in vivo *34*: 857-862 (2020)
doi:10.21873/invivo.11849

Risk Factors for Postoperative Anastomosis Leak After Esophagectomy for Esophageal Cancer

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Abstract. *Background/Aim: The present study aimed to identify risk factors for anastomosis leak (AL) after esophagectomy for esophageal cancer. Patients and Methods: One-hundred twenty-two patients who underwent esophagectomy for esophageal cancer between 2008 and 2018 were included. The rate of AL was measured based on the definition of leak as adapted from the Surgical Infection Study Group. To identify the risk factors for AL, logistic regression analysis was used. Results: AL was found in 44 of the 122 patients (36.1%). Among the factors examined, the lymph node dissection status (p=0.007) and preoperative serum albumin level (p=0.022) were significant independent risk factors for AL. The incidence of AL was 26.7% (20 of 75) among patients who received 2-field lymph node dissection and 51.1% (24 of 47) among those who received 3-field lymph node dissection. The incidence of AL was 29.9% (23 of 77) in the preoperative serum albumin levels ≥4.0 g/dl group and 46.7% (21 of 45) in the serum albumin levels <4.0 g/dl group. Conclusion: Lymph node dissection status and preoperative serum albumin levels were risk factors for AL in patients who received esophagectomy for esophageal cancer.*

Esophageal cancer is a major cause of cancer death worldwide (1). Complete resection is essential for curing esophageal cancer (2-3). However, the morbidity rate after esophagectomy for esophageal cancer ranges from 30% to 60%, and the morality rate is 1-5% (4-6). Some studies have shown that the development of anastomosis leak (AL) increased the risk of disease recurrence and reduced the overall survival in esophageal cancer patients who received esophagectomy (7-8). Therefore, it is important to predict the occurrence of AL before surgery and determine the most appropriate approach to perioperative care.

Recently, the importance of multidisciplinary team efforts, such as oral care and perioperative nutritional care, for preventing AL has been reported (9, 10). However, few studies have investigated the risk factors for AL after esophageal cancer surgery (11-16). Thus, further studies are required to identify these risk factors. If they can be clarified, it will be possible to determine the appropriate indications of oral care and perioperative nutritional care and to select suitable surgical procedures considering the balance between risks and benefits.

The aim of the present study was to identify risk factors for AL after esophagectomy for esophageal cancer.

Patients and Methods

Patients. The patients were selected from the medical records of consecutive patients who received curative resection for esophageal cancer at Yokohama City University from 2005 to 2018. The inclusion criteria were as follows: 1) histologically proven primary esophageal adenocarcinoma or squamous cell carcinoma, 2) clinical stage IB to III (excluding T4) according to the 7th edition of the tumor-node-metastasis classification, and 3) complete (R0) resection of the esophageal cancer with radical lymph node dissection. Patients who had undergone R2 or R1 resection were excluded from the study.

Surgical procedure. Our subtotal esophagectomy defined as subtotal esophagectomy with resection of both lesser curve and subcardial area of the stomach. Greater curvature tube was used for reconstruction. In addition, cervical anastomosis was performed in all cases. In principle, two-field lymph node dissection is indicated when tumors are located at the middle thoracic to lower thoracic esophagus, while three-field dissection is applied for upper thoracic tumors.

Perioperative care. The patients were managed using the same perioperative care (17). Briefly, cefazolin (1 g) was administered 30 min before the surgical incision, every 3 h during surgery, and at a

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Key Words: Esophageal cancer, anastomosis leak, risk factor.

