European Journal of Cardio-Thoracic Surgery 49 (2016) 1650–1659
doi:10.1093/ejcts/ezv395 Advance Access publication 15 November 2015

ORIGINAL ARTICLE

Cite this article as: Harustiak T, Pazdro A, Snajdauf M, Stolz A, Lischke R. Anastomotic leak and stricture after hand-sewn versus linear-stapled intrathoracic oesophagogastric anastomosis: single-centre analysis of 415 oesophagectomies. Eur J Cardiothorac Surg 2016;49:1650–9.

Anastomotic leak and stricture after hand-sewn versus linear-stapled intrathoracic oesophagogastric anastomosis: single-centre analysis of 415 oesophagectomies

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Received 16 June 2015; received in revised form 21 September 2015; accepted 6 October 2015

Abstract

OBJECTIVES: There seems to be a decreased anastomotic leak rate and a late stricture formation after linear-stapled (LS) cervical oesophagogastric anastomosis compared with hand-sewn (HS) technique. The aim of our study was to compare the surgical outcomes of intrathoracic side-to-side LS and end-to-end HS anastomosis after transthoracic oesophagectomy.

METHODS: We conducted a retrospective review of all patients undergoing Ivor Lewis oesophagectomy with LS or HS anastomosis for neoplasia at our institution from 2005 to 2012. Anastomotic leak was radiologically and clinically graded as minor or major. End-points included overall and major leak rate, morbidity, mortality, length of hospital stay and endoscopically identified late anastomotic stricture. A propensity score-matched analysis was done to compensate for the differences in baseline characteristics between HS and LS groups. Multivariable analyses of the associations of anastomotic technique and other preoperative and pathological variables with anastomotic leak and stricture were performed.

RESULTS: There were 415 patients, 134 with HS and 281 with LS anastomoses. Anastomotic leak occurred in 56 patients (13.5%), significantly more after HS than LS technique (20.9 vs 10.0%; $P = 0.002$). Major leak rate was not significantly different (9.0 vs 5.7%; $P = 0.216$, respectively). Overall morbidity (54.7%), in-hospital mortality (3.9%) and length of hospital stay (median 12 days) were not affected by the anastomotic technique. A follow-up endoscopic evaluation was available in 248 patients (59.8%). An anastomotic stricture was detected in 24 patients (9.7%), significantly more after HS than LS technique (20.3 vs 6.3%; $P = 0.002$). The propensity score-matched analysis of 105 patient pairs confirmed a significantly decreased overall leak rate (11.4 vs 22.9%; $P = 0.045$) and stricture formation (7.5 vs 18.2%; $P = 0.041$) in LS technique compared with HS technique. The multivariable analyses found obesity and HS anastomotic technique associated with an increased overall leak rate, chronic hepatopathy and diabetes associated with major leak and HS technique, female sex and the absence of arterial hypertension associated with increased stricture formation.

CONCLUSIONS: Our non-randomized study showed that side-to-side LS technique is the preferred method of intrathoracic oesophagogastric anastomosis due to a decreased overall anastomotic leak rate and anastomotic stricture formation compared with HS technique.

Keywords: Intrathoracic oesophagogastric anastomosis • Hand-sewn • Linear-stapled

INTRODUCTION

Ivor Lewis oesophagectomy with intrathoracic oesophagogastric anastomosis is one of the most commonly performed operations for the treatment of oesophageal and oesophagogastric junction cancer. Uncomplicated anastomosis is a prerequisite for uneventful postoperative course after oesophagectomy. Despite the improvements in surgical technique and perioperative care, oesophageal anastomotic leakage remains an important cause of postoperative morbidity, mortality and prolonged hospital stay. Complicated healing of the anastomosis predisposes to late stricture and dysphagia with the necessity of serial anastomotic dilatation, which significantly impairs long-term quality of life [1, 2]. The causes of anastomotic leakage are multifactorial. Besides systemic causes, important factors include local ischaemia and tension at the anastomotic site [2]. It explains the well-known fact that the cervical location of anastomosis has a higher risk of leakage than the intrathoracic one [3, 4]. Another possible moment affecting the anastomotic healing is the technique of anastomotic construction. There are currently three most commonly used anastomotic techniques after oesophagectomy: hand-sewn (HS), circular-stapled and semi-mechanical linear-stapled (LS). The last one was successfully introduced for cervical anastomosis by Collard *et al.* and subsequently popularized by Orringer *et al.* [5, 6]. Unlike the round shape of lumen of HS and circular-stapled anastomoses, the wide triangulated lumen of the side-to-side LS anastomosis is believed to create a basis for better healing and less stricture formation. Several non-randomized studies reported a significant reduction of anastomotic leakage and stricture formation after LS cervical anastomosis compared with the HS technique [6–8]. There are only a few retrospective studies comparing both methods in the construction of intrathoracic anastomoses. In these studies, the use of the LS technique did not prove to decrease intrathoracic anastomotic leak rate, while stricture formation was favourably influenced [4, 9, 10]. The only randomized trial comparing intrathoracic HS, circular-stapled and LS anastomosis was focused on late stricture development and did not evaluate anastomotic leakage [11].

In this study, we compared our results of the LS and HS anastomotic techniques in a consecutive series of Ivor Lewis oesophagectomy patients.

MATERIALS AND METHODS

Between 1 January 2005 and 31 December 2012, 529 patients underwent oesophagectomy at our institution. Of these patients, 415 had Ivor Lewis oesophagectomy with intrathoracic oesophagogastric anastomosis and they constituted the study group. Institutional ethical committee approval was obtained to review the data. Consent for the study was waived.

