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Retrospective Study

Incidence and treatment of mediastinal leakage after esophagectomy: Insights from the multicenter study on mediastinal leaks

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Abstract

BACKGROUND

Mediastinal leakage (ML) is one of the most feared complications of esophagectomy. A standard strategy for its diagnosis and treatment has been

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statement: The publication of this manuscript has been reviewed and approved by the institutional review board of the Department of Clinical and Experimental Sciences of the University of Brescia, Brescia, Italy.

Informed consent statement:

Patients were not required to provide informed consent to this study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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difficult to establish because of the great variability in their incidence and mortality rates reported in the existing series.

AIM

To assess the incidence, predictive factors, treatment, and associated mortality rate of mediastinal leakage using the standardized definition of mediastinal leaks recently proposed by the Esophagectomy Complications Consensus Group (ECCG).

METHODS

Seven Italian surgical centers (five high-volume, two low-volume) affiliated with the Italian Society for the Study of Esophageal Diseases designed and implemented a retrospective study including all esophagectomies ($n = 501$) with intrathoracic esophagogastric anastomosis performed from 2014 to 2017. Anastomotic MLs were defined according to the classification recently proposed by the ECCG.

RESULTS

Fifty-nine cases of ML were recorded, yielding an overall incidence of 11.8% (95%CI: 9.1%-14.9%). The surgical approach significantly influenced the occurrence of ML: the proportion of leakage was 10.5% and 9% after open and hybrid esophagectomy (HE), respectively, and doubled (20%) after totally minimally invasive esophagectomy (TMIE) ($P = 0.016$). No other predictive factors were found. The 30- and 90-d overall mortality rates were 1.4% and 3.2%, respectively; the 30- and 90-d leak-related mortality rates were 5.1% and 10.2%, respectively; the 90-d mortality rates for TMIE and HE were 5.9% and 1.8%, respectively. Endoscopy was the first-line treatment in 49% of ML cases, with the need for retreatment in 17.2% of cases. Surgery was needed in 44.1% of ML cases. Endoscopic treatment had the lowest mortality rate (6.9%). Removal of the gastric tube with stoma formation was necessary in 8 (13.6%) cases.

CONCLUSION

The incidence of ML after esophagectomy was high mainly in the TMIE group. However, the general and specific (leak-related) mortality rates were low. Early treatment (surgical or endoscopic) of severe leaks is mandatory to limit related mortality.

Key words: Transthoracic esophagectomy; Minimally invasive esophagectomy; Mediastinal leak; Esophagectomy complications

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Core tip: Anastomotic mediastinal leaks represent one of the most feared complications of esophageal resection. The incidence of mediastinal leaks and their associated mortality rates are reported with great variability, and a standard strategy for the diagnosis and treatment has been difficult to establish. Data on all esophagectomies performed in seven Italian centers from 2014 to 2017 were collected and analyzed. The two take-home messages of our multicenter retrospective study are as follows: (1) the surgical approach significantly influenced the rate of mediastinal leaks, with the highest leakage rate occurring after totally minimally invasive esophagectomy and lowest rate occurring after hybrid esophagectomy; and (2) early (surgical or endoscopic) treatment of mediastinal leaks is an essential tool to address this complication and prevent other major complications of esophagectomy.

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INTRODUCTION

Cancer of the esophagus is a highly malignant disease with a poor prognosis. Surgical treatment is usually indicated for localized disease. Notwithstanding recent improvements in perioperative care, esophagectomy is still a highly invasive surgical procedure, with significant morbidity rates ranging from 50% to 60%^[1-3] and 30- and 90-d mortality rates as high as 3% and 7.4%, respectively^[4].

Minimally invasive esophagectomy was introduced with the aim of improving postoperative morbidity rates^[5]. However, the application of this approach may require a modification of the technique for esophagogastric anastomosis, possibly affecting the results of esophagectomy in terms of the leakage rate^[6].

