Intrathoracic *versus* cervical anastomosis and predictors of anastomotic leakage after oesophagectomy for cancer

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Background: Studies comparing the anastomotic leak rate in patients with an intrathoracic *versus* a cervical anastomosis after oesophagectomy are equivocal. The aim of this study was to compare clinical outcome after oesophagectomy in patients with an intrathoracic or cervical anastomosis, and to identify predictors of anastomotic leakage in a nationwide audit.

Methods: Between January 2011 and December 2015, all consecutive patients who underwent oesophagectomy for cancer were identified from the Dutch Upper Gastrointestinal Cancer Audit. For the comparison between an intrathoracic and cervical anastomosis, propensity score matching was used to adjust for potential confounders. Multivariable logistic regression modelling with backward stepwise selection was used to determine independent predictors of anastomotic leakage.

Results: Some 3348 patients were included. After propensity score matching, 654 patients were included in both the cervical and intrathoracic anastomosis groups. An intrathoracic anastomosis was associated with a lower leak rate than a cervical anastomosis (17·0 *versus* 21·9 per cent; $P = 0.025$). The percentage of patients with recurrent nerve paresis was also lower (0·6 *versus* 7·0 per cent; $P < 0.001$) and an intrathoracic anastomosis was associated with a shorter median hospital stay (12 *versus* 14 days; $P = 0.001$). Multivariable analysis revealed that ASA fitness grade III or higher, chronic obstructive pulmonary disease, cardiac arrhythmia, diabetes mellitus and proximal oesophageal tumours were independent predictors of anastomotic leakage.

Conclusion: An intrathoracic oesophagogastric anastomosis was associated with a lower anastomotic leak rate, lower rate of recurrent nerve paresis and a shorter hospital stay. Risk factors for anastomotic leak were co-morbidities and proximal tumours.

Introduction

Oesophageal cancer is the sixth leading cause of cancer-related mortality, and its incidence continues to increase every year[1]. According to international guidelines[2], oesophagectomy is the cornerstone of curative treatment for non-metastasized oesophageal cancer, often combined with neoadjuvant or perioperative chemo(radio)therapy. Improvement in surgical techniques, perioperative management and patient selection have resulted in a reduction in postoperative mortality after oesophagectomy[3]. However, anastomotic leakage remains relatively common, and is a major cause of morbidity and mortality. The percentage of patients with anastomotic leakage varies from 6 to 41 per cent[4−8].

Several factors are associated with an increased risk of anastomotic leakage, including patient-related characteristics[5,9,10], intraoperative factors[11−13], postoperative factors and surgical technique[14−16]. Controversy remains about the optimal anatomical location of the oesophagogastric anastomosis (intrathoracic *versus* cervical) after oesophagectomy. Several retrospective studies and one RCT reported increased leak rates in patients with a cervical anastomosis[9,17,18]. Other studies, including three RCTs[19−21], did not show a statistically significant difference in leak rates. Some surgeons accept a possible higher leak rate associated with a cervical anastomosis, because a wider oncological resection margin can be achieved. Furthermore, in patients with an anastomotic leak, the

sequela may be less severe for a cervical anastomosis than for an intrathoracic anastomosis[22]. Others advocate that an intrathoracic anastomosis is associated with a lower leak rate because the gastric tube is shorter and better vascularized[9].

The scientific evidence for an association between the location of the anastomosis and risk of anastomotic leakage, postoperative morbidity and positive oncological resection margins after oesophagectomy is equivocal. Therefore, the primary aim of this study was to assess anastomotic leakage rates, postoperative morbidity and radical resection rates after oesophageal resection with either an intrathoracic or cervical oesophagogastric anastomosis. A secondary objective was to identify predictors of anastomotic leakage.