Medical records of the patients were reviewed for age, gender, preoperative weight loss, body mass index (BMI) at the time of surgery, comorbidities, neoadjuvant therapy, histology, pathological stage, anastomotic technique, perioperative outcomes and endoscopic follow-up. End-points included anastomotic leak and stricture rates, operative morbidity and mortality. All tumours were staged by the TNM classification system of the American Joint Committee for Cancer Staging [12]. Obesity was defined as BMI greater than or equal to 30 kg/m^2. Operative mortality included all patients who died within 30 days of operation or later but during the same hospitalization or early rehospitalization (within 30 days after surgery). Operative morbidity was defined as any postoperative complication occurring during the primary hospitalization or rehospitalization (within 30 days after surgery). The integrity of the anastomosis was routinely checked by water-soluble contrast oesophagography on postoperative day 7 or earlier if clinically indicated. Anastomotic leak was defined as disruption of the anastomosis identified radiographically as an extralumination of contrast of any size from the site of intrathoracic anastomosis on routine oesophagogram or chest computed tomography (CT), clinically by altered chest tube drainage, endoscopically or during reoperation. On the basis of the radiographic finding, clinical presentation and subsequent treatment, all anastomotic leaks were classified according to the classification system proposed by the Esophagectomy Complications Consensus Group (ECCG) [13]. For the purpose of our study, we further simplified leak classification into two categories: minor leak (corresponds to Type I of ECCG classification) and major leak (corresponds to Type II and III of ECCG classification). Essentially, all radiographically contained leaks with no or minor clinical presentation and necessitating no interventional therapy were considered as minor leaks whereas all leaks with clinical signs of sepsis, irrespective of contained or uncontained appearance on oesophagography, and necessitating therapeutic intervention were classified as major leaks. Conduit necrosis requiring reoperation was also considered a major leak. As an end-point for statistical analysis, we used overall anastomotic leak (minor + major) and separately major anastomotic leak.

Stricture was defined endoscopically as a significant anastomotic narrowing requiring at least one endoscopic dilatation to relieve dysphagia.

Statistical analysis

Continuous variables were reported as means ± standard deviation (SD) or medians with range or interquartile range (IQR) and two-sample *t*-test or Mann–Whitney *U*-test were used to compare groups in univariable analysis. Categorical variables were reported as proportions and Pearson's χ^2 test was used to compare groups in univariable analysis.

Univariable analyses were performed to determine associations of clinical and pathological variables with overall anastomotic leak, major leak and stricture as end-points. Those variables with $P < 0.25$ from univariable analyses were entered into multivariable logistic regression analyses. Backward stepwise elimination (using highest *P*-value as an elimination criterion) was utilized to derive the final multivariable logistic regression models to determine an adjusted effect size of variables on outcome. The results of multivariable analyses were expressed as odds ratios (OR) with a 95% confidence interval (CI) and *P*-value. A value of $P \leq 0.05$ was considered significant. A Hosmer–Lemeshow goodness-of-fit test was used to evaluate each logistic regression model fit. A value of $P > 0.05$ confirmed good fit of the model. All tests have only been analysed by referring to cases without missing values (complete case analysis).

Propensity score matching was then used to reduce the bias caused by the differences in baseline characteristics between HS and LS groups [14]. All clinical and pathological variables were entered into the multivariable logistic regression in order to create propensity score model. Using stepwise backward elimination, 10 variables were chosen to generate propensity score for each patient: weight loss (OR, 1.012; 97.5% CI, 0.972–1.052; $P = 0.551$), hypertension (OR, 0.567; 97.5% CI, 0.331–0.960; $P = 0.036$), chronic hepatopathy (OR, 3.314; 97.5% CI, 0.771–15.719; $P = 0.113$), peptic ulcer disease (OR, 2.929; 97.5% CI, 0.949–9.279; $P = 0.062$), history of deep venous thrombosis or pulmonary embolism (OR, 0.394; 97.5% CI, 0.018–3.155; $P = 0.436$), dyslipidaemia (OR, 0.780; 97.5% CI, 0.280–2.007; $P = 0.617$), neoadjuvant therapy–chemotherapy (OR, 0.085; 97.5% CI, 0.040–0.166; $P \leq 0.001$), neoadjuvant therapy–chemoradiation (OR, 0.657; 97.5% CI, 0.327–1.313; $P = 0.235$), histological cell type—other (OR, 0.140; 97.5% CI, 0.007–0.989; $P = 0.090$), histological cell type-squamous cell cancer (OR, 0.359; 97.5% CI, 0.179–0.700; $P = 0.003$), pathological tumour stage pT 3–4 (OR, 1.827; 97.5% CI, 1.013–3.339; $P = 0.047$), pathological lymph node stage pN 1–3 (OR, 0.874; 97.5% CI, 0.495–1.533; $P = 0.638$). The Hosmer–Lemeshow test proved good fit of the model ($P = 0.612$). One-to-one matching without replacement was performed to create matched pairs of patients. Comparisons of the two groups were done using the paired Wilcoxon signed-rank test and the McNemar's test for continuous and discrete variables, respectively.

All analyses were performed using R software, version 2.14.2. (Vienna, Austria: R Foundation for Statistical Computing. 2012).

Surgical technique

All patients underwent transthoracic oesophagectomy with gastric conduit reconstruction. Operation usually started with laparotomy and mobilization of the stomach with preservation of right gastroepiploic vessels. The gastric conduit with a width of ∼4 cm was created with multiple firings of a linear stapler along the greater gastric curvature. The longitudinal staple line was routinely oversewn with running absorbable suture. No pyloric drainage procedure was performed. Lymph node dissection along the left gastric artery, coeliac trunk, common hepatic artery and proximal splenic artery was added. Thoracic phase consisted of a right thoracotomy and oesophageal mobilization along with perioesophageal fatty tissue and lower mediastinal and subcarinal lymph nodes. The level of anastomosis was at or above the level of the azygos vein arch. A HS oesophagogastric anastomosis was constructed in an end-to-end fashion using single- or double-layered running or interrupted absorbable monofilament suture (Fig. 1E and F). A stapled anastomosis was constructed similarly to the technique described previously [6, 9]. The anastomosis was performed in a side-to-side fashion with the oesophageal stump overlying the anterior wall of the stomach. Small gastrostomy was made 4 cm inferior to the tip of the conduit (Fig. 1A), full-thickness stay stitch was used to approximate posterior oesophageal wall to the anterior gastric wall. A 45-mm endoscopic linear cutting stapler with blue 3.5-mm staple load (Endo GIA II, Ethicon, Johnson & Johnson) was used to create the posterior wall of the anastomosis (Fig. 1B and C). The anterior wall of the anastomosis was constructed using an inner layer of full-thickness running absorbable suture. The outer layer of running or interrupted seromuscular absorbable suture was used to reinforce staple, as well as inner suture line (Fig. 1D). A nasogastric

