



Risk factors for benign anastomotic stricture post-oesophagectomy: single-centre analysis of 702 oesophagectomies with squamous cell carcinoma

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Background: Benign stricture formation after oesophagectomy makes a considerable impact on postoperative recovery, nutritional status and quality of life. Our aim was to investigate the incidence and risk factors for benign anastomotic stenosis post-oesophagectomy in a large series of patients.

Methods: We conducted a retrospective study of all patients undergoing oesophagectomy of oesophageal squamous cell carcinoma (ESCC) in our department from August 2012 to May 2013. Anastomotic stricture was identified clinically and radiologically. A total of 14 clinicopathological variables were assessed by univariate and multivariate logistic regression analyses.

Results: The study included 702 patients, and anastomotic stricture occurred in 62 patients (8.8%), which was significantly higher after cervical (20.8%) anastomosis than below (7.4%) or above (6.6%) aortic arch anastomosis. The anastomotic stricture rate was 31.8% in single-layer hand sewn (s-HS) anastomosis, 11.7% in circular stapled (CS) anastomosis, 10.4% in double-layer hand-sewn (d-HS) anastomosis and 1.9% in semi-mechanical (SM) anastomosis. The univariate analysis found that hypertension, surgical approach, anastomotic technique, anastomosis site, total number of removed lymph node and anastomotic leakage were associated with anastomotic stricture rate ($P < 0.05$). Age, gender, body mass index (BMI), history of smoking or diabetes, the length of tumour, pT stage, pN stage and historical grading showed no statistically significant difference in the incidence of benign stenosis ($P > 0.05$). On multivariate analysis, anastomosis site ($P = 0.006$) and anastomotic technique ($P < 0.001$) were independently associated with stricture risk.

Conclusions: Our study highlighted that patients with ESCC undergoing cervical anastomosis should be cautiously monitored postoperatively as a result of relative high stricture rate. SM technique is the preferred method of oesophago-gastric anastomosis due to a decreased stricture formation compared with other techniques.

Keywords: Oesophageal cancer; oesophagectomy; anastomotic stricture; risk factor

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Introduction

Despite the advances in staging, neoadjuvant therapy, surgical technique and perioperative care, benign stricture formation after oesophagectomy with gastric tube interposition remains a major source of deterioration of

postoperative recovery, nutritional status and quality of life (1). The subsequent need for serial oesophageal dilatations negates the merits of an operation intended to restore comfortable swallowing. The development of anastomotic stricture is multi-factorial. In addition to

patient's systemic status, important causes include ischaemia of anastomosis and local complicated healing (2). Surgical-related factors may also affect anastomotic healing (3,4). Developing a comprehensive understanding of preoperative, intraoperative and postoperative factors related to stricture formation may facilitate strategies to enhance quality of life and reduce health economic burden. However, few systematic and large series studies have addressed the issue to date.

Methods

Patient selection and data collection

Between August 2012 and May 2013, 714 patients with oesophageal squamous cell carcinoma (ESCC) underwent oesophagectomy in our department. Of these patients, 702 had oesophagectomy with oesophago-gastric anastomosis, and they constituted the study group. All patients were treated with radical resection. Post-operative water-soluble radiologic contrast swallow and endoscope verified that there was no malignant recurrence in anastomosis. This study was approved to review the data by local ethics committee and conducted according to the Declaration of Helsinki in a university hospital. Patients undergoing emergent surgery, reoperation, and jejunal or colonic interposition were excluded.

Patient age, gender, body mass index (BMI) at the time of diagnosis, history of smoking, comorbidities, tumour characteristics, surgical details, perioperative outcomes and radiological follow-up were recorded in detail and entered in our dedicated database. Outcomes included anastomotic stricture and leakage rates.

Surgical intervention

All patients were treated with radical resection. Left thoracotomy (Sweet) was performed for tumours located in the lower 2/3 of the oesophagus, as long as there was no clinical indication of superior mediastinum or neck lymph node metastasis. Right thoracoabdominal (Ivor-Lewis) and triple incision (McKeown) surgery was performed using VATS for middle and upper thoracic oesophageal cancers or when clinical indications/suspicions existed regarding superior mediastinum or neck lymph node metastasis.