Methods

All patient data were obtained from the Dutch Upper Gastrointestinal Cancer Audit (DUCA), a registry of all patients undergoing surgery with curative intent for oesophageal or gastric cancer in the Netherlands. The DUCA is a subdivision of the Dutch Institute for Clinical Auditing, founded in 2011, with the objective to facilitate and organize the initiation of nationwide auditing in a uniform format. The DUCA collects data to monitor national guideline adherence and to provide surgical teams with reliable information on outcome measures. Participation is mandatory for all Dutch hospitals performing oesophageal resections, and data are registered for each patient during the hospital stay and until 30 days after discharge. Detailed descriptions of definitions used in the DUCA are provided in an online registry program to stimulate uniform data registration. An independent monitoring team audits the data to evaluate completeness and concordance. The organization of the DUCA has been described in more detail previously[23].

Patients

All patients undergoing oesophagectomy for oesophageal cancer with gastric tube reconstruction between January 2011 and December 2015 were included. For the comparison between intrathoracic and cervical anastomoses, transhiatal resections were excluded because an intrathoracic anastomosis was never performed during this approach. All proximal tumours were also excluded because a cervical anastomosis is constructed in patients with a proximal tumour. To assess factors associated with anastomotic leakage, all patients were studied.

Treatment

Surgical treatment consisted of an open (both abdomen and chest), hybrid (abdomen minimally invasive and open chest) or totally minimally invasive transthoracic oesophagectomy followed by gastric tube construction with a cervical or intrathoracic anastomosis. Details of anastomotic techniques (stapled *versus* handsewn, end-to-side *versus* side-to-side) are not specified in the DUCA. Patients received neoadjuvant treatment according to national guidelines.

Outcome measures

Patient and treatment-related characteristics were extracted from the DUCA. Histopathological, surgical and short-term oncological outcomes were analysed. Surgical outcome parameters included: clinical or radiological anastomotic leakage, pulmonary complications, recurrent nerve paresis, surgical reintervention under general anaesthesia, duration of hospital stay, duration of ICU stay, mortality within 30 days after surgery and/or in-hospital death, readmissions within 30 days after discharge, positive resection margin and number of retrieved lymph nodes.

Statistical analysis

Patient and treatment-related characteristics are described as count with percentages, mean(s.d.) or median (range), as appropriate. Missing values were encountered in 217 patients for eight variables; the percentage of missing values per variable was limited (range 0·0 to 4·9 per variable). It was not possible to recover missing data because patient and hospital identity are concealed in the DUCA. Missing data were considered at random and handled using imputation with the iterative Markov chain Monte Carlo method (5 iterations)[24].

To account for the effect of possible confounders on outcomes, propensity score matching was performed for the analysis of intrathoracic *versus* cervical anastomosis. First, propensity scores (the probability, ranging from 0 to 1, that a patient was assigned to an intrathoracic or cervical anastomosis) were derived using a logistic regression model, which included all patient and treatment-related characteristics presented in *Table 1*. One-to-one propensity score matching was performed with nearest-neighbour matching without replacement, using a calliper width of 0·25 multiplied by the standard deviation of the estimated propensity score[25]. Balance in measured patient and treatment-related characteristics of the matched cohort was assessed using standardized mean differences, with differences of less than 10 per cent and close to 0 per cent taken to indicate

Table 1 Patient and treatment-related characteristics according to location of the anastomosis, before and after propensity score matching