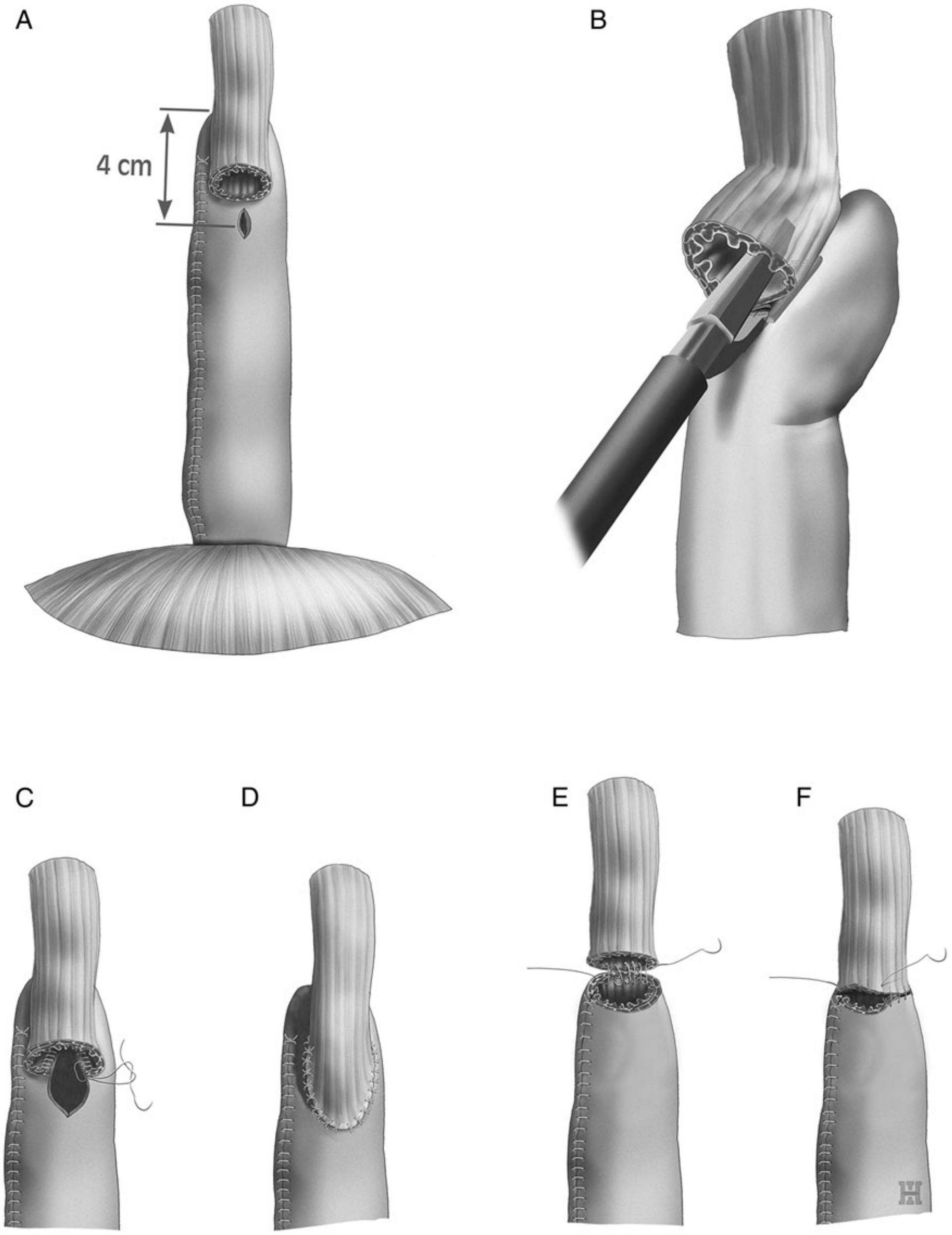

Figure 1: (**A–D**) Linear-stapled anastomosis; (**E** and **F**) hand-sewn anastomosis. Technical details are described in the text (Surgical technique).

tube was then inserted into the stomach and positioned above the pylorus. Postoperative nutrition was either total parenteral or enteral by means of a feeding jejunostomy or, more commonly, a nasojejunal feeding tube. The type and technique of the anastomosis and the way of postoperative nutrition was left to the discretion of the surgeon.

RESULTS

The study group included 415 consecutive patients (360 men and 55 women). Median age at the time of surgery was 61 years (range: 26–81 years). The indication for oesophagectomy was malignancy in 412 (99.3%) patients, Barrett's oesophagus with a high-grade dysplasia in 2 patients and a giant leiomyoma in 1 patient. A total of 232 (55.9%) patients received neoadjuvant therapy; 2 patients underwent endoscopic mucosal resection prior to surgery. HS anastomosis was performed in 134 (32.3%) patients and LS anastomosis was performed in 281 (67.7%) patients. The differences in demographics, comorbidities, preoperative therapy, postoperative histological findings and enteral nutrition between HS and LS groups are listed in Table 1. The two groups were homogenous in all variables except for hypertension, history of peptic ulcer disease, the use of preoperative therapy and the use of postoperative enteral nutrition. There were significantly more patients after neoadjuvant therapy in LS group ($P < 0.001$) almost exclusively at the expense of preoperative chemotherapy. Consequently, there was a non-significant difference in pathological

Table 1: Comparison of clinical and pathological variables between HS and LS group

