoma, gastric cancer, esophago-gastric junction, prognosis

Introduction

Esophagogastric junction carcinoma (EJC) is a type of cancer that occurs in the esophagogastric junction (EGJ) area. Nishi's definition is used in Japan, and Siewert's definition is used in Western countries.[1–5] In Nishi's classification, this area is defined as the area within 2 cm above or below the EGJ.[1] EGJ is an area in which the mucosa shifts from squamous epithelium to gastric glands, and it borders the negative pressure region of the thoracic cavity

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and the positive pressure region of the abdominal cavity. Since conditions such as a hiatal hernia and gastric mucosal atrophy develop at the EGJ area, it is considered to be a physiologically and anatomically unique environment.[6]

In Japan, EJC is defined as the cancer tumor located in the center of the tumor in the EJC area regardless of the histological type, and this is different from Siewert's definition that specifies adenocarcinoma as the origin of the tumor.[2–5] The EGJ area consists of a mixture of various structures such as squamous epithelium, Barrett's epithelium, esophagus-specific glands, and cardiac glands, and it therefore possesses a foundation in which various types of cancer can develop.[7] In Japan, EGC is covered by the Classification of Esophageal Cancer.[8] In addition to this, it has been reported that EGC with a <4 cm tumor does not require preventive lymphadenectomy of the distal stomach region.[9] Although the European Society for Medical Oncology Clinical Practice Guidelines state that the thoracotomy approach is superior to the transhiatal approach for resection, it does not clearly describe performing a specific procedure such as lymphadenectomy.[10] A clear answer has yet to be obtained with regards to surgical procedures and the prognosis of EGC.

The postoperative prognostic factors in 29 patients with adenocarcinoma of EGJ located in Nishi's classification who underwent radical resection in our department were investigated. These factors were based on patient characteristics, neoadjuvant and adjuvant chemotherapy, macroscopic tumor size, and pathological capillary invasion (lymphatic invasion and/or venous invasion).

Methods

Patients

The present report was approved by the Ethics Review Board of the Toho University Medical Center Sakura Hospital (Reference No. S17107). The present study included 29 patients who were diagnosed with adenocarcinoma of the EGJ and underwent radical resection (R0) at the Department of Surgery of Toho University Medical Center Sakura Hospital between January 2007 and December 2016. The criteria of this study was defined as adenocarcinoma whose center was within 2 cm above (esophagus side) or below (gastric cardia side) the EGJ. The center of the tumor was determined macroscopically using the resected specimens. For diagnostic imaging, modalities such as upper endoscopic examination, barium swallow examination, computed tomography scanning, and ultrasonography of the abdomen were performed preoperatively. Proximal gastrectomy with D1 plus No.7 lymphadenectomy was performed in patients with a preoperative diagnosis of stage II or earlier, and total gastrectomy with D2 minus No.10 lymphadenectomy was performed in those with a preoperative diagnosis of stage III and later.[2, 11]

Clinicopathological criteria were as follows: patient characteristics (age, sex ratio), maximum tumor size based on pathological specimen examination (maximum tumor size before chemotherapy for patients who received neoadjuvant chemotherapy), positional relationship between the EGJ and the center of the tumor, pathological characteristics (tumor histological type, lymphatic invasion, vascular invasion, depth of tumor invasion, lymph node metastasis, multi-organ metastasis, pathological disease stage), surgical method (residual tumor from surgery, number of metastatic lymph nodes from dissection, surgical approach, esophageal resection, gastrectomy), and neoadjuvant and adjuvant chemotherapy (with, without).[2, 11] Histopathological characteristics were classified into differentiated adenocarcinoma and undifferentiated adenocarcinoma.

Classification of patient factors for survival analysis

Contribution to survival was analyzed with regards to each of the following factors: sex (male vs. female), age (<70 y vs. ≥ 70 y), maximum tumor size (<4 cm vs. ≥ 4 cm), Histopathological type (undifferentiated vs. differentiated), depth of tumor invasion ($<$pT2 vs. $\geq$pT3), lymph node metastasis (pN0 vs. $\geq$pN1), pathological stage classification ($\leq$stage II vs. $\geq$stage III), neoadjuvant chemotherapy (with vs. without), adjuvant chemotherapy (with vs. without), and nomogram of lymphatic and vascular invasion (high vs. low).