		Before matching (n = 2086)			After matching (n = 1308)		
		Intrathoracic anastomosis (n = 928)	Cervical anastomosis (n = 1158)	SMD (%)	Intrathoracic anastomosis (n = 654)	Cervical anastomosis (n = 654)	SMD (%)
Age (years)*		64·1(9·0)	63·9(8·6)	2·7	64·1(8·9)	64·0(8·3)	2·7
Sex	M	779 (83·9)	835 (72·1)	32·2	526 (80·4)	533 (81·5)	2·9
	F	149 (16·1)	323 (27·9)		128 (19·6)	121 (18·5)	
BMI (kg/m²)*		26·2(4·2)	25·4(4·2)	21·0	26·0(4·2)	26·2(4·2)	1·2
ASA fitness grade	I	150 (16·2)	215 (18·6)	9·0	110 (16·8)	109 (16·7)	5·0
	II	571 (61·5)	726 (62·7)		423 (64·7)	408 (62·4)	
	III	207 (22·3)	212 (18·3)		121 (18·5)	134 (20·5)	
	IV	0 (0)	5 (0·4)		0 (0)	3 (0·5)	
COPD	No	807 (87·0)	1021 (88·2)	3·6	574 (87·8)	568 (86·9)	2·7
	Yes	121 (13·0)	137 (11·8)		80 (12·2)	86 (13·1)	
Coronary artery disease	No	830 (89·4)	1063 (91·8)	7·7	593 (90·7)	597 (91·3)	2·0
	Yes	98 (10·6)	95 (8·2)		61 (9·3)	57 (8·7)	
History of myocardial infarction	No	861 (92·8)	1102 (95·2)	9·2	616 (94·2)	614 (93·9)	1·2
	Yes	67 (7·2)	56 (4·8)		38 (5·8)	40 (6·1)	
History of arrhythmia	No	844 (90·9)	1072 (92·6)	5·7	598 (91·4)	598 (91·4)	0·0
	Yes	84 (9·1)	86 (7·4)		56 (8·6)	56 (8·6)	
Hypertension	No	643 (69·3)	793 (68·5)	1·8	449 (68·7)	449 (68·7)	0·0
	Yes	285 (30·7)	365 (31·5)		205 (31·3)	205 (31·3)	
Peripheral vascular disease	No	891 (96·0)	1126 (97·2)	6·3	634 (96·9)	634 (96·9)	0·0
	Yes	37 (4·0)	32 (2·8)		20 (3·1)	20 (3·1)	
Diabetes mellitus	No	780 (84·1)	1010 (87·2)	8·6	553 (84·6)	561 (85·8)	3·3
	Yes	148 (15·9)	148 (12·8)		101 (15·4)	93 (14·2)	
History of stroke	No	872 (94·0)	1102 (95·2)	5·0	618 (94·5)	615 (94·0)	1·9
	Yes	56 (6·0)	56 (4·8)		36 (5·5)	39 (6·0)	
Thromboembolic events	No	887 (95·6)	1120 (96·7)	5·5	632 (96·6)	631 (96·5)	0·7
	Yes	41 (4·4)	38 (3·3)		22 (3·4)	23 (3·5)	
Endocrine disorder	No	895 (96·4)	1113 (96·1)	1·8	630 (96·3)	628 (96·0)	1·7
	Yes	33 (3·6)	45 (3·9)		24 (3·7)	26 (4·0)	
Previous abdominal or thoracic surgery	No	657 (70·8)	822 (71·0)	0·4	470 (71·9)	475 (72·6)	1·7
	Yes	271 (29·2)	336 (29·0)		184 (28·1)	179 (27·4)	
Histology	ADC	814 (87·7)	723 (62·4)	77·0	545 (83·3)	533 (81·5)	5·6
	SCC	96 (10·3)	392 (33·9)		92 (14·1)	104 (15·9)	
	Other	18 (1·9)	43 (3·7)		17 (2·6)	17 (2·6)	
Tumour location†	Middle	42 (4·5)	319 (27·5)	110·7	42 (6·4)	47 (7·2)	3·7
	Distal	886 (95·5)	839 (72·5)		612 (93·6)	607 (92·8)	
cT category	T1	49 (5·3)	64 (5·5)	6·4	35 (5·4)	42 (6·4)	0·3
	T2	190 (20·5)	216 (18·7)		125 (19·1)	117 (17·9)	
	T3	665 (71·7)	819 (70·7)		474 (72·5)	470 (71·9)	
	T4	24 (2·6)	59 (5·1)		20 (3·1)	25 (3·8)	
cN category	N0	364 (39·2)	370 (32·0)	18·9	230 (35·2)	242 (37·0)	0·4
	N1	388 (41·8)	503 (43·4)		283 (43·3)	268 (41·0)	
	N2	156 (16·8)	238 (20·6)		125 (19·1)	117 (17·9)	
	N3	20 (2·2)	47 (4·1)		16 (2·4)	27 (4·1)	
Neoadjuvant therapy	No	79 (8·5)	95 (8·2)	0·4	50 (7·6)	54 (8·3)	1·3
	nCT	52 (5·6)	75 (6·5)		49 (7·5)	46 (7·0)	
	nCRT	797 (85·9)	988 (85·3)		555 (84·9)	554 (84·7)	
Type of surgery	Open	199 (21·4)	355 (30·7)	22·4	161 (24·6)	170 (26·0)	3·4
	MI	716 (77·2)	791 (68·3)		487 (74·5)	479 (73·2)	
	Hybrid	13 (1·4)	12 (1·0)		6 (0·9)	5 (0·8)	
Year of surgery	2015	328 (35·3)	225 (19·4)	61·7	174 (26·6)	164 (25·1)	1·9
	2014	248 (26·7)	234 (20·2)		157 (24·0)	178 (27·2)	
	2013	190 (20·5)	212 (18·3)		164 (25·1)	135 (20·6)	
	2012	108 (11·6)	279 (24·1)		105 (16·1)	125 (19·1)	
	2011	54 (5·8)	208 (18·0)		54 (8·3)	52 (8·0)	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). Patients with proximal tumours and those who underwent a transhiatal resection were excluded from the analysis. All variables presented in *Table 1* were used for propensity matching. †Middle indicates 24–32 cm from teeth, and distal more than 32 cm from teeth. SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; ADC, adenocarcinoma; SCC, squamous cell carcinoma; nCT, neoadjuvant chemotherapy; nCRT, neoadjuvant chemoradiotherapy; MI, minimally invasive.

