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Clinical Influence of Anastomotic Leakage on Esophageal Cancer Survival and Recurrence

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Abstract. *Background: We investigated the clinical influence of anastomotic leak (AL) on esophageal cancer survival and recurrence after curative surgery. Patients and Methods: This study included 122 patients who underwent curative surgery for esophageal cancer between 2008 and 2018. The patients were classified into those with AL and those without. The risk factors for overall (OS) and recurrence-free (RFS) survival were identified. Results: AL was found in 44 out of the 122 patients (36.1%). The respective OS rates at 3 and 5 years after surgery were 43.9% and 40.2% in the AL group and 63.9% and 53.2% in the non-AL group, which were significantly different (p=0.0049). In contrast, the respective RFS rates at 3 and 5 years after surgery were 44.8% and 29.8%, and 44.9% and 42.4%, which were not significantly different (p=0.2306). A multivariate analysis showed that AL was a significant independent risk factor for both poorer OS and RFS in patients who underwent curative surgery for esophageal cancer. Conclusion: To improve survival of patients with esophageal cancer, the surgical procedure, perioperative care and surgical strategy must be carefully planned in order to prevent AL.*

More than 450,000 new esophageal cancer diagnoses and more than 400,000 deaths per year were reported to occur worldwide in 2012. Esophageal cancer is the eighth-most common cancer in the world and the sixth-most common cause of death due to cancer (1). Complete resection is essential for curing esophageal cancer (2, 3), however, 20% to 60% of patients who undergo esophagectomy for esophageal cancer suffer postoperative surgical complications.

Recent studies have suggested that postoperative surgical complications clinically influence a patient's survival and pattern of recurrence (4-7). Among surgical complications, anastomotic leak (AL) is one of the most clinically influential factors in survival and recurrence pattern in patients with several different malignancies (8-10). AL can lead to difficulty with oral intake, malnutrition, and a prolonged hospital stay (11, 12). These adverse events might lead to early recurrence or death.

Based on previous findings, we hypothesized AL to be clinically influential on survival and recurrence in patients undergoing curative resection for esophageal cancer. The present retrospective study explored whether or not overall (OS) and recurrence-free (RFS) survival were affected by the development of AL in patients who underwent curative resection for esophageal cancer.

Patients and Methods

Patient data. The patients were selected from the medical records of consecutive patients who underwent esophagectomy for esophageal cancer at Yokohama City University from January 2005 to September 2018. The inclusion criteria were as follows: (i) histologically proven primary esophageal squamous cell carcinoma or adenocarcinoma, (ii) clinical stage IB to III disease as evaluated using the seventh edition of the tumor-node-metastasis classification established by the Union for International Cancer Control, and (iii) complete (R0) resection of esophageal cancer with radical lymph node dissection (13). Patients who had undergone R2 or R1 resection were excluded from the study.

Surgical procedure. Our standard procedures consisted of open subtotal esophagectomy *via* right thoracotomy. Reconstruction used a gastric tube through the retrosternal route or posterior mediastinal route. Anastomosis was made at the cervical incision. In principle, two-field lymph node dissection was indicated when tumors were located at the lower to middle thoracic esophagus, while three-field dissection was applied for upper thoracic tumors.

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Key Words: Esophageal cancer, anastomosis leak, overall survival, recurrence.

Table I. *Definition of anastomotic leak as adapted from the Surgical Infection Study Group (14).*

Leak	Definition	Treatment
Radiological	No clinical signs	No change in management
Clinical, minor	Local inflammation cervical wound X-ray indicated leak (thoracic anastomosis)	Drain wound Delayed oral intake
	Elevation of: fever, white blood cell count, C reactive protein	Antibiotics
Clinical, major	Severe disruption on endoscopy Sepsis	Computed tomography-guided drainage (Reintervention)
Conduit necrosis	Endoscopic confirmation	Reintervention