Variable	HS (*n* = 134) Mean ± SD median (IQR) *n* (%)	LS (*n* = 281) Mean ± SD median (IQR) *n* (%)	*P*-value
Age (mean, years)	60.2 ± 7.2	60.5 ± 8.7	0.701
Female gender	16 (11.9)	39 (13.8)	0.586
BMI (mean, kg)	26.0 ± 4.7	26.3 ± 5.4	0.619
Obesity	22 (16.4)	62 (22.1)	0.181
Loss of weight (median, kg)	4 (0, 10)	5 (0, 10)	0.520
Comorbidities			
Diabetes	21 (15.7)	44 (15.7)	0.997
Hypertension	56 (41.8)	152 (54.1)	0.019
Coronary artery disease	16 (11.9)	36 (12.8)	0.802
History of myocardial infarction	9 (6.7)	17 (6.0)	0.793
Chronic nephropathy	3 (2.2)	6 (2.1)	0.946
COPD	16 (11.9)	45 (16.0)	0.273
Chronic hepatopathy	8 (6.1)	8 (2.8)	0.122
Brain stroke	3 (2.2)	7 (2.5)	0.876
Peripheral vascular disease	4 (3.0)	11 (3.9)	0.635
Atrial fibrillation	3 (2.2)	10 (3.6)	0.471
Peptic ulcer disease	11 (8.2)	9 (3.2)	0.026
History of malignity	9 (6.7)	14 (5.0)	0.471
History of DVT/PE	2 (1.5)	8 (2.8)	0.401
Dyslipidaemia	8 (6.0)	29 (10.3)	0.146
Neoadjuvant therapy			<0.001
No	92 (68.7)	91 (32.4)	
Chemotherapy	15 (11.2)	124 (44.1)	
Chemoradiation	27 (20.1)	66 (23.5)	
Histological cell type			0.538
Adenocarcinoma	104 (77.6)	204 (72.6)	
Squamous cell carcinoma	29 (21.6)	69 (24.6)	
Other	1 (0.7)	8 (2.8)	
pT stage			0.061
pT0–2	48 (35.8)	128 (45.6)	
pT3–4	86 (64.2)	153 (54.4)	
pN stage			0.219
pN0	58 (43.3)	139 (49.5)	
pN1–3	72 (53.7)	139 (49.5)	
pNx	4 (3.0)	3 (1.1)	
Pathological stage			0.078
0/pCR	6 (4.5)	29 (10.3)	
I	26 (19.4)	60 (21.4)	
II	31 (23.1)	76 (27.0)	
III	64 (47.8)	110 (39.1)	
IV	3 (2.2)	1 (0.4)	
Unknown	4 (3.0)	5 (1.8)	
Postoperative enteral nutrition	47 (35.1)	133 (47.3)	0.018

SD: standard deviation; IQR: interquartile range; BMI: body mass index: COPD: chronic obstructive pulmonary disease; DVT: deep venous thrombosis; PE: pulmonary embolism; pCR: pathological complete response.

stage distribution between the two groups with a smaller proportion of advanced stages in LS group.

Postoperative anastomotic evaluation by water-soluble contrast swallow or CT with oral contrast was performed in all patients. Anastomotic leak occurred in 56 (13.5%) patients, of which 22 (39.3%) had asymptomatic leak detected only radiographically, 6 (10.7%) had radiographically contained leak with minor clinical presentation and 28 (50.0%) had major leak or conduit necrosis (2 patients) causing systemic sepsis. All patients with minor leaks were managed conservatively with a delay in oral intake (usually 7 days), parenteral or enteral nutrition via nasojejunal tube or nutritive jejunostomy and selectively antibiotics. Major leaks were managed with CT-guided percutaneous drainage in 2 patients; endoscopic oesophageal stent placement was used in 18 patients and 8 patients underwent revisional surgery, which consisted of anastomotic takedown and construction of cervical oesophagostoma and gastrostoma in all cases. Eight (1.9%) patients died postoperatively due to major leaks. Table 2 shows postoperative outcomes in all patients, as well as the differences in outcomes between HS and LS groups. No significant difference between HS and LS groups was noted in time-to-leak detection, overall length of stay, length of stay of patients with leak, overall morbidity, pulmonary and cardiac morbidity, mortality, mortality due to leak and mortality of patients with documented leak. Overall anastomotic leak and minor leak significantly less often occurred in the LS group compared with the HS group (10 vs 20.9%; $P = 0.002$) and (4.3 vs 11.9%; $P = 0.004$), respectively, but major leak occurrence was not significantly different (5.7 vs 9.0%; $P = 0.216$), respectively.

Postoperative endoscopy was routinely scheduled 2–3 months after surgery or earlier in the case of dysphagia, but not all patients underwent the procedure at our institution. We performed a follow-up endoscopic evaluation in 248 (59.8%) patients and only these were analysed in terms of stricture formation. Stricture was noted and dilated in 24 (9.7%) patients in the median of 3 months (range: 1–19 months) after operation. Differences in endoscopic evaluation rates and stricture rates between HS and LS groups are listed in Table 2. A total of 28 (66.7%) of 42 patients with documented leak who survived perioperative period with preserved oesophagogastric anastomosis (not with oesophageal diversion) were endoscopically evaluated. Stricture occurred in 5 (17.9%) patients with previously documented leak compared with 19 (8.6%) of 220 endoscopically evaluated patients without leak ($P = 0.120$). No patient with major leak developed stricture compared with every third patient with minor leak.