Table 2 Outcome after oesophagectomy according to location of the anastomosis, before and after propensity score matching

	Before matching (*n* = 2086)			After matching (*n* = 1308)			*P* for interaction by type of surgery¶¶
	Intrathoracic anastomosis (*n* = 928)	Cervical anastomosis (*n* = 1158)	*P*‡‡	Intrathoracic anastomosis (*n* = 654)	Cervical anastomosis (*n* = 654)	*P*‡‡	
Anastomotic leakage†			0·230			0·025	0·523
No	756 (81·5)	919 (79·4)		543 (83·0)	511 (78·1)		
Yes	172 (18·5)	239 (20·6)		111 (17·0)	143 (21·9)		
Pulmonary complications‡			0·688			0·408	0·267
No	598 (64·4)	756 (65·3)		421 (64·4)	432 (66·1)		
Yes	330 (35·6)	402 (34·7)		233 (35·6)	222 (33·9)		
Recurrent nerve paresis§			<0·001			<0·001	0·086
No	924 (99·6)	1063 (91·8)		650 (99·4)	608 (93·0)		
Yes	4 (0·4)	95 (8·2)		4 (0·6)	46 (7·0)		
Surgical reintervention¶			0·340			0·444	0·055
No	783 (84·4)	959 (82·8)		558 (85·3)	548 (83·8)		
Yes	145 (15·6)	199 (17·2)		96 (14·7)	106 (16·2)		
Duration of hospital stay (days)*	12 (3–172)	14 (3–386)	<0·001§§	12 (3–145)	14 (4–386)	<0·001§§	0·427
Duration of ICU stay (days)*	2 (0–125)	2 (0–155)	0·024§§	2 (0–125)	2 (0–155)	0·123§§	0·493
Postoperative death#			0·749			0·458	0·061
No	889 (95·8)	1106 (95·5)		633 (96·8)	628 (96·0)		
Yes	39 (4·2)	52 (4·5)		21 (3·2)	26 (4·0)		
Readmission**			0·991				
No	794 (85·6)	991 (85·6)		556 (85·0)	547 (83·6)	0·494	0·674
Yes	134 (14·4)	167 (14·4)		98 (15·0)	107 (16·4)		
Positive resection margin††			0·497			0·618	0·780
No	877 (94·5)	1102 (95·2)		618 (94·5)	622 (95·1)		
Yes	51 (5·5)	56 (4·8)		36 (5·5)	32 (4·9)		
No. of lymph nodes harvested			0·752			0·223	0·070
<20	444 (47·8)	546 (47·2)		356 (54·4)	334 (51·1)		
≥20	484 (52·2)	612 (52·8)		298 (45·6)	320 (48·9)		