Table I. *Definition of leak as adapted from the Surgical Infection Study Group.*

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

Table II. *Clinicopathological data of patients with and without postoperative anatomic leakage.*

			Postoperative anatomic leakage				
	All cases		No (n=78)		Yes (n=44)		
Characteristics	Number	%	Number	%	Number	%	*p*-Value
Age							0.586
<68 years old	65	53.3	43	55.1	22	50.0	
≥68 years old	57	46.7	35	44.9	22	50.0	
Gender							0.492
Male	106	86.9	69	88.5	37	84.1	
Female	16	13.1	9	11.5	7	15.9	
ASA-PS							0.073
1	10	8.2	9	11.5	1	2.3	
2-3	112	91.8	69	88.5	43	97.7	
Site of tumor							0.097
Upper thoracic	36	29.5	19	24.4	17	38.6	
Middle-Lower thoracic	86	70.5	59	75.6	27	61.4	
Body mass index*	20.9	14.5-29.0	20.8	16.1-27.6	21.1	14.5-29.0	0.355
Smoking habit							0.100
Yes	109	89.3	67	85.9	42	95.5	
No	13	10.7	11	14.1	2	4.5	
Alcohol habit							0.284
Yes	112	91.8	70	89.7	42	95.5	
No	10	8.2	8	10.3	2	4.5	
White blood cell*	6100	2800-14000	6300	3000-12500	5900	2800-14000	0.907
Hemoglobin*	12.5	6.8-16.1	12.5	6.8-15.6	12.3	8.1-16.1	0.940
Albumin*	4.1	1.5-5.0	4.2	1.5-5.0	3.9	2.3-4.7	0.073
C reactive protein*	0.14	0.01-8.95	0.09	0.01-8.15	0.24	0.02-8.95	0.139

ASA-PS: ASA physical status; *median and range.

dose of 2 g on postoperative day (POD) 2. The patients remained on ventilation overnight. On POD1, ambulation and enteral nutrition were started. On POD5, oral intake was initiated. On POD10, the patients began to eat solid food.

Definition of AL. All data were retrospectively retrieved from the medical records. The rate of AL was measured based on the definition of leak as adapted from the Surgical Infection Study Group (Table I) (18).

Definition of habitable alcohol consumption. Patients reported their alcohol consumption and were then categorized into the following 4 groups based on these data: 1) lifelong nondrinkers; 2) mild drinkers (3 to 10 standard drinks/week); 3) moderate drinkers (11 to 20 standard drinks/week); 4) heavy drinkers (>20 standard drinks/week) (19).

Evaluations and statistical analyses. Logistic regression analysis was used in order to predict the risk factors for AL. The chi-square test was used to compare two groups. We used fitted linear regression models in the multivariate analysis. We also used backwards elimination to select a model. *p*-Values of <0.05 were considered to indicate statistical significance. The SPSS software package (v11.0 J Win; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Table III. *Surgical and pathological findings of patients with and without postoperative anatomic leakage.*

			Postoperative anatomic leakage				
	All cases		No (n=)		Yes (n=)		
Characteristics	Number	%	Number	%	Number	%	*p*-Value
Neoadjuvant chemotherapy							0.594
Yes	51	41.8	34	43.6	17	38.6	
No	71	58.2	44	56.4	27	61.4	
Surgery type							0.875
Transthoracic	87	71.3	56	71.8	31	70.5	
Thoracoscopic	35	28.7	22	28.2	13	29.5	
Lymph node dissection							0.006
Two-field	75	61.5	55	70.5	20	45.5	
Three-field	47	38.5	23	29.5	24	54.5	
Operative duration	592	259-911	586	295-877	623	259-911	0.305
Blood loss	540	70-3000	500	70-3000	765	136-2756	0.059
Blood transfusion							0.667
Yes	39	32.0	26	33.3	13	29.5	
No	83	68.0	52	66.7	31	70.5	
Pathological depth of invasion							0.403
T1	43	35.2	25	32.1	18	40.9	
T2 or more	79	64.8	53	67.9	26	59.1	
Pathological lymph node status							0.536
Negative	62	50.8	38	48.7	24	54.5	
Positive	60	49.2	40	51.3	20	45.5	
Lymph vascular invasion							0.598
Negative	38	31.1	23	29.5	15	34.1	
Positive	84	68.9	55	70.5	29	65.9	

Ethics. The present study was conducted in compliance with the 'ethical guidelines for clinical research'. Informed consent for using clinical data without identifying personal information was obtained before surgery from all patients.