Senior surgeon subgroup analysis

Since the operations were performed by 10 surgeons with varying degrees of experience and anastomotic technique preferences, we performed a subgroup analysis of oesophagectomies performed only by experienced senior surgeons who had both anastomotic techniques in their portfolio (at least 15% of anastomoses performed by the other technique). In this subgroup analysis, there were 298 patients operated by five senior surgeons, 74 patients with HS anastomosis and 224 patients with LS anastomosis. Similarly as in the whole patient group, the overall

Table 2: Comparison of operative outcomes between HS group and LS group (entire patient population)

	All (*n* = 415) Median (range) *n* (%)	HS (*n* = 134) Median (range) *n* (%)	LS (*n* = 281) Median (range) *n* (%)	*P*-value
Time to leak (median days)	7 (1–23)	7 (4–19)	7 (1–23)	0.171
Leak				
Overall	56 (13.5)	28 (20.9)	28 (10.0)	0.002
Minor	28 (6.7)	16 (11.9)	12 (4.3)	0.004
Major	28 (6.7)	12 (9.0)	16 (5.7)	0.216
Leak management				
Conservative	28	16	12	
Oesophageal stent placement	18	6	12	
Percutaneous drainage	2	1	1	
Reoperation	8	5	3	
Length of stay (median days)				
Overall	12 (7–115)	12 (9–74)	12 (7–115)	0.197
Patients with leak (*n* = 56)	23 (10–115)	22.5 (14–81)	23 (10–115)	0.431
Morbidity				
Overall	227 (54.7)	79 (59.0)	148 (52.7)	0.229
Pulmonary	139 (33.5)	46 (34.3)	93 (33.1)	0.804
Cardiac	64 (15.4)	19 (14.2)	45 (16.0)	0.628
Mortality				
Overall	16 (3.9)	6 (4.5)	10 (3.6)	0.649
Mortality due to leak in all patients	8 (1.9)	4 (3.0)	4 (1.4)	0.279
Mortality of patients with leak (*n* = 56)	8 (14.3)	4 (14.3)	4 (14.3)	1.000
Stricture				
Endoscopic evaluation	248 (59.8)	59 (44.0)	189 (67.3)	<0.001
Stricture	24 (9.7)[a]	12 (20.3)[a]	12 (6.3)[a]	0.002
Time to stricture (median months)	3 (1–19)	2 (1–9)	5 (1–19)	0.553

[a] Percentage from endoscopically evaluated patients.
HS: hand-sewn; LS: linear-stapled; IQR: interquartile range.

Table 3: Comparison of operative outcomes between propensity score-matched groups

	HS (*n* = 105) *n* (%) Median (IQR)	LS (*n* = 105) *n* (%) Median (IQR)	*P*-value
Leak			
Overall	24 (22.9)	12 (11.4)	0.045
Minor	13 (12.4)	3 (2.9)	0.025
Major	11 (10.5)	9 (8.6)	0.823
Morbidity			
Overall	63 (60.0)	56 (53.3)	0.391
Pulmonary	36 (34.3)	38 (36.2)	0.890
Cardiac	18 (17.1)	15 (14.3)	0.663
Mortality			
Overall	5 (4.8)	3 (2.9)	0.724
Due to leak	3 (2.9)	1 (1.0)	0.617
Length of stay	12 (11, 16)	12 (11, 15)	0.539
	HS (*n* = 44)	LS (*n* = 67)	
Stricture	8 (18.2)	5 (7.5)	0.041

HS: hand-sewn; LS: linear-stapled; IQR: interquartile range.

anastomotic leak rate was significantly reduced by LS technique (20.1% in HS vs 10.7% in LS; *P* = 0.035) while major leak rate was not different (6.8% in HS vs 7.1% in LS; *P* = 0.91). Anastomotic stricture was noted in 4 of 31 endoscopically evaluated HS patients (12.9%) and in 10 of 145 endoscopically evaluated LS patients (6.9%). As opposed to the entire patient population, the difference in the stricture rate in senior surgeon subgroup was not statistically significant (*P* = 0.262).

Propensity score-matched analysis

The propensity score matching resulted in 105 pairs of patients with similar risk profile. All clinical and pathological variables listed in Table 1 were not statistically different after matching between the HS and LS groups (data not shown). Similarly to the findings in the unmatched groups, HS patients had a higher incidence of overall leak (22.9 vs 11.4%; *P* = 0.045) and minor leak (12.4 vs 2.9%; *P* = 0.024) when compared with LS patients (Table 3). Major leak and other surgical outcomes were not significantly different between the matched groups. The follow-up endoscopic evaluation was performed in 44 HS and 67 LS patients of 105 matched pairs. The difference in the anastomotic stricture rate remained statistically significant in matched groups (18.2% in HS vs 7.5% in LS; *P* = 0.041).

Univariable and multivariable analyses

Univariable analyses of variables predicting overall leak, major leak and stricture and primary models of multivariable analyses are listed in Tables 4–6, respectively. The final models of multivariable logistic regression analyses after stepwise backward elimination for overall leak, major leak and stricture as end-points are listed in Table 7. We found two statistically significant predictors of overall leak: HS anastomosis and obesity. Major leak was significantly influenced by the presence of two comorbidities: diabetes and chronic hepatopathy, but not the anastomotic technique. The development of anastomotic stricture was significantly associated with the HS anastomotic technique, female sex and the absence of arterial hypertension.

DISCUSSION

In our study, we retrospectively evaluated factors affecting the outcome of intrathoracic oesophagogastric anastomosis after Ivor Lewis oesophagectomy with a special focus on the comparison of HS and LS anastomotic techniques. By 2005, we were using exclusively the HS technique for intrathoracic anastomoses. Since 2006, being concerned about a relatively high overall anastomotic leak rate (though predominantly minor), we have gradually adopted the LS technique based on the reports of favourable results of this technique used for cervical anastomosis [6–8]. The reason for using the particular technique was the preference of the surgeon, not the patient characteristics. During the study period, there were 10 surgeons (7 senior and 3 junior) performing oesophagectomies in our department. More conservative surgeons used the traditional HS technique and resisted for a longer time to change the anastomotic technique to the stapled one. Junior surgeons were trained almost exclusively in the stapled technique. By 2010, we were using both techniques simultaneously, but on the basis of our growing good experience with LS anastomosis, this technique has become our exclusive anastomotic technique since 2011 and all our surgeons have finally converted to the LS technique.

We routinely investigate the integrity of anastomosis on postoperative day 7 by means of water-soluble contrast swallow. We advocate the routine use of contrast radiography to assess the integrity and patency of anastomosis. In case of occult asymptomatic leak detection, we keep the patient on clear liquids and continue with enteral or parenteral nutrition for another 7 days. Oral intake of soft diet is allowed after radiological confirmation of healed or reduced contained leak (usually after 7–14 days). There is no general consensus on whether to perform routine radiographic evaluation of anastomosis after oesophagectomy. Some authors do not consider routine contrast swallow to be beneficial and investigate anastomosis only when leak is clinically suspected [15, 16].