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Any clinically or radiologically proven anastomotic leakage. ‡Clinically proven pneumonia, pleural effusion leading to drainage, pleural empyema, acute respiratory distress syndrome or reintubation. §Any vocal cord dysfunction after resection. ¶Any postoperative surgical reintervention under general anesthesia. #Death during initial hospital admission or within 30 days after surgery. **Readmission to hospital within 30 days after initial discharge. ††The resection margin was evaluated using the College of American Pathologists criteria[27]. ‡‡χ^2 test, except §§Mann–Whitney *U* test. ¶¶Stratified analysis for type of surgery (open approach *versus* minimally invasive approach).

good balance[26]. To evaluate the significance of differences between the two treatment groups, the χ^2 test was used for categorical variables, and the Student's *t* test and Mann–Whitney *U* test for continuous variables with a normal and skewed distribution respectively. Logistic regression analysis was used to stratify by type of surgery (open *versus* total minimally invasive approach) in the propensity-matched cohort by adding an interaction term between surgical approach and anastomotic location for each outcome. For this analysis, hybrid procedures were added to the minimally invasive group.

The potential association between preoperative patient characteristics and anastomotic leakage was evaluated using univariable analyses in all patients (also including proximal tumours and patients who underwent a transhiatal resection). Variables with $P < 0.250$ in univariable analysis were entered into a multivariable logistic regression model with backward stepwise selection to determine

independent predictors of anastomotic leakage. Multivariable Poisson regression with log link and robust error variance of the final model was used to determine relative risk (RR) estimates with 95 per cent confidence intervals.

Statistical analyses were undertaken using SPSS® version 23.0 (IBM, Armonk, New York, USA), and R 3.1.2 open-source software with MatchIt and optmatch, sandwich, lmtest and Mice packages (http://www.R-project.org). $P < 0.050$ was considered statistically significant.

Results

Of 3348 patients selected for the study, 2086 were included in the comparison between an intrathoracic anastomosis (928) and a cervical anastomosis (1158) (*Fig. 1*). Patients were predominantly men (77·4 per cent), and the mean(s.d.) age was 64·6(9·0) years. The percentage of patients with an intrathoracic anastomosis increased during the study interval from 20·6 per cent in 2011

Table 3 Characteristics of 3348 patients with oesophageal cancer according to anastomotic leakage

		No anastomotic leakage (n = 2692)†	Anastomotic leakage (n = 656)†	P¶	Missing data‡
Age (years)*		64·4(9·1)	65·4(8·5)	0·014#	11 (0·3)
Sex	M	2087 (77·5)	519 (79·1)	0·379	1 (0·0)
	F	605 (22·5)	137 (20·9)		
BMI (kg/m²)*		25·9(4·4)	26·1(4·3)		30 (0·9)
ASA fitness grade	I	487 (18·1)	90 (13·7)	<0·001	23 (0·7)
	II	1656 (61·5)	369 (56·3)		
	III	541 (20·1)	191 (29·1)		
	IV	8 (0·3)	6 (0·9)		
COPD	No	2348 (87·2)	540 (82·3)	0·001	0 (0)
	Yes	344 (12·8)	116 (17·7)		
Coronary artery disease	No	2440 (90·6)	576 (87·8)	0·029	0 (0)
	Yes	252 (9·4)	80 (12·2)		
History of myocardial infarction	No	2522 (93·7)	597 (91·0)	0·015	0 (0)
	Yes	170 (6·3)	59 (9·0)		
History of arrhythmia	No	2490 (92·5)	582 (88·7)	0·002	0 (0)
	Yes	202 (7·5)	74 (11·3)		
Hypertension	No	1840 (68·4)	417 (63·6)	0·019	0 (0)
	Yes	852 (31·6)	239 (36·4)		
Peripheral vascular disease	No	2593 (96·3)	626 (95·4)	0·285	0 (0)
	Yes	99 (3·7)	30 (4·6)		
Diabetes mellitus	No	2302 (85·5)	524 (79·9)	<0·001	0 (0)
	Yes	390 (14·5)	132 (20·1)		
History of stroke	No	2535 (94·2)	609 (92·8)	0·201	0 (0)
	Yes	157 (5·8)	47 (7·2)		
Thromboembolic events	No	2578 (95·8)	630 (96·0)	0·756	0 (0)
	Yes	114 (4·2)	26 (4·0)		
Endocrine disorder	No	2604 (96·7)	626 (95·4)	0·104	0 (0)
	Yes	88 (3·3)	30 (4·6)		
Previous abdominal or thoracic surgery	No	1881 (69·9)	457 (69·7)	0·917	0 (0)
	Yes	811 (30·1)	199 (30·3)		
Histology	ADC	2095 (77·8)	505 (77·0)	0·849	20 (0·6)
	SCC	528 (19·6)	135 (20·6)		
	Other	69 (2·6)	16 (2·4)		
Tumour location§	Proximal	28 (1·0)	16 (2·4)	0·015	23 (0·7)
	Middle	312 (11·6)	81 (12·3)		
	Distal	2352 (87·4)	559 (85·2)		
cT category	T1	154 (5·7)	41 (6·3)	0·568	163 (4·9)
	T2	543 (20·2)	126 (19·2)		
	T3	1896 (70·4)	458 (69·8)		
	T4	99 (3·7)	31 (4·7)		
cN category	N0	986 (36·6)	234 (35·7)	0·811	116 (3·5)
	N1	1131 (42·0)	287 (43·8)		
	N2	492 (18·3)	118 (18·0)		
	N3	83 (3·1)	17 (2·6)		
Neoadjuvant therapy	No	260 (9·7)	73 (11·1)	0·062	0 (0)
	nCT	205 (7·6)	34 (5·2)		
	nCRT	2227 (82·7)	549 (83·7)		

