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ORIGINAL ARTICLE

비후성 또는 켈로이드 창상 흉터는 식도암 수술 후 식도-위 문합 부위의 협착에 대한 위험인자인가?

성용원, 김지현[1], 옥유정, 오세진, 최재성, 이정상, 문현종

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Is Hypertrophic or Keloid Wound Scar a Risk Factor for Stricture at Esophagogastric Anastomosis Site after Esophageal Cancer Operation?

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Background/Aims: Anastomotic stricture at the esophagus and the conduit anastomosis site after the surgical resection of esophageal cancer is relatively common. This study examined whether a hypertrophic scar or keloid formation at a surgical wound is related to an anastomotic stricture.
Methods: From March 2007 to July 2017, 59 patients underwent curative surgery for esophageal cancer. In 38 patients, end-to-end anastomosis (EEA) of the esophagus and the conduit was performed using EEA 25 mm. A hypertrophic wound scar was defined when the width of the midline laparotomy wound scar exceeded 2 mm. The relationship between the hypertrophic scar and stricture and the other risk factors for anastomotic stricture in these 38 patients was analyzed.
Results: Of the 38 patients, eight patients (21.1%) had an anastomotic stricture, and a hypertrophic skin scar was observed in 14 patients (36.8%). Univariate analysis revealed lower BMI and hypertrophic scars as risk factors (p=0.032, p=0.001 respectively). Multivariate analysis revealed a hypertrophic scar as an independent risk factor for an anastomotic stricture (p=0.010, OR=27.06, 95% CI 2.19-334.40).
Conclusions: Hypertrophic wound scars can be a risk factor for anastomotic stricture after surgery for esophageal cancer. An earlier prediction of anastomotic stricture by detecting hypertrophic wound healing in patients undergoing esophagectomy may improve the patients' quality of life and surgical outcomes by earlier treatments. **(Korean J Gastroenterol 2021;78:213-218)**

Key Words: Esophageal neoplasms; Esophageal stenosis; Esophagectomy; Anastomosis, surgical

INTRODUCTION

The incidence of esophageal cancer has increased steadily over the past few decades. The prognosis of patients with esophageal cancer is currently unfavorable, and the 5-year survival rate rarely exceeds 40%.[1] Surgery is considered the best curative treatment option for patients with esophageal cancer, whether preceded by neoadjuvant therapy or not. An anastomotic site after esophagectomy is an important part of the postoperative complications. Anastomotic leak is an

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earlier complication after surgery, and anastomotic stricture is a relatively late complication after surgery.[2] Anastomotic strictures lead patients to have dysphagia, which frequently requires repetitive dilation procedures, such as esophagogastroduodenoscopic balloon dilatation or bougienation.[3,4] These repetitive procedures are burdensome to the patient and the gastroenterologists because of procedure-related complications that can decrease the postoperative quality of life. Anastomotic stricture after esophagectomy is not an uncommon postoperative complication, with a reported incidence of 9.1-46.0%, depending in part on the criteria used for the diagnosis of strictures.[3]

The mechanism of anastomotic stricture has been studied, including postoperative anastomotic leakage, gastrointestinal ischemia, tumor recurrence, and gastric acid reflux.[2,5,6] Factors potentially increasing the risk of developing benign cervical strictures are diverse. Among the other factors, postoperative anastomotic leakage, neoadjuvant therapy, and a history of cardiac disease have been reported to increase this risk.[7] Briel et al.[5] reported a four-fold increased risk of cervical anastomotic stricture among patients with endoscopic evidence of conduit ischemia or anastomotic leak postoperatively. On the other hand, risk factors for anastomotic stricture after esophagogastric anastomosis, including intrathoracic anastomosis, have not been studied systematically, and most reports had a small series.[2,5]

A hypertrophic and keloid scar is a cutaneous condition characterized by deposits of excessive amounts of collagen that gives rise to a raised scar.[8] They result from an overgrowth of dense fibrous tissue that usually develops after the healing of a skin injury. In a keloid scar, the tissue extends beyond the borders of the original wound, does not usually regress spontaneously, and tends to recur after excision. Numerous methods, such as surgical resection, steroid injection, freezing therapy, and laser therapy, have been described for the treatment of abnormal scars, but the optimal treatment method has not been established.[9] One study examined the relationship between anastomotic stricture following radical prostatectomy and hypertrophic skin scar, but there has been no study of esophageal anastomotic stricture and hypertrophic wound healing.[10] This study examined whether a hypertrophic scar or keloid formation of a skin wound is related to stricture of the anastomotic site after esophagectomy.

SUBJECTS AND METHODS

1. Study design and ethical consideration

The medical records of patients undergoing esophagectomy for primary esophageal and esophagogastric junction cancer at Seoul Metropolitan Government-Seoul National University Boramae Medical Center from January 2006 to July 2017 were reviewed retrospectively. The Ethical Committee at Seoul National University Hospital approved this study (IRB No. 16-2016-24).