Table II. *Clinicopathological data according to anastomotic leak (AL).*

			Postoperative AL, n (%)		
Characteristics		All cases, n (%)	No (n=78)	Yes (n=44)	*p*-Value
Age	<68 Years	65 (53.3)	43 (55.1)	22 (50.0)	0.586
	≥68 Years	57 (46.7)	35 (44.9)	22 (50.0)	
Gender	Male	106 (86.9)	69 (88.5)	37 (84.1)	0.492
	Female	16 (13.1)	9 (11.5)	7 (15.9)	
Site of tumor	Upper thoracic	36 (29.5)	19 (24.4)	17 (38.6)	0.097
	Lower-Middle thoracic	86 (70.5)	59 (75.6)	27 (61.4)	
Pathological depth of invasion	T1	43 (35.2)	25 (32.1)	18 (40.9)	0.403
	T2-T4	79 (64.8)	53 (67.9)	26 (59.1)	
Pathological lymph node status	Negative	62 (50.8)	38 (48.7)	24 (54.5)	0.536
	Positive	60 (49.2)	40 (51.3)	20 (45.5)	
Lymphovascular invasion	Negative	38 (31.1)	23 (29.5)	15 (34.1)	0.598
	Positive	84 (68.9)	55 (70.5)	29 (65.9)	
Lymph node dissection	Two-field	75 (61.5)	55 (70.5)	20 (45.5)	0.006
	Three-field	47 (38.5)	23 (29.5)	24 (54.5)	
Neoadjuvant chemotherapy	Yes	51 (41.8)	34 (43.6)	17 (38.6)	0.594
	No	71 (58.2)	44 (56.4)	27 (61.4)	

Perioperative care. In principle, all of the patients received the same perioperative management. Antibiotics were administered 30 min before surgery and then again every 3 h during surgery, as well as on postoperative day (POD) 2. The patients were allowed to eat rice porridge until midnight the day before the surgery. The patients remained on ventilation overnight. Enteral nutrition and ambulation were started on POD 1. Oral intake was initiated on POD 5, beginning with water and gelatinous foods. The patients began to eat solid food on POD 10, starting with rice gruel and soft food and progressing in three steps to regular food intake.

Definition of AL. All data were retrospectively retrieved from the patients' records. The rate of AL was determined based on the definition of leak adapted from the Surgical Infection Study Group (Table I) (14).

Follow-up. The patients were followed-up at outpatient clinics. The follow-up program of postoperative surveillance principally consisted of a physical examination; blood chemistry assessments, including squamous cell carcinoma tumor markers, every 3 months for the first year and every 6 months thereafter; and computed tomography of the neck, chest, and abdomen every 6 months. Disease recurrence was diagnosed based on radiographic evidence of a new suspicious low-density mass in the region of the mediastinum and lymph nodes or at other distant sites.

Evaluations and statistical analyses. Recurrence-free survival (RFS) was defined as the period between surgery and the occurrence of an event, recurrence or death, whichever came first. The overall survival (OS) was defined as the period between the date of surgery and death. The data of patients who had not experienced an event were censored at the date of the final observation. The RFS and OS curves were calculated using the Kaplan-Meier method and compared by the log-rank test. The Cox proportional hazards model was used for the univariate and multivariate survival analyses to identify prognosticators. An unpaired Student's *t*-test or the chi-squared method was used to compare the two groups. *p*-Values of less than 0.05 were considered to indicate statistical significance. The survival data were obtained from hospital records. The SPSS software program (v11.0J Win; SPSS, Chicago, IL, USA) was used to perform all of the statistical analyses.

Ethics. The present study was conducted in compliance with the 'ethical guidelines for clinical research'. Informed consent for using

Table III. *Univariate and multivariate Cox proportional hazards analysis of the relationship between clinicopathological factors and overall survival.*

			Univariate analysis			Multivariate analysis		
Characteristic		%	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age	<68 Years	65	1.000		0.121			
	≥68 Years	57	1.507	0.898-2.529				
Gender	Female	16	1.000			1.000		
	Male	106	2.153	0.780-5.949	0.139	2.467	0.888-6.858	0.083
Site of tumor	Lower-Middle thoracic	86	1.000					
	Upper thoracic	36	1.331	0.691-2.564	0.392			
Pathological depth of invasion	T1	43	1.000			1.000		
	T2/T3	79	2.387	1.286-4.430	0.006	2.706	1.437-5.094	0.002
Pathological lymph node status	Negative	62	1.000			1.000		
	Positive	60	1.885	1.111-3.196	0.019	1.295	0.713-2.355	0.396
Lymphovascular invasion	Negative	38	1.000			1.000		
	Positive	84	2.182	1.131-4.210	0.020	1.587	0.754-3.339	0.224
Postoperative AL	No	78	1.000			1.000		
	Yes	44	2.019	1.154-3.531	0.014	2.078	1.209-3.572	0.008
Neoadjuvant chemotherapy	No	71	1.000					
	Yes	51	1.041	0.612-1.771	0.881			