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Data set after imputation. ‡Data missing for each variable before imputation. §Proximal indicates less than 24 cm from teeth, middle indicates 24–32 cm from teeth, and distal more than 32 cm from teeth. COPD, chronic obstructive pulmonary disease; ADC, adenocarcinoma; SCC, squamous cell carcinoma; nCT, neoadjuvant chemotherapy; nCRT, neoadjuvant chemoradiotherapy. ¶χ² test, except #Student's *t* test.

to 59·3 per cent in 2015. Patient and treatment-related characteristics according to location of the anastomosis are shown in *Table 1*. After propensity matching, 654 patients were included in both groups and all baseline variables including year of surgery were equally distributed (SMD less than 10 per cent).

Intrathoracic *versus* cervical anastomoses

Postoperative complications and pathological data are shown in *Table 2*. Anastomotic leakage was less frequent in patients who underwent an intrathoracic anastomosis than in those with a cervical anastomosis: 111 of 654 (17·0 per cent) *versus* 143 of 654 (21·9 per cent) respectively
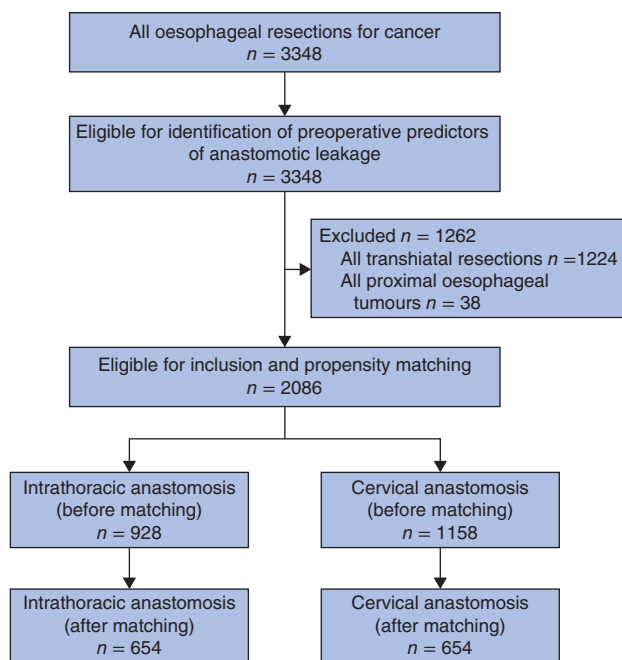
Fig. 1 Study flow chart