The standard operation usually started with exploration and mobilisation of oesophageal lesion (5,6). Gastric conduit reconstruction consisted of creating a 4–6 cm

wide gastric tube with multiple firings of a linear stapler [Proximate Linear Cutter-TLC75, Johnson & Johnson Medical (China) Co. Ltd., Shanghai, China] along the greater curvature. Lymph node dissection along the left gastric artery, coeliac trunk, common hepatic artery and proximal splenic artery was added. After oesophagectomy and lymphadenectomy, the subsequent oesophago-gastric anastomosis was performed.

In the HS group, the anastomosis was constructed in an end-to-end fashion using intermittent 4-0 Vicryl antibacterial single- or double-layer sutures. The posterior wall was completed by inverted suture, while everted suture was used at the anterior wall. In the CS group, the anastomosis was performed by circular stapler [CDH25 or SDH25, Johnson & Johnson Medical (China) Co. Ltd., Shanghai, USA]. In the SM group, patients underwent side-to-side oesophagogastrostomy with oesophageal stump lying upon the anterior wall of stomach, positioned 3 cm below the tip of the gastric tube. Then, a linear stapler was used to extend the anastomosis orifice by cutting the posterior oesophageal wall and anterior gastric wall. The remaining openings were closed using everted interrupted 4-0 absorbable sutures. Furthermore, reinforcement was performed with 3-0 absorbable stitches between the muscular layer of the oesophagus and the seromuscular layer of the stomach.

Once the anastomosis was completed, a nasogastric tube was then inserted into the stomach. Postoperative nutrition was either total parenteral or enteral by means of a feeding tube which was placed in the duodenum. All the operations were performed by 5 senior surgeons with similar degree of experience. The type of anastomosis was up to the surgeon.

Follow-up

Patients were routinely followed up at 2 weeks after discharge, then at 3-, 6-month and yearly thereafter. The dysphagia score and oesophagogram were all evaluated. Symptoms related to stricture were often typical and were confirmed by radiography and/or endoscopy. We adopted the Stoller's dysphagia scoring system, which is a validated questionnaire to assess patients' postoperative dysphagia function: 0= able to eat a normal diet/no dysphagia; 1= able to swallow some solid foods; 2= able to swallow only semisolid foods; 3= able to swallow liquids only; 4= unable to swallow anything/total dysphagia (7). The anastomotic diameter was measured by averaging the two measurements of anastomotic orifice on crossed directions on still

Table 1 Clinicopathologic characteristics of study population (n=702)

Characteristics	No. in group (%)
Age, mean (range), years	59.0 (54.0–65.0)
Gender, N (% female)	132 (18.8)
BMI at diagnosis, mean (range)	21.3 (19.6–23.3)
Smoking, N (%)	470 (67.0)
Diabetes, N (%)	15 (2.1)
Hypertension, N (%)	90 (12.8)
Length of tumor, mean (range), cm	3.8 (3.0–5.0)
Pathologic T-stage, N (%)	
T ₀	13 (1.9)
T ₁	102 (14.5)
T ₂	122 (17.4)
T ₃	343 (48.9)
T ₄	122 (17.4)
Pathologic N-stage, N (%)	
N ₀	396 (56.4)
N ₁	172 (24.5)
N ₂	100 (14.2)
N ₃	34 (4.8)
Histological grading, N (%)	
G1	23 (3.3)
G2	296 (42.2)
G3	383 (54.6)
Surgical approaches, N (%)	
McKeown	58 (8.3)
Sweet	567 (80.8)
Ivor-Lewis	77 (11.0)
Anastomotic technique, N (%)	
Single-layer hand sewn (s-HS)	22 (3.1)
Circular stapled (CS)	163 (23.2)
Double-layer hand-sewn (d-HS)	308 (43.9)
Semi-mechanical (SM)	209 (29.8)
Anastomosis site, N (%)	
Cervical	106 (15.1)
Below aortic arch	121 (17.2)
Above aortic arch	475 (67.7)
Total number of removed lymph node, N (%)	
<16	332 (47.3)
≥16	370 (52.7)
Anastomotic leakage, N (%)	35 (5.0)
Anastomotic stricture, N (%)	62 (8.8)

images without regard to scale. Radiography did not yield information additional to that obtained from endoscopy (8). Anastomotic stricture was clinically and radiologically defined as the patients with dysphagia and the diameter of the anastomotic orifice <5 mm on oesophagogram. All tumours were staged by the 7th edition American Joint Committee for Cancer staging of oesophagus and oesophago-gastric junction (9).