Nomogram based on capillary invasion

On histopathological diagnosis, capillary invasions of tumor cells within the tumor tissue were divided into lymphatic invasion (ly) and vascular invasion (v). Both ly and v are classified into four types.[2, 3] The classifications are as follows: ly0, no lymphatic invasion; ly1, minimal lymphatic invasion; ly2, moderate lymphatic invasion; ly3, marked lymphatic invasion; v0, no venous invasion; v1, minimal venous invasion; v2, moderate venous invasion; and v3, marked lymphatic invasion. The sum of the lymphatic and vascular invasion classification results was designated as the "LV Index" (LV Index = ly + v).

Statistics

The correlation between the numbers of the pathologi-

Table 1 Background characteristics of patients with adenocarcinoma of esophagogastric junction

Factor	Value[b]	%	Factor	Value[b]	%
Age (years)			M category		
Median (range)	67 (47-81)[b]		M0	29	100
Sex			M1	0	0
Male	21	72.4	pStage category		
Female	8	27.6	ypT0N0M0[a]	1	3.4
Tumor size (mm)			pStageI	11	37.9
Median (range)	33 (11-113)[c]	N.A.	pStageII	9	31.0
Center of the tumor from EGJ (mm)			pStageIII	8	27.6
Median (range)	+13 (−7 to +20)[c]	N.A.	pStageIV	0	0
Histopathological type			Number of dissected lymph nodes		
Differentiated type AC	20	69.0	Median (range)	28 (9-73)[c]	N.A.
Undifferentiated type AC	9	31.0	Number of metastatic lymph nodes		
ly (lymphatic invasion)			Median (range)	1 (0-2)[c]	N.A.
ly0/ ly1/ ly2/ ly3	9/8/8/4	31.0/27.6/27.6/13.8	Approach		
v (venous invasion)			Right transthoracic	1	3.3
v0/ v1/ v2/ v3	9/13/5/2	31.0/44.2/17.2/6.9	Left transthoracic	0	0
LV Index			Transhiatal	28	96.6
LV 0/1/2/3/ 4/5/6	7/2/8/ 4/5/3/0	24.1/6.9/27.6/ 13.8/17.3/10.3/0	Type of esophageal resection		
pT category			Subtotal esophagectomy	0	0
ypT0 *	1	3.4	Lower/abdominal esophagectomy	29	100
pT1	9	31.0	Type of gastric resection		
pT2	2	6.9	Total gastrectomy	20	69.0
pT3	14	48.3	Proximal gastrectomy	9	31.0
pT4	3	10.3	Neoadjuvant chemotherapy		
pN category			Yes	4	13.8
pN0	16	55.2	No	25	86.2
pN1	6	20.7	Adjuvant chemotherapy		
pN2	3	10.3	Yes	14	48.3
pN3	4	13.8	No	15	51.7

[a]: no residual tumor cells after neoadjuvant chemotherapy, [b]: Values indicate the numbers of patients without mention, [c]: Median value and minimum and maximum values in parentheses. N.A.: not available.

cal metastatic lymph nodes and LV Index was examined by Fisher's exact test. Univariate and multivariate hazard ratio analyses were carried out using a Cox proportional hazards model approach with survival as the endpoint. The factors were: age (<70 y vs. ≥70 y), sex (male vs. female), maximum tumor size (<4 cm vs. ≥4 cm), histopathological type (low-differentiated vs. high-differentiated), pathological depth of tumor invasion (<T2 vs. >T3), pathological lymph node metastasis (negative vs. positive), pathological stage classification (≤stage II vs. ≥stage III), neoadjuvant chemotherapy (with vs. without), adjuvant chemotherapy (with vs. without), and LV Index (high vs. low). Five-year survival and the 95% CI were determined with the Kaplan-Meier method, and the log-rank test was used for comparisons between groups. $P < 0.05$ was considered significant. R 3.4.3 for Windows (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