2. Surgical technique and anastomosis

Surgery was performed by a surgeon with extensive experience in esophageal surgery. The standard operation consisted of transthoracic esophagectomy with a two-field lymph node dissection via the right thoracotomy or video-assisted thoracic surgery (VATS) and neoesophageal reconstruction using a gastric conduit by intrathoracic anastomosis. Sometimes a three-field lymph node dissection and cervical anastomosis were performed.

A wide gastric tube was adopted. A jejunal or colonic graft reconstruction was performed in patients with a history of gastrectomy or who had undergone synchronous esophagogastrectomy. The gastric tube was passed through and located at the posterior mediastinum (mediastinal route).

All anastomoses were established by a mechanical instrument in an end-to-end technique using a 25-mm circular stapler (EEA 25 mm, Medtronic, Minneapolis, MN, USA). Most studies on anastomotic stricture focused on the type of anastomosis performed. In this study, a linear stapler (GIA, Medtronic) or EEA 21 mm or EEA 28 mm were used in a few cases. Therefore, only the cases in which EEA 25 mm had been used were analyzed to determine the risk factors and stricture.

3. Definition of an anastomotic stricture

In this study, an anastomotic stricture was defined when at least one of the following criteria were met: 1) as stenosis precluding passage of the endoscope in the absence of recurrent cancer, 2) anastomotic stricture noted on postoperative chest CT, which is reported by a dedicated chest radiologist, and 3) stenosis requiring at least one dilation to relieve the dysphagia symptoms.

4. Study population and variables

This study investigated the following: preoperative clinical data (age, gender, height, weight, body mass index, comorbidities, and preoperative endoscopic findings), information related to the surgery (method of surgery, anastomotic technique, stage, histology, and adjuvant therapy), and follow up clinical data (stricture, other major complications, cancer recurrence, and overall survival). Information related to stricture included symptoms, endoscopic findings, and endoscopic balloon dilation. A doctor measured the largest width of the midline vertical incision scar to determine if the occurrence of anastomotic strictures was due to a generalized hypertrophic healing process. The size and width of the scar were measured during the postoperative outpatient clinic. A hypertrophic skin scar was defined as the width of the scar exceeding 2 mm, which was directly measured. Based on the collected data, the changes in the stenosis and chest wound scar were compared to evaluate the clinical information, such as the risk of stenosis according to the thickness of the wound.

5. Statistical analysis

The continuous variables were calculated as the mean±SD, and categorical variables as the number (%). A student's *t*-test was used to compare the continuous variables, and a χ^2 test was used to compare the categorical variables between the two groups. Furthermore, the risk factors for anastomotic stricture were evaluated using multiple logistic regression analysis. The RR and 95% CI of the significant factors were calculated. A p-value<0.05 was considered significant. Statistical analyses were performed using SPSS 18.0 software (SPSS 18.0 version for Windows, SPSS, Chicago, IL, USA).

RESULTS

1. Baseline patient characteristics

The medical records of 59 patients who underwent esophagectomy from March 2007 to July 2017 were reviewed retrospectively (Table 1). Twenty-one patients were excluded because of poor quality, a lack of data, and heterogeneity in anastomotic techniques (GIA, EEA 21 mm). Therefore, 38 patients (37 men and one woman) were included in the analysis. The mean age at the time of the esophagectomy was 67.7 years. Diabetes was present in eight patients; the mean BMI was 22.0 kg/m^2, and 18 patients smoked in the perioperative period. The histology of the tumor was squamous in 35 patients (92.1%) and adenocarcinoma in two (5.3%). The pathologic stage was 0 in one patient (2.6%), stage I in 11 patients (28.9%), stage II in 11 patients (28.9%), and stage III in 17 patients (39.6%). Neoadjuvant concurrent chemoradiation therapy was given

Table 1. Patients' Baseline Characteristics

Baseline characteristics	Value (n=38)
Age (years)	67.7±8.0
Male	37 (97.4)
BMI (kg/m^2)	22.0±3.2
Smoking	18 (47.4)
Diabetes	8 (21.1)
Surgical approach	
Thoracotomy	16 (42.1)
VATS	22 (57.9)
Anastomosis to	
Stomach	34 (89.5)
Jejunum	4 (10.5)
Location of cancer	
Upper esophagus	1 (2.6)
Mid esophagus	16 (42.1)
Lower esophagus	18 (47.4)
Gastroesophageal junction	3 (7.9)
Size of cancer (cm)	4.3±3.5
Histology	
Squamous cell carcinoma	35 (92.1)
Adenocarcinoma	2 (5.3)
Others (melanoma)	1 (2.6)
Pathologic stage	
0	1 (2.6)
I	11 (28.9)
II	11 (28.9)
III	17 (39.6)
IV	0 (0.0)
Neoadjuvant therapy	4 (10.5)
Adjuvant therapy	8 (21.1)
Adjuvant chemotherapy	6 (15.8)
Adjuvant radiotherapy	3 (7.9)
Anastomotic stricture	8 (21.1)
Hypertrophic skin scar	14 (36.8)
Width of scar (mm)	3.8±3.3