AL: Anastomotic leak; CI: confidence intervaI; HR: hazard ratio.

clinical data without identifying personal information was obtained before surgery from all patients. This study was approved by the Institutional Review Board of Yokohama City University.

Results

Patient characteristics. One-hundred and twenty-two patients underwent esophagectomy for esophageal cancer between 2008 and 2018. One-hundred and six patients were male, and 16 were female. The median age was 68 years (range=40-82 years). The median follow-up period was 72.5 months (range=13.9-125.2 months). Forty-four patients were categorized as having AL, and 78 were categorized as not having AL. Table II compares the patient characteristics between the two groups. Table II also shows the relationships between the occurrence of AL and the clinicopathological parameters. Lymph node dissection was significantly associated and tumor location marginally significantly associated with the incidence of AL (p=0.006 and p=0.097, respectively).

Survival analyses. The respective OS rates at 1, 3 and 5 years after surgery were 71.1%, 43.9% and 40.2% in the AL group and 85.5%, 63.9% and 53.2% in the non-AL group, which were significantly different (p=0.0049). The OS curves are shown in Figure 1. Univariate analyses showed that postoperative AL was a significant prognostic factor, as were the depth of tumor invasion, lymph node status and lymph vascular invasion for poorer OS (Table III). AL was selected for the final model to be analyzed by a multivariate analysis [hazard ratio (HR)=2.078, 95% confidence interval (CI)=1.209-3.572; p=0.008].

The respective RFS rates at 1, 3 and 5 years after surgery were 58.7%, 44.8% and 29.8% in the AL group and 68.4%, 44.9% and 42.4% in the non-AL group, which were not significantly different (p=0.2306). The RFS curves are shown in Figure 2. Univariate analyses for the RFS showed that AL was a marginally significant prognostic factor (Table IV). However, AL was selected for the final model by a multivariate analysis (HR=1.805, 95% CI=1.081-3.014; p=0.024).

Recurrence pattern and causes of death. Regarding the sites of first relapse, there were no significant differences between the patients with and without AL (Table V). The cause of death was analyzed for all patients. The rates of esophageal cancer-related death and death due to other causes were similar between the patients with and without AL.

Discussion

The aim of the present study was to evaluate whether or not OS and RFS were shortened by the development of AL in patients who underwent curative resection for esophageal cancer. The major findings were that AL was observed in almost 35% of patients after esophageal cancer surgery and was an independent prognostic factor for poorer OS and RFS. To improve survival among patients with esophageal cancer, it is necessary to prevent their developing AL after surgery.

Firstly, we discuss the significant difference in the oncological outcomes between patients with and without

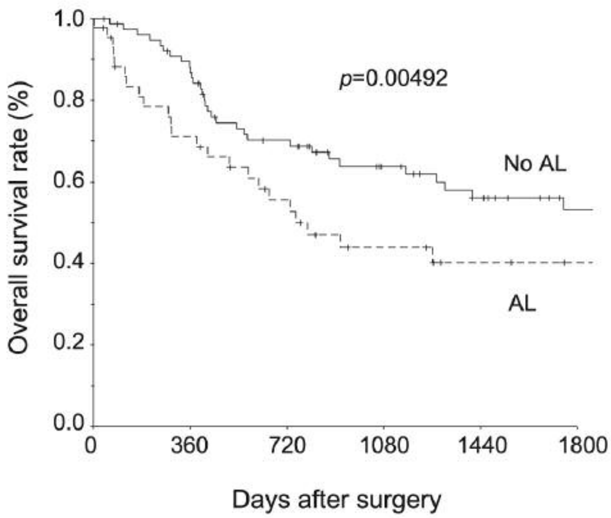

Figure 1. *The overall survival curves of the patients with and without anastomotic leak (AL). Five-year overall survival was 53.2% in the group without AL and 40.2% in that with AL.*