The definition and incidence of anastomotic leak after oesophagectomy is very diverse in the literature. In a recent systematic review of studies reporting the short-term clinical outcomes after oesophagectomy, anastomotic leak was the most frequently reported complication, described in 81.6% of papers, but defined in only 26.5% of papers using 25 different definitions [17]. In many papers, it was not always clear whether only clinical leaks or also asymptomatic radiological leaks were included. This is probably one of the reasons of a very wide range of reported oesophagogastric leak rates (0–35%) and the source of problems when comparing the published results [17].

Our definition of anastomotic leak was strict and included both routine radiographic findings and clinical, endoscopic and surgical assessments. The incidence of overall leak in our group of patients (13.5%) was somewhat higher than the recently published 9.3% of leak rate of intrathoracic anastomoses from the Society of Thoracic Surgeons Database [3]. However, in this paper, the authors admitted that the asymptomatic leak rate was likely underestimated because of the lack of leak definition in the database. Half of leaks in our group were clinically minor, not requiring any interventional therapy and causing no postoperative mortality. Our major leak rate of 6.7% compares well with the recent nationwide study from

Table 4: Univariable and multivariable analyses for overall leak as an end-point

Variables	Univariable analysis*		Multivariable analysis**		
	Overall leak		OR	95% CI	*P*-value
	Yes *n* (%)	*P*-value			
Sex		0.129			
Female (*n* = 55)	11 (20.0)		1.0		
Male (*n* = 360)	45 (12.5)		0.667	0.297–1.499	0.327
Obesity		0.031			
BMI <30 kg/m^2 (*n* = 327)	37 (11.3)		1.0		
BMI ≥30 kg/m^2 (*n* = 84)	17 (20.2)		2.453	1.198–5.022	0.014
Diabetes		0.202			
Yes (*n* = 65)	12 (18.5)		1.0		
No (*n* = 350)	44 (12.6)		0.548	0.252–1.190	0.128
Hypertension		0.242			
Yes (*n* = 208)	24 (11.5)		1.0		
No (*n* = 207)	32 (15.5)		1.637	0.846–3.168	0.143
History of malignity		0.234			
Yes (*n* = 23)	5 (21.7)		1.0		
No (*n* = 392)	51 (13.0)		0.638	0.212–1.920	0.424
Neoadjuvant therapy		0.012			
No (*n* = 183)	35 (19.1)		1.786	0.821–3.883	0.143
Chemotherapy (*n* = 139)	13 (9.4)		1.0		
Chemoradiation (*n* = 93)	8 (8.6)		1.017	0.376–2.750	0.973
Surgeon		0.135			
Junior (*n* = 56)	4 (7.1)		1.0		
Senior (*n* = 359)	52 (14.5)		1.462	0.480–4.456	0.504
Anastomotic technique		0.002			
LS (*n* = 281)	28 (10.0)		1.0		
HS (*n* = 134)	28 (20.9)		2.130	1.110–4.083	0.023

HS: hand-sewn; LS: linear-stapled; IQR: interquartile range; COPD: chronic obstructive pulmonary disease; DVT: deep venous thrombosis; PE: pulmonary embolism; SD: standard deviation; BMI: body mass index: OR: odds ratio; CI: confidence interval.

*Variables with $P \geq 0.25$ in univariable analysis: age, loss of weight, coronary artery disease, history of myocardial infarction, chronic nephropathy, COPD, chronic hepatopathy, brain stroke, peripheral vascular disease, atrial fibrillation, peptic ulcer disease, history of DVT/PE, dyslipidaemia, histological cell type, pT stage, pN stage, postoperative enteral nutrition.

**Hosmer–Lemeshow goodness-of-fit test: $P = 0.322$.

Sweden where the clinical leak rate of 7.4% requiring treatment was reported [18].

Multivariable analysis in our study showed that the only independent predictors of the overall anastomotic leak were obesity and HS anastomotic technique (Table 7). The impact of obesity on anastomotic leak rate is not uniformly reported in the literature and, even in our study, it negatively influenced only the minor leak rate [19, 20]. LS anastomosis had about half the overall leak rate compared with that of the HS one, which was significantly different both in our entire patient population and in propensity score-matched groups. However, major leak was only insignificantly reduced by using linear stapler. An explanation for the fact that the LS technique reduced the incidence of minor but not major leak may be our theory that minor leak is caused mostly by a small defect in anastomosis, which is sealed off by the surrounding tissue. This small defect is likely caused by a technical imperfection such as suture stitches put too far from each other, insufficiently tightened stitches or incorrectly adapted mucosa. The probability of such an error in completely manual anastomosis is probably higher than in semi-mechanical stapled one, where only the anterior portion of anastomosis is hand-sewn. Triple-layered stapler suture of posterior wall is structurally homogeneous, more water-tight and probably less traumatic [6]. It is also possible that the large triangulated opening created with the LS technique results in decreased early anastomotic obstruction compared with the HS technique, resulting in decreased anastomotic leakage and subsequent decreased long-term stricture formation [9].

Another issue is the anastomotic fashion. In our study, HS anastomosis was done in an end-to-end fashion, where anastomotic suture line crossed gastric stapler line, thus creating a potential ‘locus minoris resistentiae’ for leak (Fig. 1E and F). In contrast, LS anastomosis was created in a side-to-side fashion, securely away from the gastric stapler line (Fig. 1A–D).

On the other hand, a major leak is usually associated with a larger anastomotic defect that is most often caused by local tissue ischaemia and necrosis as a consequence of altered blood perfusion [21]. This condition is not affected by the anastomotic technique but rather by way of gastric conduit preparation and handling and presumably by other systemic or intrinsic factors [3, 22, 23]. Multivariable analysis in our study confirmed this presumption and showed that it was not an anastomotic technique but the comorbidities such as diabetes and chronic hepatopathy which played a significant role in the development of a major leak (Table 7).