Results

Patient's clinic pathological data. One hundred twenty-two patients received curative surgery for esophageal cancer between 2008 and 2018. Median was 68 years (range=40-82 years). One hundred six patients were male, and 16 patients were female. Forty-four patients were categorized as AL (AL group), and 78 were categorized as without AL (non-AL group). Table II shows the patients background. When comparing patient's clinic pathological data between AL and non-AL groups, the tumor location was marginally but significantly associated with the incidence of AL (p=0.097), as was the preoperative serum albumin level (p=0.073).

Operative and pathological data. The patients' surgical and pathological data are summarized in Table III. The incidence of three filed lymph node dissection was significantly higher in the AL group than in the non-Al group (p=0.006).

Risk factors for anastomosis leak. The risk factors for AL were analyzed using the preoperative and perioperative factors by logistic regression analysis. Table IV shows the analysis results. Among the factors examined, the lymph node dissection status (p=0.007) and preoperative serum albumin levels (p=0.022) were identified as significant independent risk factors for AL.

The incidence of AL was 26.7% (20 of 75) among patients who received 2-field lymph node dissection and 51.1% (24 of 47) among those who received 3-field lymph node dissection. The incidence of AL was 29.9% (23 of 77) in preoperative serum albumin levels ≥4.0 g/dl group and 46.7% (21 of 45) in serum albumin levels <4.0 g/dl group.

Discussion

The aim of the present study was to identify risk factors of AL after esophagectomy for esophageal cancer. The major finding was that the lymph node dissection status and preoperative serum albumin levels were significant risk factors for AL. Therefore, careful attention should be paid to patients with these risk factors when considering esophagectomy for esophageal cancer.

Table IV. *Results of univariate and multivariate analyses of risk factors for postoperative anatomic leakage.*

Characteristics	Number	Univariate analysis			Multivariate analysis		
		HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age				0.586			
<68 years old	65	1.000					
≥68 years old	57	1.228	0.586-2.576				
Neoadjuvant chemotherapy				0.595			
No	71	1.000					
Yes	51	1.227	0.577-2.608				
Operative type							
Transthoracic	87	1.000					
Thoracoscopic	35	1.067	0.473-2.409				
Operative duration				0.217			
<590 min	59	1.000					
≥590 min	63	1.601	0.758-3.380				
Blood loss				0.061			
<540 ml	61	1.000					
≥540 ml	61	2.055	0.967-4.369				
Lymph node dissection				0.007			0.007
Two-field	75	1.000			1.000		
Three-field	47	2.870	1.332-6.182		3.075	1.365-6.928	
Smoking habit				0.119			0.094
No	13	1.000			1.000		
Yes	109	3.447	0.728-16.322		6.031	0.734-49.554	
Alcohol habit				0.296			
No	10	1.000					
Yes	112	2.343	0.475-11.566				
Albumin				0.009			0.022
≥4.0 g/dl	77	1.000			1.000		
<4.0 g/dl	45	2.788	1.291-6.022		2.607	1.147-5.924	

HR: Hazard ratio; CI: confidence interval.

In the present study, the preoperative serum albumin levels were a significant risk factor in both univariate and multivariate analyses. Indeed, serum albumin levels <4.0 g/dl group had a higher risk of AL than the serum albumin level <4.0 g/dl group. A few previous reports have described the relationship between AL and the perioperative nutritional status in patients who received esophagectomy for esophageal cancer. Gao *et al*. have evaluated the risk factors of AL in 96 patients who had been diagnosed with esophageal cancer and underwent resection (20). They found that AL occurred in 12.5% and that a lower prealbumin level was an independent risk factor for AL. These results suggested that a poor preoperative nutritional status was the main risk factor for AL. Previous studies have further reported that the pre- and peri-operative nutrition treatment reduced the surgical complications in patients who had malnutrition (21, 22). Perioperative nutrition care might be recommended in patients who had the risk factors to reduce AL.