Statistical analysis

The aim of this paper was to investigate the risk factors for anastomotic stricture post-oesophagectomy. It was hypothesised that patient-, tumour- and surgical-factors be potentially related with the formation of anastomotic strictures. For the univariate analysis, Student's *t*-test or Mann-Whitney *U*-test was used to analyse continuous data, such as age, BMI index, and length of tumour. Pearson's χ^2 test or Fisher's exact test was used for comparing categorical data differences between groups. For the multivariate logistic regression analysis, predictors with a *P* value of 0.05 or less in univariate analysis were entered into the final model. Two-tailed *P* value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA).

Results

A total of 702 patients were screened in this study, of whom 570 were males and 132 were females; mean age was 59 years and mean BMI was 21.3 kg/m² (Table 1). Of them, 470 patients had history of smoking, 15 recipients were diagnosed with diabetes, and 90 had hypertension before surgery. Mean duration of operation was 210±36 min (range, 135–270 min), and median blood loss was 150 mL (interquartile range, 50–600 mL). Furthermore, d-HS anastomosis was used in 308 patients, s-HS anastomosis was completed in 22 patients, CS anastomosis was conducted in 163 patients, and SM anastomosis was performed in 209 patients. Anastomotic leakage occurred in 35 patients (5.0%) in this series of 702 patients. The proportion of patients with anastomotic stenosis postoperative was 8.8% (62 patients). Patients' characteristics in this study are shown in Table 1.

On univariate analysis, our results revealed that there were no statistically significant differences for anastomotic stricture when regarding potential risk factors, such as the age, gender, BMI, length of tumour, T-stage,

Table 2 A univariate analysis of the risk factor for the development of anastomotic stricture after esophagectomy

Clinical features	Total	Without stricture	With stricture	P value
Patients	702	640	62	–
Age	59.0 (54.0–65.0)	59.0 (54.0–65.0)	58.0 (51.7–63.0)	0.177
Gender (female/male)	132/570	120/520	12/50	0.907
BMI at diagnosis	21.3 (19.6–23.3)	21.3 (19.6–23.3)	21.6 (19.5–23.5)	0.734
Smoking (no/yes)	232/470	214/426	18/44	0.481
Diabetes (no/yes)	687/15	627/13	60/2	0.545
Hypertension (no/yes)	612/90	553/87	59/3	0.049*
Length of tumor	3.8 (3.0–5.0)	3.9 (3.0–5.0)	3.7 (3.0–5.0)	0.938
T-stage (T0/T1/T2/T3/T4)	13/102/122/343/122	11/92/109/313/115	2/10/13/30/7	0.597
N-stage (N0/N1/N2/N3)	396/172/100/34	354/161/93/32	42/11/7/2	0.308
Histological grading (G1/G2/G3)	383/296/23	342/276/22	41/20/1	0.148
Surgical approach (McKeown/Sweet/Ivor-Lewis)	58/567/77	47/521/72	11/46/5	0.016*
Anastomotic technique (s-HS/CS/d-HS/SM)	22/163/308/209	15/144/276/205	7/19/32/4	0.000*
Anastomosis site (cervical/below arch/above arch)	106/121/475	84/112/444	22/9/31	0.000*
Total number of removed lymph node (≥ 16 / < 16)	332/370	294/346	38/24	0.021*
Anastomotic leakage (no/yes)	667/35	612/28	55/7	0.017*

*, $P < 0.05$. Diagnostic criteria for diabetes: A fasting plasma glucose of ≥ 7.0 mmol/L, a 2-hour plasma glucose value in a 75 g oral glucose tolerance test of ≥ 11.1 mmol/L or a glycated hemoglobin (A1C) of $\geq 6.5\%$.