Unlike in our study, in two recent publications comparing LS and HS intrathoracic anastomoses, the leak rates after HS and LS were comparable (from 4.3 to 6.8%) [4, 10]. There may be several explanations for that difference. Firstly, there was probably a

Table 5: Univariable and multivariable analyses for major leak as an end-point

Variables	Univariable analysis*		Multivariable analysis**		
	Major leak		OR	95% CI	*P*-value
	Yes *n* (%)	*P*-value			
Sex		0.118			
Female (*n* = 55)	1 (1.8)		1.0		
Male (*n* = 360)	27 (7.5)		3.926	0.505–30.508	0.191
Obesity		0.112			
BMI <30 kg/m^2 (*n* = 327)	19 (5.8)		1.0		
BMI ≥30 kg/m^2 (*n* = 84)	9 (10.7)		1.590	0.628–4.026	0.327
Diabetes		0.052			
Yes (*n* = 65)	8 (12.3)		1.0		
No (*n* = 350)	20 (5.7)		0.485	0.186–1.263	0.138
Coronary artery disease		0.039			
Yes (*n* = 52)	7 (13.5)		1.0		
No (*n* = 363)	21 (5.8)		0.784	0.167–3.690	0.758
History of myocardial infarction		0.164			
Yes (*n* = 26)	4 (15.4)		1.0		
No (*n* = 386)	23 (6.0)		0.618	0.092–4.139	0.619
COPD		0.242			
Yes (*n* = 61)	2 (3.3)		1.0		
No (*n* = 354)	26 (7.3)		2.692	0.582–12.456	0.205
Chronic hepatopathy		0.051			
Yes (*n* = 16)	3 (18.8)		1.0		
No (*n* = 399)	25 (6.3)		0.302	0.072–1.265	0.101
History of malignity		0.215			
Yes (*n* = 23)	3 (13.0)		1.0		
No (*n* = 392)	25 (6.4)		0.437	0.113–1.699	0.232
Anastomotic technique		0.216			
LS (*n* = 281)	16 (5.7)		1.0		
HS (*n* = 134)	12 (9.0)		1.690	0.740–3.860	0.213

HS: hand-sewn; LS: linear-stapled; COPD: chronic obstructive pulmonary disease; BMI: body mass index: OR: odds ratio; CI: confidence interval.
*Variables with $P \geq 0.25$ in univariable analysis: age, loss of weight, hypertension, chronic nephropathy, brain stroke, peripheral vascular disease, atrial fibrillation, peptic ulcer disease, history of DVT/PE, dyslipidaemia, neoadjuvant therapy, histological cell type, pT stage, pN stage, surgeon (junior/senior), postoperative enteral nutrition.
**Hosmer–Lemeshow goodness-of-fit test: $P = 0.379$.

better quality of HS anastomosis in both reported studies. However, there are other issues that should be considered. In the study by Price *et al.*, only two thirds of patients had postoperative radiographic examinations and (maybe therefore) the majority of detected intrathoracic leaks were major [4]. That might reduce the effect of stapled anastomosis on the overall leak rate assuming that a predominantly minor leak is reduced by the LS technique. Blackmon *et al*. [10] in their study did not specify the severity of leak and whether the reported leak rate included clinically occult leaks. Another thing is that the HS group consisted of a relatively few patients (only 23).

Postoperative morbidity and mortality in our study were similar in LS and HS groups of the entire patient population, as well as in propensity score-matched patients. This is not surprising as there was predominantly a reduction of minor leakage which did not contribute significantly to morbidity and was not associated with any mortality. One would expect that at least the median length of hospital stay would be longer in the HS group, but it was not demonstrated in our study.

The treatment of minor leak was the same in both anastomotic techniques and consisted of conservative management. The major leak in the LS group was more often managed with oesophageal stent placement. That resulted from the fact that this method of leakage treatment was adopted later in the study period. The mortality rate of anastomotic leak was identical in both groups (14.3%) implying that the anastomotic technique did not affect the success of treatment of the leak.

Long-term outcome of anastomosis was assessed only in patients who had follow-up endoscopy at our institution, so we could achieve more homogeneous stricture evaluation. Earlier in the study period, we were more liberal and let patients have their follow-up endoscopies performed by their referring gastroenterologists. Later, though, we more insisted that the first postoperative follow-up endoscopy was performed at our institution in order to have more consistent information about the late anastomotic results. This was the reason of incomplete and unequal endoscopic evaluation rate where the LS group had a higher follow-up endoscopy rate than the HS group (Table 2). We acknowledge this is a potential source of bias as the endoscopic evaluation of patients with HS anastomosis might have been more selective and, thus, more likely performed in symptomatic patients with dysphagia which might have artificially increased the stricture rate. Nonetheless, HS anastomosis was associated with approximately three times higher stricture rate than that of the LS one in our entire patient population (Table 2). In propensity score-matched group, the difference was less marked but still statistically significant (Table 3). The significant reduction of stricture formation using LS technique is obvious in most published studies,

Table 6: Univariable and multivariable analyses for stricture as an end-point

	Univariable analysis*		Multivariable analysis**		
	Stricture Yes *n* (%)	*P*-value	OR	95% CI	*P*-value
Categorical variables					
Sex		0.006			
Female (*n* = 36)	8 (22.2)		1.0		
Male (*n* = 212)	16 (7.6)		0.600	0.184–1.953	0.396
Hypertension		0.010			
Yes (*n* = 124)	6 (4.8)		1.0		
No (*n* = 124)	18 (14.5)		3.054	1.053–8.861	0.040
Chronic nephropathy		0.047			
Yes (*n* = 6)	2 (33.3)		1.0		
No (*n* = 242)	22 (9.1)		0.203	0.025–1.673	0.138
Neoadjuvant therapy		0.010			
No (*n* = 96)	16 (16.7)		3.103	0.848–11.350	0.087
Chemotherapy (*n* = 97)	4 (4.1)		1.0		
Chemoradiation (*n* = 55)	4 (7.3)		0.800	0.139–4.588	0.801
Histological cell type		0.115			
Squamous cell carcinoma (*n* = 59)	9 (15.3)		1.0		
Adenocarcinoma (*n* = 183)	15 (8.2)		0.467	0.133–1.643	0.236
Anastomotic technique		0.002			
LS (*n* = 189)	12 (6.4)		1.0		
HS (*n* = 59)	12 (20.3)		2.642	1.001–6.977	0.050
Continuous variables	Mean ± SD	*P*-value			
Age (years)		0.176	0.977	0.925–1.032	0.413
Stricture: yes (*n* = 24)	57.7 ± 8.83				
Stricture: no (*n* = 224)	60.2 ± 7.45				