Values are presented as the mean±standard deviation or number (%).
BMI, body mass index; VATS, video-assisted thoracoscopic surgery; EEA, end-to-end anastomosis; GIA, gastrointestinal anastomosis; CCRT, concurrent chemoradiation therapy.

to four patients (10.5%). Thoracotomy was performed in 16 patients (42.1%) and VATS was performed in 22 patients (57.9%). All anastomoses were intrathoracic and performed using an end-to-end anastomosis (EEA) 25mm stapler. Anastomosis to the stomach was 34 (89.5%) and jejunum in four (10.5%). Eight patients (21.1%) received adjuvant therapy. Of the 38 patients, eight patients (21.1%) developed an anastomotic stricture. The mean time interval between the surgical procedure and diagnosis of stricture was 5.8 months. Hypertrophic skin scars were observed in 14 patients (36.8%), and the mean width of the scar was 3.8 mm.

Table 2. Comparison of Baseline Characteristics between no Stricture Group and Anastomotic Stricture Groups

Baseline characteristics	No stricture group (n=30)	Stricture group (n=8)	p-value
Age (years)[a]	67.9±8.5	66.8±6.0	0.715
Male gender[b]	29 (96.7)	8 (100.0)	0.601
BMI (kg/m^2)[a]	22.3±3.4	20.6±1.2	0.032
Smoking[b]	14 (46.7)	4 (50.0)	0.755
Diabetes[b]	6 (20.0)	2 (25.0)	0.842
Surgical approach[b]			0.767
Thoracotomy	13 (43.3)	3 (37.5)	
VATS	17 (56.7)	5 (62.5)	
Anastomosis to[b]			0.275
Stomach	26 (86.7)	8 (100.0)	
Jejunum	4 (13.3)	0 (0.0)	
Location of cancer[b]			0.745
Upper esophagus	1 (3.3)	0 (0.0)	
Mid esophagus	12 (40.0)	4 (50.0)	
Lower esophagus	14 (46.7)	4 (50.0)	
Gastroesophageal junction	3 (10.0)	0 (0.0)	
Size of cancer (cm)[a]	4.7±3.8	2.7±1.7	0.152
Histology[b]			0.648
Squamous cell carcinoma	27 (90.0)	8 (100.0)	
Adenocarcinoma	2 (6.7)	0 (0.0)	
Others (melanoma)	1 (3.3)	0 (0.0)	
Pathologic stage[b]			0.220
0	0 (0.0)	1 (12.5)	
I	8 (26.7)	3 (37.5)	
II	9 (30.0)	2 (25.0)	
III	13 (43.3)	2 (25.0)	
Neoadjuvant therapy[b]	2 (6.7)	2 (25.0)	0.133
Adjuvant therapy[b]	7 (23.3)	1 (12.5)	0.504
Adjuvant chemotherapy	5 (16.7)	1 (12.5)	0.774
Adjuvant radiotherapy	3 (10.0)	0 (0.0)	0.351
Hypertrophic skin scar[b]	7 (25.0)	7 (87.5)	0.001
Width of scar (mm)[a]	3.0±2.1	5.3±4.9	0.169

Values are presented as the mean±standard deviation or number (%).
BMI, body mass index; VATS, video-assisted thoracoscopic surgery; EEA, end-to-end anastomosis; GIA, gastrointestinal anastomosis; CCRT, concurrent chemoradiation therapy.
[a]Student's *t*-test; [b]Fisher exact test; [c]Pearson's Chi-square test.

Table 3. Risk Factors for Development of Anastomotic Stricture after Esophagectomy

Variable	Multivariate analysis		
	OR	95% CI	p-value
BMI	0.73	0.49-1.09	0.122
Hypertrophic skin scar	27.06	2.19-334.40	0.010

BMI, body mass index; OR, odds ratio; CI, confidence interval.

2. Comparison of baseline characteristics between the no stricture and stricture groups

Table 2 compares the baseline characteristics in patients who did and did not develop anastomotic stricture. The baseline characteristics of the no stricture group and stricture group were similar in age, gender, surgical approach, anastomotic technique, stage of cancer, neoadjuvant therapy, or adjuvant therapy. The BMI was lower in the stricture group than the no stricture group. Furthermore, the formation of a hypertrophic scar was strongly associated with the development of stricture. The mean width±SD of the scar was 5.3±4.9 mm and 3.0±2.1 mm for the anastomotic stricture and no stricture groups, respectively. There were no significant differences in cancer recurrence rate or survival rate between the no stricture and stricture groups.