Previous retrospective studies have reported on the relationship between the lymph node dissection status and the incidence of AL in patients who underwent esophagectomy for esophageal cancer. Igaki *et al*. have evaluated the oncological outcomes with 2- and 3-field lymph node dissection among 156 patients who had been diagnosed with esophageal cancer and undergone resection (23). Among these 156 patients, 55 (35%) received 2-field lymph node dissection, and 101 (65%) received 3-field lymph node dissection. They found that AL occurred in 55 (35%) patients. Although no significant difference was noted, the incidence of AL tended to be higher in the 3-field lymph node dissection group than in the 2-field lymph node dissection group (39% *vs*. 29%, p=0.234). In addition, a recent meta-analysis including 2 randomized control trials and 18 observational studies with over 7000 patients has shown that 3-field lymph node dissection was associated with a significantly higher incidence of AL than 2-field lymph node dissection (relative risk=1.26; 95% confidence interval=1.05-1.52; p=0.09) (24). Given the present and previous findings, the lymph node dissection status might have some clinical influence on AL in patients who undergo esophagectomy.

An important limitation associated with AL is the lack of consensus regarding the appropriate definition for the

evaluation of AL. In the present study, AL was reported by individual physicians and was not based on a specific protocol. In addition, we defined AL based on the definition of leak adapted from the Surgical Infection Study Group, and the incidence of AL was 36%. However, the incidence of AL varies widely and has been reported to range from 0% to 53% (25). The main reason for this wide variation is the lack of an optimal definition of AL. For example, Markar *et al*. have defined AL as a symptomatic disruption of the intrathoracic anastomosis classified as grade III or IV according to the Clavien-Dindo classification (26). A postoperative barium swallow examination was not routinely performed in their study. Andreou *et al*. have also used the Clavien-Dindo classification, but the definition of AL was not described. A postoperative radio contrast agent swallow examination was routinely performed at day 5 after surgery in their study (27). In addition, a recent systematic literature review of all articles dealing with AL after esophagectomy found only 13 out of 33 publications that included a definition of AL (28). Although the majority of these studies have reported the routine postoperative use of radiographic studies, their timing ranged from 3 to 14 days after the surgery.

There are several potential limitations associated with this study. First, this study was a retrospective, single-center study with a relatively small sample size. Furthermore, this study might have selection bias. Second, a surgical stress marker was not evaluated in the present study. Previous studies have shown that the risk of AL in patients with esophageal cancer is influenced by the general status, nutrition status and immune status. However, we were unable to evaluate these factors in the present study. Given these limitations, the current results should be validated in other series with a larger number of patients.

In conclusion, the lymph node dissection status and preoperative serum albumin levels were risk factors for AL in patients who underwent curative esophagectomy for esophageal cancer. To avoid AL after esophagectomy for esophageal cancer, it is necessary to carefully plan the surgical strategy, surgical procedure, and perioperative treatment including adjuvant treatment.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

TA and YA made substantial contributions to conception and design. TA, KH, HT, AT, KK (Keisuke Komori), YM, KK2 (Kazuki Kano), KK3 (Keisuke Kazama), IH, MM1 (Masaaki Murakawa), MN, TO, NY, MM2 (Munetaka Masuda), and YR made substantial contributions to acquisition of data, or analysis and interpretation of data. TA, KK, YA, HT, AT, KK2 and YR have been involved in drafting the manuscript or revising it critically for important intellectual content. TA, YM, KK3, KH, MM, MN, TO, and MM have given final approval of the version to be published. Each Author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and 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 manuscript.

Acknowledgements

This work was supported, in part, by the nongovernmental organization Yokohama Surgical Research Group, Dr. Masumi Kamachi (Tokyo Shinagawa Hospital), Dr. Ryuji Tominaga (Fukuoka Wajiro Hospital), Dr. Nobuko Yoshiki (Yoshiki Dermatology Clinic Ginza). The Authors express their sincere gratitude to Ms. Akiko Yoshida, Ms. Yuka Maruyama, Ms. Minako Igarashi and Ms. Mariko Yamauchi for their excellent data management in this study.

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Received December 11, 2019
Revised January 3, 2020
Accepted January 7, 2020