HS: hand-sewn; LS: linear-stapled; SD: standard deviation; COPD: chronic obstructive pulmonary disease; BMI: body mass index: OR: odds ratio; CI: confidence interval; DVT: deep venous thrombosis; PE: pulmonary embolism.
*Variables with $P \geq 0.25$ in univariable analysis: obesity, loss of weight, diabetes, coronary artery disease, history of myocardial infarction, COPD, chronic hepatopathy, brain stroke, peripheral vascular disease, atrial fibrillation, peptic ulcer disease, history of malignity, history of DVT/PE, dyslipidaemia, pT stage, pN stage, surgeon (junior/senior), postoperative enteral nutrition.
**Hosmer–Lemeshow goodness-of-fit test: $P = 0.431$.

including two randomized trials [4, 6, 8, 9, 10, 11, 24]. It seems clear that the wider triangular lumen of LS anastomosis reduces the risk of stricture formation and the need for subsequent dilatations [6]. Multivariable analysis in our study confirmed the LS technique as a significant factor reducing the risk of stricture formation, together with the male sex and the presence of arterial hypertension (Table 7). The protective effect of arterial hypertension on the formation of anastomotic stricture was a surprising finding for us and we have no clear explanation for it.

Anastomotic leak is considered an important predisposing factor for late stricture formation [2, 21]. However, we noted just a non-significant trend towards a higher stricture rate in patients with documented anastomotic leaks ($P = 0.12$). Similar non-significant differences in late stricture rates between leaking and non-leaking intrathoracic and cervical oesophagogastric anastomoses were reported by other authors [9, 24]. An interesting finding in our study was the observation that only minor leak was associated with the late stricture formation. Similarly, a lower incidence of stricture rate after major leak when compared with minor leak was reported by Price [4]. It seems that the use of oesophageal stents for treatment of major leaks prevented later stricture formation [25].

There are several inherent limitations creating a potential for bias in our study. Firstly, it is the retrospective nature of the study where the study groups were not completely homogeneous. We addressed this issue by propensity score matching, which enabled us to perform more robust comparison of groups than in the entire patient population. It is important to note the propensity score can only adjust for observed confounding covariates and not unobserved ones. Another limitation is the time factor. The stapled technique was mainly used in the latter half of the study period. There might be some learning curve effect not only in the LS anastomotic technique, but also in gastric conduit preparation and handling. Furthermore, operations were performed by 10 different surgeons, some of them (the younger ones) trained exclusively in the LS technique. This concern was addressed by senior surgeon subgroup analysis. Another issue is the variation in HS anastomotic technique, where running or interrupted sutures and single- or double-layered anastomosis were used. Finally, incomplete and unequal stricture evaluation weakened the validity of stricture formation analysis in our study. Well-designed randomized trial, sufficiently powered to detect difference in anastomotic leak rates between both techniques, would bring a higher level of evidence to support one technique over another. To our knowledge, however, there are no such trials for intrathoracic oesophagogastric anastomosis so far.

In conclusion, oesophagectomy with intrathoracic side-to-side LS oesophagogastric anastomosis is safe and effective. In our non-randomized study, it was associated with a lower overall and clinically minor anastomotic leak rate and decreased stricture formation compared with the traditionally used HS technique. We

Table 7: Final models of multivariable analyses for end-points: overall leak, major leak and stricture

Variables	OR	95% CI	*P*-value
Overall leak[a]			
Anastomotic technique			
HS (*n* = 134)	2.804	1.554–5.060	0.0006
LS (*n* = 281)	1.0		
Obesity			
BMI $\geq$30 kg/m^2 (*n* = 84)	2.224	1.160–4.261	0.016
BMI <30 kg/m^2 (*n* = 327)	1.0		
Major leak[b]			
Chronic hepatopathy			
Yes (*n* = 16)	4.085	1.067–15.647	0.040
No (*n* = 399)	1.0		
Diabetes			
Yes (*n* = 65)	2.692	1.109–6.531	0.029
No (*n* = 350)	1.0		
Stricture[c]			
Anastomotic technique			
HS (*n* = 59)	3.431	2.982–3.881	0.007
LS (*n* = 189)	1.0		
Sex			
Female (*n* = 36)	3.263	2.764–3.762	0.020
Male (*n* = 212)	1.0		
Hypertension			
No (*n* = 124)	3.053	2.560–3.547	0.027
Yes (*n* = 124)	1.0		

HS: hand-sewn; LS: linear-stapled; BMI: body mass index: OR: odds ratio; CI: confidence interval.
[a] Hosmer–Lemeshow goodness-of-fit test: *P* = 0.368.
[b] Hosmer–Lemeshow goodness-of-fit test: *P* = 0.769.
[c] Hosmer–Lemeshow goodness-of-fit test: *P* = 0.463.

consider the LS technique the preferred method for oesophageal anastomosis and we do not see any contraindication for using it in open Ivor Lewis oesophagectomy.

ACKNOWLEDGEMENTS

The authors thank Marian Rybar and Barbora Zemanova for the statistical analyses and Ivan Helekal for the illustrations.

Funding

This work was supported by the grant of Ministry of Health of the Czech Republic (IGA NT 12331-5).

Conflict of interest: none declared.

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