3. Risk factor for stricture at the esophagogastric anastomosis site

Using these valid factors in univariate analysis, the risk factors associated with anastomotic stricture were evaluated by multivariate analysis. Table 3 lists the results of multivariate analysis of the risk factors for developing anastomotic strictures. In multivariate analysis, only hypertrophic scar formation (OR 27.06; p=0.010) was a significant risk factor for anastomotic stricture development.

DISCUSSION

Benign strictures are a distinct complication of the esophago-enteric anastomosis following an esophagectomy. The etiology of stricture formation is likely multifactorial and includes exposure to excess gastric acid, subclinical leaks, degree of tension, and local ischemia on the anastomosis. The reported incidence of anastomotic strictures ranges from as low as 1% to almost 50%, with a trend toward the latter being more common.[2] The varying incidences of anastomotic strictures may reflect differences in surgical technique, thresholds for pursuing the diagnosis of strictures, and the definitions of a stricture.

There is no generalized classification or grading system with global consensus regarding anastomotic strictures. Because of this lack of uniform reporting criteria, a comparison of the reported rates between studies is difficult. In this study, an anastomotic stricture was defined as stenosis precluding the passage of an endoscope in the absence of recurrent cancer, anastomotic stricture noted on postoperative chest CT, and stenosis needing at least one dilation to relieve the dysphagia symptom. In the present series of 38 consecutive esophagectomies, the 21.1% incidence of anastomotic strictures is comparable to that of other reports.[2,11,12]

Most benign strictures of the anastomosis occur within the first few months after surgery. Strictures presenting later should be evaluated specifically to exclude tumor recurrence. If not due to tumor recurrence, late strictures are usually the result of reflux from the gastric conduit.[2] In the present study, the mean time interval between surgery and the diagnosis of the stricture was 5.8 months, and there were no significant differences in the recurrence rate of cancer between the no stricture and stricture groups.

The concurrent or preceding occurrence of an anastomotic leak is the factor most often cited in the etiology of benign anastomotic strictures.[2] Therefore, all the factors related to the incidence of anastomotic leaks may play some role in the development of anastomotic strictures. In the present study, there were no cases of anastomotic leak. Strictures appear to be more common and are more severe after gastric pull-up than colonic interposition.[2] On the other hand, in the present study, the type of conduit used was not associated with the occurrence of stricture.

Most studies on anastomotic strictures focused on the type of anastomosis.[6,11,13-16] Various surgical techniques have been used to construct the esophagectomy and produce better outcomes, such as circular stapled anastomosis, linear stapled anastomosis, and hand-sewn anastomosis. Using a standardized two-layer hand-sewn anastomosis site, Heitmiller et al.[12] reported that approximately 26% of patients required at least one postoperative dilation. Two-layer hand-sewn anastomoses have a slightly higher rate of stricture than their one-layer counterparts.[17] A meta-analysis comparing hand-sewn and stapled anastomoses for the development of strictures found no difference between the two techniques.[16] When comparing hand-sewn anastomoses with stapled ones, a distinction must be made between EEA using a circular stapler and side-to-side anastomosis using a linear stapler. The circular EEA has consistently shown a higher rate of associated strictures. A recent meta-analysis comparing circular and linear stapled anastomoses for stricture development found that a linear stapled method decreased the incidence of developing anastomotic strictures compared to the circular stapled method (risk ratio 0.26, p=0.002).[13] In the present study, there was a limitation that the difference in the incidence of stricture according to the type of mechanical anastomosis is unknown because the EEA was performed in all operations.

In the present series, the maximal width of the midline vertical incisional scar was associated with the development of anastomotic strictures. Those patients who developed an anastomotic stricture had a maximal scar width greater than the patients in the no stricture group, and those patients with scars greater than 2 mm were 27 times more likely to have an anastomotic stricture than men with smaller scars. This suggests that some patients who develop anastomotic stricture may have a generalized, systemic tendency to develop a hypertrophic scar.

The retrospective design and small number of patients are the limitations of this study. The total number of patients with a stricture was small, which must be considered. A prospective study with a larger number of studies will be needed.

The development of anastomotic strictures in some patients may be related to the systemic hypertrophic wound-healing mechanism. The present study showed that a hypertrophic wound scar is a risk factor for anastomotic stricture. Earlier prediction of anastomotic stricture by detecting hypertrophic wound healing in patients undergoing esophagectomy may improve the patients' quality of life and surgical outcomes by enabling the management and treatment of stenosis earlier.

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