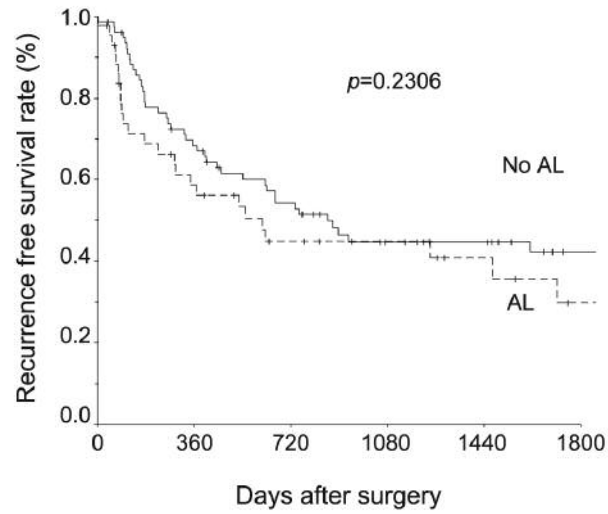

Figure 2. *The recurrence-free survival curves of the patients with and without anastomotic leak (AL). Five-year recurrence-free survival was 42.4% in the group without AL and 29.8% in that with AL.*

AL. A few reports have described the relationship between AL and survival in patients who underwent esophagectomy for esophageal cancer (15, 16). For example, Andreou *et al*. evaluated the clinical influence of AL in patients with gastric or esophageal cancer who underwent curative resection (17). Among 471 patients, 53% were diagnosed with gastric cancer and 47% with esophageal cancer. In their study, AL was observed in 8.7% of patients (5.3% gastric cancer and 12.9% esophageal cancer). The OS of the patients with AL was shorter than that of patients without (HR=2.29, 95% CI=1.43-3.69; p=0.001). The OS rate at 5 years after surgery was 39% in the AL group and 61% in the non-AL group. The RFS was also shorter in the patients with AL than in those without (HR=1.74, 95% CI=1.03-2.95; p=0.037). The RFS rate at 3 years after surgery was 35% in the AL group and 58% in the non-AL group. Our results support the findings of these previous studies. Markar *et al*. evaluated the prognostic impact of AL in 2,944 patients with esophageal cancer who underwent esophagectomy at 30 university hospitals between 2000 and 2010 (18). In that study, among the 2,439 patients included in the final analysis, 208 (8.5%) developed severe esophageal AL after surgery. The median OS after surgery was 35.8 months in the AL group and 54.8 months in the non-AL group (p=0.002). The uni- and multivariate analyses showed that AL was a significant prognostic factor for OS (HR=1.28; 95% CI=1.04-1.59; p=0.022).

There are several possible explanations as to why postoperative AL affects the long-term outcome of patients with esophageal cancer. For example, the patients who developed AL after esophagectomy for esophageal cancer might have had some factors that led to reduced host immunity against residual tumor. However, the detailed mechanism underlying this is unclear at present (19-21).

In the present study, we defined postoperative AL based on the definition of leak adapted from the Surgical Infection Study Group, and the incidence of the AL was 36%. However, the incidence of AL varies widely and has been reported to range from 0% to 53% (22). The main reason for this wide variation is the lack of an optimal definition of AL. For example, Markar *et al*. defined AL as a symptomatic disruption of the intrathoracic anastomosis classified as grade III or IV according to the Clavien-Dindo classification (18). Postoperative barium swallow was not routinely performed in their study. Andreou *et al*. also used the Clavien-Dindo classification, but a definitive definition of AL was not described. A postoperative radio contrast agent swallow examination was routinely performed at day 5 after surgery in their study (17). In addition, a recent systematic literature review of all articles dealing with anastomosis leak after esophagectomy only found 13 out of 33 publications that included a definition of AL (23). The clinical features used to define AL included evidence of hematoma or seroma at the neck wound, septicemia, peritonitis, peri-anastomosis collection, leak, local inflammation, evacuation of air or saliva, mediastinitis, abscess, empyema and pneumothorax. The majority of these studies reported the routine postoperative use of radiographic water-soluble contrast studies, but the timing of the contrast study ranged from 3 to 14 days after surgery.