Anastomotic mediastinal leakage (ML) represents one of the most feared complications of esophageal resection. MLs are associated with a wide spectrum of complications, such as mediastinitis, sepsis, and acute respiratory distress syndrome, in addition to prolonged hospitalization and decreased quality of life. Studies have also shown that MLs are associated with a reduced life expectancy^[7,8]. The incidence, the associated mortality rates, and the treatment strategies of MLs reported in the literature vary widely^[5].

Additionally, a variety of factors have been described as correlated with this complication^[9,10]. Therefore, a standard strategy for both the diagnosis and treatment of MLs remains difficult to establish.

In this context, studies using standardized and commonly agreed upon definitions of postoperative complications and relying on large and comprehensive datasets of esophagectomies are very welcome. The aim of this retrospective study [multicenter study on mediastinal leaks (MuMeLe)] was to evaluate the incidence, predictive factors, treatments, and associated mortality rates of ML after transthoracic esophagectomy in seven Italian surgical centers (5 high-volume and 2 low-volume), which are members of the Italian Society for the Study of Esophageal Diseases (SISME) and form a representative sample of Italian centers with surgical teams having significant expertise in esophageal resection.

MATERIALS AND METHODS

Ethics

The study was approved by the Institutional Review Board of the Department of Clinical and Experimental Sciences of the University of Brescia, Italy. Informed consent for the surgical procedure was obtained from the patients after explaining to them that they were suitable candidates for transthoracic esophagectomy with intrathoracic esophagogastric anastomosis given their diagnosis. Patients were not required to provide informed consent for the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Patients and surgical procedures

A total of 501 patients (416 men and 85 women; **Table 1**) were identified by retrospective review of the prospectively maintained medical databases of the seven Italian surgical centers participating in this study. Five centers were considered high-volume centers, performing more than 20 esophagectomies per year. The global database included all patients who underwent transthoracic esophagectomy with intrathoracic esophagogastric anastomosis from 2014 to 2017. Esophago-jejunal, esophago-colic, and neck anastomoses were excluded.

Most (78.6%) patients had adenocarcinoma. Neoadjuvant treatment was administered to 62.7% of the patients. Body mass index (BMI) ranged from 15 to 35 kg/m².

Common approaches for performing transthoracic esophagectomy were laparotomy and thoracotomy (152 patients), laparoscopy and thoracotomy [hybrid esophagectomy (HE); 244 patients], and laparoscopy and thoracoscopy [totally minimally invasive esophagectomies (TMIE); 105 patients]. Minimally invasive techniques were routinely used in four surgical centers, whereas robotic surgery was a routine procedure in one center. These four centers had a large experience with the hybrid technique, whereas the number of totally minimally invasive esophagectomies should be considered to be still in the learning curve for all 7 centers. One center had the largest experience with TMIE including more than 60 cases.

Mechanical, semimechanical, and manual anastomosis was performed according to thoracic access and the surgeon's preference at each center. Most (90.3%) patients did not undergo any pyloric procedures during surgery. Nutritional jejunostomy was

Table 1 Patients' characteristics and perioperative information

	Number of patients	Patients with ML n (%)	P value
Total	501	59 (11.8)	
ASA score			0.43
1-2	266	32 (12.0)	
3-4	158	24 (15.2)	
Histology			0.96
Adenocarcinoma	385	44 (11.4)	
Squamous carcin.	101	12 (11.8)	
Other	7	2 (28.5)	
T			0.34
1-2	212	34 (16.0)	
3-4	280	34 (12.1)	
N			0.098
0	200	36 (18.0)	
+	274	31 (11.3)	
Neoadjuvant chemotherapy			0.89
Yes	314	37 (11.8)	
No	187	22 (11.8)	
Pyloric procedure			0.14
Yes	53	10 (18.9)	
No	448	49 (10.9)	
	Patients with no ML	Patients with ML	P value
Median body mass index (range)	25 (15-33.3)	27.5 (17.7-35)	0.0328
Median surgery duration (range)	360 (127-700)	330 (173-615)	0.6707

ML: Mediastinal leakage.

routinely positioned in only some surgical centers.