Results

Patients' characteristics

The median patient age was 67 years (range: 47-81 years). There were 21 men and 8 women. Postoperative follow-up ranged between 75 and 3738 days (median 1697 days). On pathological examination, the median maximum tumor size was 33 mm (range: 11-113 mm), and the median location of the center of the tumor relative to the EGJ was 13 mm distal to the EGJ (range: 7 mm proximal to the EGJ to 20 mm distal to the EGJ). The median tumor size was 33 mm (range: 11-113 mm), and the tumor occurred 13 mm toward the stomach from the EGJ (range: 7 mm toward the esophagus- 20 mm toward the stomach). Histopathological

types were differentiated adenocarcinoma (n = 20, 69.0%) and undifferentiated adenocarcinoma (n = 9, 31.0%). The classification for lymphatic invasion of the tumor (ly, 0/1/2/3) was n = 9/8/8/4 (31.0/27.6/27.6/13.8%). The classification for vascular invasion of the tumor (v, 0/1/2/3) was n = 9/13/5/2 (31.0/44.2/17.2/6.9%). The classification of the depth of tumor invasion (pT, yT0/pT1/pT2/pT3/pT4) was n = 1/9/2/14/3 (3.4/31.0/6.9/48.3/10.3%). The classification of lymph node metastasis (pN, pN0/pN1/pN2/pN3) was n = 16/6/3/4 (55.2/20.7/10.3/13.8%). The classification of lymph node metastasis to other areas, or distant metastasis (M, M0/M1) was n = 29/0 (100/0%). The classification of pathological stage (ypT0N0M0/pStage I/pStage II/pStage III/pStage IV) was n = 1/11/9/8/0 (3.4/37.9/31.0/27.6/0%)(Table 1).

Surgery's characteristics

The median number of surgical lymph node dissections was 28 (range: 9-73). The surgical procedure involved a right thoracotomy approach in one patient (3.3%) and a transhiatal laparotomy approach in 28 patients (96.6%). None of the Esophageal resection included subtotal esophagectomy and lower and abdominal esophagectomy (n = 29, 100%). Gastric resection included total gastrectomy (n = 20, 69.0%) and proximal gastrectomy (n = 9, 31.0%). Regional lymphadenectomy of Nos. 1, 2, and 3 at the upper body of the stomach was primarily performed. Four patients (13.8%) underwent preoperative neoadjuvant chemotherapy, while 25 (86.2%) did not, and 14 (48.3%) patients underwent postoperative adjuvant chemotherapy, while 15 (51.7%) did not (Table 1).

The correlation between pathological metastatic lymph nodes and LV Index

The numbers of pathological metastatic lymph nodes and LV Index were analyzed. The result was statistically correlated ($P = 0.007$, Fisher's exact test).

Univariate and multivariate analysis

Univariate analysis was performed with the following factors divided into two groups: age, sex, tumor size, histopathological type, pathological depth of tumor invasion, pathological lymph node metastasis, pathological disease stage, neoadjuvant chemotherapy, adjuvant chemotherapy, and LV Index. The results showed that a low LV Index had the lowest hazard ratio of 0.1364 (95%CI, 0.016-1.171), with $P = 0.069$ (Table 2). Multivariate analysis was performed with the following factors divided into two groups: histopathological type, pathological lymph node metastasis, and LV Index. The results showed that a low LV Index had the lowest hazard ratio of 0.1020 (95%CI, 0.009-1.115), with $P = 0.061$ (Table 3).

Table 2 Univariate analysis of adenocarcinoma of esophagogastric junction

Factor	Number of patients	Univariate analysis		
		HR	95%CI[d]	P[e]
Age (years)				
<70	16	0.727	0.146-3.617	0.697
≥70	13	1		
Sex				
Male	21	0.837	0.153-4.573	0.837
Female	8	1		
Tumor size (mm)				
<40	16	1.812	0.335-9.908	0.493
≥40	13	1		
Histopathological type				
undifferentiated type	9	3.189	0.630-16.140	0.161
differentiated type	20	1		
LV Index[a]				
Low (0, 1, 2)	17	0.136	0.016-1.171	0.069
High (3, 4, 5, 6)	12	1		
Depth of tumor invasion				
pT0, pT1, pT2	12	0.270	0.031-2.342	0.235
pT3, pT4	17	1		
Lymph Node metastasis				
pN1, pN2, pN3	13	3.416	0.6174-18.90	0.159
pN0	16	1		
pStage category				
Early[b]	21	0.680	0.123-3.750	0.658
Advanced[c]	8	1		
Neoadjuvant chemotherapy				
No	25	0.334	0.061-1.844	0.209
Yes	4	1		
Adjuvant chemotherapy				
No	15	0.353	0.063-1.967	0.235
Yes	14	1		

[a]: sum of the numbers of ly and v, [b]: ypT0N0M0*/pStageI/pStageII, [c]: pStageIII/pStageIV, [d]: Confidence Interval, [e]: Cox proportional hazards model.