N-stage, histological grading, smoking and diabetes. However, anastomotic stricture was significantly more common in patients with oesophagectomy undergoing cervical anastomosis (20.8%) than below (7.4%) or above (6.6%) aortic arch anastomosis ($P < 0.05$). However, it was significantly less common after SM anastomosis (1.9%) than after the other anastomotic techniques ($P < 0.001$), such as s-HS (31.8%), d-HS (10.4%) or CS (11.7%) anastomosis. Furthermore, anastomotic stricture occurred more often in patients with anastomotic leakage (11.3%) than in those without leakage (4.4%) ($P = 0.017$).

Furthermore, surgical approach ($P = 0.016$), and total number of removed lymph node ($P = 0.021$) were also connected with an increased rate of anastomotic stricture. As for comorbidities, anastomotic stricture occurred significantly more frequently in the patients without hypertension ($P = 0.049$) than in those with (Table 2).

On multivariate analysis, the data indicated that anastomosis site (OR 0.556, $P = 0.005$) and anastomotic technique (OR 0.502, $P = 0.000$) were independently associated with postoperative stenosis formation risk (Table 3).

In statistics, the Bonferroni correction was used to

counteract the problem of multiple comparisons, and the significance level was adjusted accordingly. The multiple comparisons analysis confirmed a significantly decreased stricture formation in SM technique compared with s-HS, d-HS and CS (1.9 vs. 31.8%, 1.9 vs. 10.4%, 1.9 vs. 11.7%; $P < 0.001$, respectively). Stricture appeared less often in the d-HS group compared to s-HS group (10.4 vs. 31.8%; $P = 0.008$). The analysis also found that cervical anastomosis was associated with increased stricture formation compared with below (20.8 vs. 7.4%; $P = 0.004$) and above arch anastomosis (20.8 vs. 6.6%; $P < 0.001$).

Discussion

ESCC accounts for approximately 80–90% of the incident oesophageal cancers each year (10), especially in China, a region of high incidence (11). Benign anastomotic stricture after oesophagectomy is a burdensome complication with associated physical and psychological challenges. However, previous reports investigating risk factors for stricture show contradictory results, and some of these studies use univariate analysis or small data sets in their assessment

Table 3 A multivariate analysis of the risk factor for the development of anastomotic stricture after esophagectomy

Risk factors and coding	Regression coefficient	Wald value	Odds ratio	95% CI	P value
Hypertension (0= no; 1= yes)	-1.065	3.027	0.345	0.104–1.144	0.082
Surgical approach (0= McKeown; 1= Sweet; 2= Ivor-Lewis)	0.039	0.024	1.040	0.639–1.691	0.876
Anastomotic technique (0= s-HS; 1=CS; 2= d-HS; 3= SM)	-0.689	14.228	0.502	0.351–0.718	0.000*
Anastomosis site (0= cervical; 1= below aortic arch; 2= above aortic arch)	-0.586	8.001	0.556	0.371–0.835	0.005*
Total number of removed lymph node (0= less than 16; 1= more than or equal to 16)	-0.309	1.165	0.734	0.418–1.287	0.280
Anastomotic leakage (0= no; 1= yes)	0.655	1.925	1.926	0.763–4.861	0.165

*, P<0.05. s-HS, single-layer hand sewn; CS, circular stapled; d-HS, double-layer hand-sewn; SM, semi-mechanical; CI, confidence interval.

(12-15). To our knowledge, the current study is the largest sample size retrospective study investigating the potential risk factors for anastomotic stricture formation.

We performed a standardised surgical procedure for oesophagectomy, including lymph node dissection, reconstruction, and proper postoperative management. Several anastomotic techniques have been used for over 5 years, with a consistent anastomotic leak rate of less than 2% over this period, thus, enabling comprehensive analysis of possible factors. Our result revealed that high stricture rate might be associated with cervical anastomosis when contrasted with thoracic anastomosis, whereas SM anastomosis could reduce stricture risk compared with HS or CS anastomosis. The incidence of benign anastomotic stricture ranges from 5% to 46% in more recent literature (12,13,16,17). Differing from previous reports, the postoperative anastomotic stricture rate was lower in our institution (12). This might be due to performing a relatively large sample size of oesophagectomies by a standardised operation procedure.