Standardization of the definitions of major postoperative complications is a fundamental step for delivering accurate analyses and facilitating global comparisons, which are prerequisites for proposing quality improvement strategies^[11,12]. Therefore, anastomotic leakages were defined here according to the taxonomy recently proposed by the Esophagectomy Complications Consensus Group^[13]: Full thickness GI defect involving the esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification and graded into 3 types: Type I - local defect requiring no change in therapy or treated medically or with dietary modification; Type II - localized defect requiring interventional but not surgical therapy, for example, interventional radiology drain, stent or bedside opening, and packing of incision; Type III - localized defect requiring surgical therapy.

Statistical analysis

The following variables were coded and analyzed to assess their correlation with ML development: patient ASA score and BMI, tumor histology and stage, use of neoadjuvant treatment, pyloric procedure, duration of surgery, surgical approach, and anastomotic technique.

The Mann-Whitney *U* test was used to compare continuous variables not normally distributed [presented as the median and interquartile range (IQR)]. The normality of the distribution of variables was determined using the D'Agostino-Pearson test. Chi-square or Fisher's exact tests, when appropriate, were used to compare categorical variables. Statistical analysis was performed with statistical software for biomedical research (MedCalc Software for Windows).

The statistical methods of this study were reviewed by Giuseppe Verlato, Professor of Biostatistics, Department of Diagnostics and Public Health, University of Verona, Verona, Italy.

RESULTS

The analysis of the entire set of 501 esophagectomies performed from 2014 to 2017 in seven Italian centers with expertise in esophageal resection delivered the following findings.

First, the overall incidence of ML was 11.8%, with a leakage rate varying across centers from 1.6% to 20% (Table 2). Leakage incidence did not correlate with center volume.

The median postoperative day of diagnosis of the ML was the third postoperative day (range: 1-58) (Table 3). Leaks were diagnosed as follows: 38 radiologically, 18 endoscopically, 2 clinically, and 1 surgically.

Second, the 30- and 90-d total mortality rates were 1.4% and 3.2%, respectively. Meanwhile, the 30- and 90-d leak-related mortality rates were 0.6% and 1.8%, respectively. Among the patients who developed this postoperative complication, the 30- and 90-d mortality rates were 5.1% and 10.2, respectively.

Third, the ASA score, tumor histology and stage, use of preoperative (neoadjuvant) treatment, and duration of surgery did not correlate with the occurrence of ML. BMI was significantly correlated with an increased risk of ML ($P = 0.032$) (Table 1).

Fourth, the surgical approach significantly influenced the incidence rate of ML (Table 4): the proportion of leakages was 10.5% and 9% after open Ivor Lewis esophagectomy (IL) and HE, respectively, and doubled (20%) after TMIE ($P = 0.016$). The 30-d mortality rates for TMIE and HE were 5.9% and 1.8%, respectively ($P = 0.03$). Most anastomoses in TMIE were performed with a semimechanical linear side-to-side technique, whereas only a few were performed manually.

Fifth, conservative treatment was the first-line treatment in 13.6% of ML cases (Table 5). Endoscopy was the first-line treatment in 49% of ML cases; most of these patients either had an endoscopic stent or a nasoesophageal extraluminal drain placed. Other endoscopic treatments (clips or glue) were seldom used. Surgery, as a first-line treatment, consisting of surgical debridement with or without stent placement, re-anastomosis or demontage, was performed in 37.3% of patients. Surgery was generally the preferred treatment for very early leaks when a redo anastomosis was considered the elective treatment before septic signs would appear. The presence of ischemic tissue at the anastomotic site or septic patients with non-contained leaks represented the other instances in which surgery was considered the recommended treatment and, as such, it was performed. Surgery was also performed when conservative treatment had failed.