Degree of contribution to survival

In the analysis of each factor's contribution to survival, a significant difference was observed only with the LV Index classification ($P = 0.033$, log-rank test, Fig. 1).

Discussion

Thirty patients with adenocarcinoma of EGJ in our department were investigated. The EGJ is an area where both squamous cell carcinoma and adenocarcinoma can arise. In Western countries, most are adenocarcinomas with Barrett's esophagus in the background, while in Ja-

Table 3 Multivariate analysis and log-rank test of adenocarcinoma of esophagogastric junction

Factor	Number of patients	Multivariate analysis			log-rank test
		HR	95%CI[b]	*P*[c]	
Histopathological type					
undifferentiated type	9	4.777	0.634-35.98	0.129	0.140
differentiated type	20	1			
LV Index[a]					
Low (0, 1, 2)	17	0.102	0.009-1.115	0.061	0.033 *
High (3, 4, 5, 6)	12	1			
Lymph node metastasis					
pN1, pN2, pN3	13	0.936	0.111-7.894	0.952	0.135
pN0	16	1			

[a]: sum of the numbers of ly and v, [b]: Confidence Interval, [c]: Cox proportional hazards model. $*P<0.05$.

pan, squamous cell carcinoma accounts for the majority of histological types of esophageal cancer.[12, 13] Since the present report was a status report from a single rural hospital in Japan, an overall analysis was carried out for adenocarcinoma of EGJ. In Japan, as per an agreement between the Japanese Classification of Esophageal Cancer and the Japanese Classification of Gastric Carcinoma, EGC is covered by the former.[14] The possibility of No.16a2lat (paraaortic lymph nodes) dissection in EGC was indicated in a retrospective investigation.[15] In the Japan Clinical Oncology Group study (JCOG9502), which compared the left thoracoabdominal approach and the transhiatal approach for EGC, a preventive dissection of No.16a2lat was implemented, and metastasis was observed in 22/145 patients who underwent No.16a2lat dissection.[16] Yamashita et al. reported that, in EGC surgery, dissection of the paracardial and lesser curvature nodes yielded the greatest therapeutic benefit.[17] Nonetheless, there are distinct types of procedures ranging from total esophagogastrectomy to lower esophagectomy and proximal gastrectomy, and there are differences in surgical approach and lymphadenectomy region between institutions.

According to Seto et al., the area of lymph node metastasis differs depending on the tumor size. For EGC with a ≤ 4 cm tumor, guidelines to perform lymphadenectomy according to the histological type and the distance between the tumor and the EGJ were presented.[11] The extent of resection is determined based on whether or not dissections of No. 3b, 4d, 5, and 6 lymph nodes are necessary. It has been reported that, in gastric cancer up to T3 (subserosal invasion) encompassing a tumor with a lower margin that stops at the U region, there is no lymph node metastasis to this region, and proximal gastrectomy is indicated.[18] Wang et al. conducted a retrospective study in 373 Siewert Type II adenocarcinoma patients who underwent total gastrectomy with a transhiatal approach and found that No.5, 6 lymph node metastases occurred similarly to stage IV patients, regardless of the disease stage. Since No. 5, 6 lymphadenectomy in patients with adenocarcinoma of the EGJ area is ineffective, they concluded that such lymphadenectomy can be excluded from the area of radical lymphadenectomy.[19] In other words, it may be unsuitable to perform lymphadenectomy according to total gastrectomy with a transhiatal laparotomy approach to treat such adenocarcinomas.

The present study was conducted at a single center and included only 29 patients with adenocarcinoma of EGJ. Yabusaki et al. reported that there was no significant difference in the 5year survival between patients with squamous cell carcinoma (n = 51) and adenocarcinoma (n = 72) who underwent resection. Specifically, right and left thoracotomy approaches were used in just over 70% of squamous cell carcinomas, while a thoracotomy approach was used in just over 30% of adenocarcinomas. This also suggests that there are differences in the extent of lymphadenectomy; thus, attention is necessary when making comparisons.[20] Kurokawa et al. retrospectively investigated mediastinal lymph node recurrence in 315 patients with pT2-T4 Siewert type II/III adenocarcinomas who underwent R0 or R1 surgery, and they found that recurrence was significantly lower when the tumor is <3.0 cm from the EGJ.[21]