It was an unexpected finding for us that hypertension had protective effect on stenosis formation using univariate analysis but the difference was not significant on multivariate analysis. To date, only one study has reported that hypertension was a negative factor for the development of stenosis (16), and we have no clear elucidation for this. We were unable to demonstrate a significant difference in the incidence of anastomotic stricture among the three approaches. Nevertheless, Li *et al.* (18-20) found no difference in the occurrence of anastomotic complications among the several randomised or retrospective series. The choice of operative approach should be based on surgeons' preference and appropriate patient selection (21).

As more experience and data is gathered for minimally invasive oesophagectomy strategies, approaches that avoid thoracotomy are preferable (22,23), and details on quality of life and long-term survival need further follow-up. Similar to the variable of total number of removed lymph node, it was not demonstrated in our multivariate analysis. Hence, all of them are less reliably associated with anastomotic strictures. Further study may be needed to investigate possible mechanisms.

Controversies still exist with respect to the ideal anastomosis site post-oesophagectomy. A multi-centre study from England reported that intrathoracic anastomosis was associated with less benign anastomotic strictures and a lower incidence of recurrent laryngeal nerve palsy compared with cervical anastomosis (24). In the present study, the cervical stricture rate was 20.8%, consistent with reported series, and those in patients with intrathoracic sites were 7.4% after below arch anastomosis and 6.6% after above arch anastomosis, respectively. Our multivariate analysis revealed that anastomosis site was identified as an independent risk factor for development of anastomotic stricture (P=0.006). There are at least two possible explanations for this result: a higher anastomotic position may lead to low perfusion and low oxygenation of the proximal segment of conduit or a higher position may result in a greater anastomotic tension. Veeramootoo *et al.* randomised trial using laser Doppler flowmeter demonstrated associations between gastric conduit perfusion and anastomotic complication (25). However, the relatively high rate observed in the previous reports was explained by anastomotic leakage (26,27). The result of this study suggested that the patients with upper oesophageal cancer needing the level of anastomosis pulled up to the neck

should be more cautious about monitoring anastomotic stricture formation after surgery.

Another risk factor found to influence the development of anastomotic stricture was the anastomotic technique. In the previous studies, some series advocated no statistically significant association between surgical technique and stricture formation (28). Due to several prospective and retrospective studies, however, the use of SM anastomosis could significantly lower the incidence of stenosis occurrence (16,29-32). The results of this study confirm and extend previous findings that the stricture rate was remarkably reduced in patients with SM anastomosis compared with HS or CS anastomoses. Minor anastomotic leak may precede anastomotic stricture (33). The following are several possible mechanisms that elucidate the fact. One is the differences between anastomotic fashion. When it comes to HS and CS techniques, the anastomosis was performed in end-to-end mode where the anastomosis suture line crossed the gastric stapler line, thus creating a potential minor leak which could result in scar formation. In contrast, SM was carried out in a side-to-side anastomosis, safely avoiding the prior shortcomings. Another interpretation is that SM technique was performed with a triangle-shaped anastomosis, and the anastomotic orifice was more spacious than in the HS and CS techniques, resulting in a decrease in early anastomotic obstruction and long-term stenosis formation. However, the cause of this problem is not fully understood, and further study is required. In addition, our trial found that stricture was less often occurred in d-HS group compared with s-HS group ($P=0.008$). Several retrospective studies have been conducted to compare s-HS with d-HS anastomosis; however, controversies still exist regarding the best technique option (34,35). Further randomised controlled studies are needed to verify our preliminary results.

Some limitations in our study should also be acknowledged. Firstly, the essence of retrospective study resulted in the study population not being completely homogeneous. Secondly, the relationship between stenosis and leakage were unavailable in our data because the number of patients with leakage in our study was too small. Finally, follow-up time was inadequate, and long-term survival should increase continually.

Conclusions

In conclusion, the causes of anastomotic stricture formation post-oesophagectomy were presumably multifactorial.

The location of the tumour in the upper oesophagus was independently associated with benign anastomotic stricture risk. Compared with other anastomotic techniques, SM oesophagogastronomy is the preferred method for oesophago-gastric anastomosis due to a decrease in anastomotic stricture formation.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.05.06>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research was approved by the human participants committee of West China Hospital of Sichuan University (No. 2017134), and written informed consent was obtained from all patients.

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