Endoscopy had the highest rate of retreatment (17.2%) but the lowest mortality rate (6.9%). Surgery as a primary, secondary, or tertiary treatment was needed globally in 44.1% of ML cases. Removal of the gastric tube with stoma formation was considered necessary in 8 (13.6%) cases.

DISCUSSION

The MuMeLe study group, consisting of 5 high-volume and 2 low-volume surgical centers affiliated with the Italian Society for the Study of Esophageal Diseases, serves as a representative sample of the Italian surgical community with expertise in esophageal resection. Similar to a recent worldwide trend^[3,13], minimally invasive techniques were used in a significantly high percentage of the total number (349/501, 69.6%) of esophagectomies performed in these seven Italian surgical centers from 2014 to 2017.

The incidence of ML reported in the MuMeLe series (11.8%) was higher than expected (although widely varying across the seven surgical centers) and higher than rates reported in other recent western series^[7,14], which vary from 6.8% to 9.3% (the incidence of ML in the Swedish database including 559 patients undergoing surgery from 2001 to 2005 was 7.9%^[9]). The western series, however, display incidence rates of ML that are significantly higher than those in eastern series (Table 6): for example, Guo *et al*^[15] recently reported an incidence rate of ML after esophagectomy of 1.8%, significantly lower than the 6.3% reported in the latest results from the United Kingdom National Oesophago-Gastric Cancer Audit^[14].

The main novel finding from the analysis of our series is that technical aspects of esophageal resection, more specifically the use of a minimally invasive approach, seem to be one of the two predictive factors for the occurrence of ML (BMI being the other). In contrast, other factors, such as tumor histology and stage, multimodality treatment, and duration of surgery, did not seem to influence the occurrence of this postoperative surgical complication. From this perspective, the findings from our series are consistent with similar findings in the literature. More specifically, Rutegård *et al*^[8] found no statistically significant predictive factors for the occurrence of ML; however, the period examined in that series did not include minimally invasive IL

Table 2 Number of esophagectomies and leaks by center

Center	1	2	3	4	5	6	7	All
Number of esophagectomies	64	66	16	127	62	151	15	501
Number of leaks	1	3	1	10	11	30	3	59
Leak/esophagectomies (%)	1.6	4.5	6.3	7.9	17.7	19.9	20.0	11.8

Centers 1, 2, 4, 5, and 6 are high-volume centers, whereas centers 3 and 7 are low-volume centers.

(MIIL) esophagectomies. Another study found that neoadjuvant therapy did not seem to carry an inherent risk of esophageal leakage greater than the baseline risk^[16].

Other predictive factors for anastomotic leakage have been reported in the literature, such as factors involved in vascularization of the gastric tube, associated diseases (cardiovascular diseases, diabetes, renal insufficiency), active smoking, corticosteroid use^[9], center volume for esophagectomy^[17], intraoperative hypotensive episodes^[18], intraoperative blood loss, and anastomosis site (cervical *vs* thoracic). Given these findings, strategies to reduce the incidence of ML include techniques for improving the detection of gastric tube vascularization. Intraoperative tools for detecting vascular insufficiency of the gastric tube are now being used routinely in some centers; a significant advantage in reducing the rate of ML with the use of these tools has been reported in the literature^[19-22].

In our series, the main predictive factor for ML occurrence was the use of a totally minimally invasive approach. One can speculate that such approaches require the introduction of a new technique for constructing the anastomosis, thus generating a learning curve before reaching satisfactory results in terms of the rate of ML. Interestingly, in a recently published paper on the MIIL approach, the reported mean incidence of anastomotic leakage was 18.8% during the learning curve and 4.5% after the plateau had been reached^[23]. The length of the learning curve for preventing anastomotic leakage using the MIIL approach was 119 cases. The four centers performing TMIE are still in the learning curve for this type of procedure, and this factor may partly explain the higher incidence of ML with this approach.