Table 4 Results of multivariable logistic regression analysis assessing preoperative risk of developing anastomotic leakage after oesophagectomy in 3348 patients with oesophageal cancer

	Relative risk	P
ASA fitness grade		
I	1·00 (reference)	
II	0·99 (0·77, 1·30)	0·990
III	1·31 (1·09, 1·78)	0·009
IV	1·98 (1·27, 3·64)	0·026
COPD	1·21 (1·02, 1·45)	0·031
History of arrhythmia	1·25 (1·01, 1·55)	0·044
Diabetes mellitus	1·26 (1·06, 1·49)	0·009
Tumour location		
Proximal	1·86 (1·25, 2·77)	0·022
Middle	1·07 (0·87, 1·32)	0·514
Distal	1·00 (reference)	

Values in parentheses are 95 per cent confidence intervals. COPD, chronic obstructive pulmonary disease.

($P = 0.025$). Recurrent nerve paresis occurred less often in patients with an intrathoracic anastomosis: 4 of 654 (0·6 per cent) *versus* 46 of 654 (7·0 per cent) respectively ($P < 0.001$). The median duration of hospital stay was shorter in patients with an intrathoracic anastomosis: 12 (range 3–145) *versus* 14 (4–386) days ($P < 0.001$). Surgical reinterventions, duration of ICU stay, in-hospital mortality and number of readmissions were comparable between the two groups. The associations between location of the anastomosis and outcome parameters were not statistically significant when stratified by type of surgical approach (P for interaction > 0·050) (*Table 2*).

Among patients with an anastomotic leak, there was no significant difference between the anastomosis groups in the percentage of patients who had a surgical reintervention (53·2 per cent of patients with an intrathoracic anastomosis *versus* 44·8 per cent with a cervical anastomosis; $P = 0.184$) or in-hospital mortality (8·1 *versus* 10·5 per cent respectively; $P = 0.520$). Duration of hospital stay (median 40 (range 9–132) *versus* 28 (4–132) days; $P < 0.001$) and length of ICU stay (median 8 (1–111) *versus* 4 (1–155) days; $P = 0.021$) were longer after an intrathoracic compared with a cervical anastomotic leak.

Predictors of anastomotic leakage

Some 656 of 3348 patients (19·6 per cent) had an anastomotic leak (*Table 3, Fig. 1*). The median duration of hospital

stay was 26 (range 3–200) days in patients with anastomotic leakage compared with 11 (1–386) days in patients without an anastomotic leak ($P < 0.001$). Mortality rates were 9·1 and 2·7 per cent respectively ($P = 0.001$).

Univariable analysis revealed that anastomotic leakage was associated with several patient-related factors including age, ASA fitness grade, tumour location and co-morbidities (*Table 3*). Tumour histology, TNM stage and neoadjuvant therapy did not differ between the groups with or without an anastomotic leak.

Independent predictors of the development of anastomotic leakage included: an ASA grade of III (RR 1·31, 95 per cent c.i. 1·09 to 1·78; $P = 0.009$) or IV (RR 1·98, 1·27 to 3·64; $P = 0.026$), history of chronic obstructive pulmonary disease (COPD) (RR 1·21, 1·02 to 1·45; $P = 0.031$), history of cardiac arrhythmia (RR 1·25, 1·01 to 1·55, $P = 0.044$), diabetes mellitus (RR 1·26, 1·06 to 1·49; $P = 0.009$) and tumour of the proximal oesophagus (RR 1·86, 1·25 to 2·77; $P = 0.022$) (*Table 4*).

Discussion

This nationwide multicentre cohort study compared clinical outcome in patients with an intrathoracic *versus* cervical anastomosis following oesophagectomy. An intrathoracic anastomosis was associated with lower rates of anastomotic leak and recurrent nerve paresis. This may explain the observed shorter duration of hospital stay among patients with an intrathoracic anastomosis than for those with a cervical anastomosis. However, among patients with an anastomotic leak, ICU and hospital stay was longer in the group with an intrathoracic anastomosis. Independent risk factors for anastomotic leakage include an ASA fitness

grade of III or IV, history of cardiac arrhythmia, COPD, diabetes mellitus and proximally located tumours.