Special attention is required when interpreting the current results, as there are some potential limitations associated

Table IV. *Univariate and multivariate Cox proportional hazards analysis of the relationship between clinicopathological factors and recurrence-free survival.*

			Univariate analysis			Multivariate analysis		
Characteristic		%	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age	<68 Years	65	1.000					
	≥68 Years	57	1.091	0.651-1.828	0.742			
Gender	Female	16	1.000			1.000		
	Male	106	1.590	0.683-3.702	0.282	2.227	0.952-5.208	0.065
Site of tumor	Lower-middle thoracic	86	1.000					
	Upper thoracic	36	1.032	0.737-1.447	0.853			
Pathological depth of invasion	T1	43	1.000			1.000		
	T2/T3	79	4.623	2.265-9.434	<0.001	3.835	2.060-7.142	<0.001
Pathological lymph node status	Negative	62	1.000			1.000		
	Positive	60	2.664	1.546-4.590	<0.001	1.475	0.841-2.587	0.175
Lymphovascular invasion	Negative	38	1.000			1.000		
	Positive	84	2.588	1.341-4.995	0.005	1.623	0.831-3.168	0.156
Postoperative AL	No	78	1.000			1.000		
	Yes	44	1.393	0.845-2.298	0.194	1.805	1.081-3.014	0.024
Neoadjuvant chemotherapy	No	71	1.000					
	Yes	51	1.620	0.928-2.827	0.089			

AL: Anastomotic leak; CI: confidence interval; HR: hazard ratio.

Table V. *Patterns of recurrence between the patients with postoperative anastomosis leakage (AL) and those without.*

			Postoperative AL, n (%)		
Recurrence site		All cases, n (%)	No (n=78)	Yes (n=44)	*p*-Value
Lymph node	Regional	23 (18.9)	14 (17.9)	9 (20.5)	0.734
	Distant	7 (5.7)	5 (6.4)	2 (4.5)	0.671
Local		12 (9.8)	10 (12.8)	2 (4.5)	0.195
Distant site	Lung	12 (9.8)	8 (10.3)	4 (9.1)	0.977
	Liver	11 (9.0)	6 (7.7)	5 (11.4)	0.290
	Bone	5 (4.1)	2 (2.6)	3 (6.8)	0.255
	Other	9 (8.0)	8 (10.3)	1 (2.3)	0.105
Disseminated		3 (2.5)	2 (2.6)	1 (2.3)	0.921

Some patients had a first relapse at more than one site.

with this study. Firstly, this was a retrospective, single-center study with a small sample size. Our findings may therefore have been the result of chance in this series. Secondly, there may have been a selection bias in the present study. Generally, esophagectomy itself has a 30-40% morbidity rate and 1-2% mortality rate. Surgeons thus avoid performing esophagectomy for certain patients, particularly elderly ones. The impact of AL may therefore have been artificially emphasized in this cohort. Thirdly, there was a time bias in this study, as the data were collected between 2008 and 2018. Surgical procedures and perioperative care might have changed over this period. Considering these limitations, the current results should be validated by another study.

In conclusion, the present study confirmed that the development of AL was a risk factor for poorer OS and RFS in patients who underwent esophagectomy for esophageal cancer. To improve survival of these patients, the development of AL after esophagectomy needs to be prevented.

Availability of Data and Materials

Data and materials are available to any researcher interested upon reasonable request to the corresponding author.

Conflicts of Interest

The Authors declare no competing interests in association with the present study.

Authors' Contributions

Keisuke Kazama, Toru Aoyama and Ayaka Tamagawa made substantial contributions to conception and design. All Authors made substantial contributions to acquisition of data, or analysis and interpretation of data. Toru Aoyama, Keisuke Kazama, Yosuke Atsumi, Hiroshi Tamagawa, Ayaka Tamagawa, Keisuke Komor and Yasushi Rino were involved in drafting the article or revising it critically for important intellectual content. All Authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All Authors read and approved the final article.

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