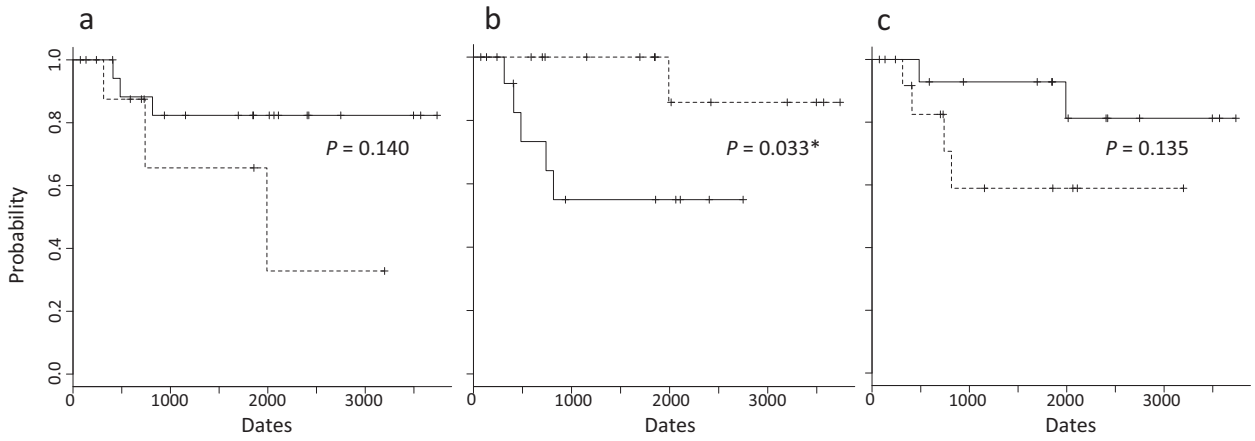

Fig. 1 Survival curve by factor. a: Histopathological type (solid line, undifferentiated type; dashed line, differentiated type), b: LV Index (solid line, high; dashed line, low), c: Lymph node metastasis (solid line, pN0; dashed line, pN1/pN2/pN3). *P*: log-rank test. *: <0.05.

The present study did not demonstrate a significant difference in the 5 year survival between tumor size <4 cm vs. ≥ 4 cm, a finding that was reported by Seto et al. Wang et al. reported that there was no difference in the 5year survival between adenocarcinomas with maximum tumor size of ≤ 4 cm vs. >4 cm.[19] Since these studies were retrospectively conducted, prospective reports on the effects of lymphadenectomy from other institutions are awaited in the future.

We devised an LV Index based on the lymphatic and vascular invasion of the tumor (ly, v), and evaluated its effectiveness as a prognostic risk evaluation factor in 29 EGC patients who underwent R0 surgeries. The numbers of pathological metastatic lymph nodes and LV Index were statistically correlated ($P = 0.007$, Fisher's exact test) and LV Index might refer the metastatic status of lymph nodes. Univariate analysis was carried out with the LV Index and other patient characteristics divided into two groups. Although a significant difference was not obtained, the LV Index had the lowest hazard ratio ($P = 0.069$), suggesting that it could potentially be used as a risk evaluation factor. Multivariate analysis also showed that the LV Index had the lowest hazard ratio ($P = 0.061$), suggesting its effectiveness as a risk evaluation factor that contributes to survival. Moreover, Kaplan-Meier analysis showed that the low LV Index group had a significantly greater 5 year survival, indicating that lymphatic and vascular invasion within the tumor is effective in determining survival ($P = 0.033$, log-rank test).

Conclusion

Prognostic evaluation factors were investigated in 29 patients with adenocarcinoma of EGJ from a rural institutional hospital. Clear differences in prognosis were not observed based on tumor size classification. Based on the results from the multivariate analysis and 5 year survival rates, it appears that the LV Index affects prognosis. Nonetheless, due to the small sample size, the results were only speculative. Furthermore, because an association with the type of metastasis was not found, further reports of results from a prospective study or a multi-center study are needed.

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Conflicts of interest: None declared.

Ethical statement: The authors declare that their work conforms to the guidelines set forth in the Helsinki Declaration of 1975, as revised in 2000 (5), concerning Human and Animal Rights, and that they followed the policy concerning Informed Consent.

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