Four RCTs[18−21] have investigated clinical outcome in patients with an intrathoracic or cervical anastomosis. The results of these studies are equivocal regarding which anastomotic technique is preferred in reducing the risk of anastomotic leakage. The conflicting results can be explained by these studies being underpowered, with few events (range 2–13 per study), resulting in uncertain estimates. Other methodological shortcomings are the large degree of variation in surgical approaches, definitions of anastomotic leakage, and variation in stapled and hand-sutured anastomosis. Two meta-analyses[15,28], including 298 patients, found that anastomotic leakage occurred less often after an intrathoracic anastomosis than a cervical anastomosis. The present results are in line with these analyses.

Although the anastomotic leak rate was lower in patients with an intrathoracic anastomosis, and this may appear the preferred location of the oesophagogastric anastomosis, leak rates in the present study are high compared with those in other studies[5,9]. Leak rates after an intrathoracic and cervical anastomosis range from 9 to 21 per cent[9,17,29,30] and 8 to 35 per cent[9,17,29,31] respectively. Some studies included only clinically relevant or radiologically proven anastomotic leaks, whereas others included both[32]. This discrepancy in definitions makes it difficult to compare leak rates between studies. In the present study, the definition of anastomotic leakage remained the same throughout the study, and included (subtle) clinical and radiological signs of leakage.

Between 2011 and 2016, some centres moved from a cervical to an intrathoracic anastomosis; 20·6 per cent of anastomoses were intrathoracic in 2011 and 59·3 per cent in 2015. The introduction of an intrathoracic anastomosis is associated with a learning curve[33,34]. Furthermore, the proportion of minimally invasive procedures increased from 53·1 to 85·4 per cent during the study period. The introduction of minimally invasive oesophagectomy is also associated with a learning curve when looking at reinterventions, morbidity and mortality[35,36]. Although there were no differences in year of surgery and type of surgery between the groups after propensity score matching, a potential learning curve may explain the high leak rate in the present study.

Despite a reduced risk of leakage and shorter hospital stay after an intrathoracic anastomosis, some surgeons prefer a cervical anastomosis. The possibility of a wider resection margin and less severe complications in patients with an anastomotic leak are claimed benefits of a cervical anastomosis[37]. The present study demonstrated that an anastomotic leak in a patient with an intrathoracic anastomosis led to a longer intensive care and hospital stay. This suggests that the clinical course in patients with an intrathoracic anastomotic leak is indeed more severe[38]. There were no differences in R0 resection rates, surgical reinterventions and postoperative mortality between intrathoracic and cervical anastomoses. The safety of the intrathoracic technique is supported by a recent meta-analysis[28] that found no difference in in-hospital mortality between intrathoracic and cervical anastomoses.

Previous studies[9,15,28,39] have defined factors associated with anastomotic leakage after an intrathoracic anastomosis. Factors resulting in poor tissue perfusion and vascular impairment are considered important[5,9,10,40]. This is in accordance with the present findings, as COPD, diabetes mellitus, ASA grades of III and IV, and proximal tumours were identified as independent risk factors for the development of anastomotic leakage. Although the present study did not identify risk factors other than those already described in the literature, these findings suggest that it may be important to improve the preoperative physical status of high-risk patients before oesophagectomy.

Strengths of this study include the population-based design, the adjustment for important confounders, and the relatively large sample size. Furthermore, data from the DUCA are collected prospectively, and controlled for completeness and validity by an independent monitoring team. There are also limitations to this study, including its retrospective design and lack of randomization. Although propensity score matching was performed, the inability of propensity score matching to adjust for unknown confounders (such as surgical decision-making) is a limitation. Details of anastomotic techniques that may influence the healing of the anastomosis are not recorded in the DUCA. In addition, centre- and surgeon-specific data on leak rates were not available for the purpose of this study, although these data are available for the individual centres. At present, a randomized trial[41] comparing the intrathoracic and cervical approach is under way that should resolve these limitations and make an important contribution to the current literature.

Acknowledgements

nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the DUCA at onderzoek@dica.nl.

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