There is still no consensus on the safest anastomotic technique in the MIIL approach; some studies argue that a semimechanical side-to-side anastomotic approach is better^[24], whereas other studies maintain that an end-to-side circular anastomosis, though technically more complex, may be safer^[25]. Robotic anastomosis may be a suitable alternative^[26]. However, data on the different techniques are scant and cannot be used for clinical evidence.

In our series (Table 3), the time of ML diagnosis (median = 3 d) was earlier than that (median = 7 d; range: 3-18) reported in other studies^[7], even if the range was definitely wider (1-58 d), with 13 leaks being diagnosed later than 10 d postoperatively. Earlier diagnosis supports the hypothesis that a technical problem during construction of the anastomosis was likely the factor associated with the occurrence of the complication (vascular insufficiency of the gastric tube is usually considered responsible for later leaks^[27]).

The 30- and 90-d mortality rates (total and leak-related) in our series can be compared to the corresponding rates reported recently in the literature (Table 7).

The early diagnosis and treatment of ML are key factors for achieving a low mortality rate^[28] because one can treat the cause of contamination and sepsis, which in turn increase the mortality rate. MLs are generally associated with a high rate of postoperative mortality, even in a series with a low incidence of ML, which reported a mortality rate of 21.2%^[15]. The overall 90-d mortality rate for all patients undergoing esophagectomy was 2.1% in Dent's series^[28], quite close to our 90-d mortality rate of 3.2%, which is lower than corresponding values reported in other series.

Even in the totally minimally invasive Ivor Lewis group in our series, in which the incidence of ML was higher than the incidence reported in other series, the ML-related mortality rate was lower than those previously reported in the literature. This means that either the leaks in our series were different (less severe) or the treatment of this complication was quite effective. This latter scenario is in line with the concept of rescuing patients from severe complications. From this perspective, other factors beyond the occurrence of a severe complication such as ML need to be considered: for example, the surgeon and hospital volume^[29], the nurse-to-patient ratio, and the multidisciplinary approach to the treatment of the complication can definitely be important in reducing the mortality rate^[30].

In our series, most patients with a leak were initially treated either conservatively or endoscopically (Table 5). Endoscopic treatment was usually limited to either

Table 3 Mediastinal leaks and mortality rates in the multicenter study on mediastinal leaks

	TEG	30-d mortality		90-d mortality		Post-op day of diagnosis ¹
		Leak <i>n</i> (%)	All <i>n</i> (%)	Leak <i>n</i> (%)	All <i>n</i> (%)	
Patients	501	3 (0.6)	7 (1.4)	9 (1.8)	16 (3.2)	
Leaks ²	59 (11.8)	3 (5.1)		6 (10.2)		3 (1-58)
Necrosis ²						
Type I	5			0		8 (4-8)
Type II	30			2 (6.7)	2 (6.7)	4 (1-28)
Type III	24	3 (12.5)		7 (29.2)	10 (41.7)	7 (4-58)
<i>P</i> value		0.038		< 0.001		

¹Median values for the postoperative day on which the mediastinal leak was diagnosed;

²Mediastinal leak was defined according to the taxonomy recently proposed by the Esophageal Complications Consensus Group^[11]. TEG: Transthoracic esophagectomy with intrathoracic anastomosis.

endoscopic stenting or nasoesophageal extraluminal drainage because Eso-SPONGE is not yet commercially available in Italy. This factor, as well as the fact that several leaks were diagnosed earlier than the typical timing reported in the literature (indicating a possible technical problem in the construction of the anastomosis), may explain the relatively high number of redo anastomoses.

The need for surgery was similar in our study and in other reported series^[15,31], even if the rate of esophageal diversion was higher in our series. Surgical intervention is recommended for septic patients with uncontained leaks or when conservative treatment has failed. Based on our experience and the insights from the analysis of our large series, it is extremely important not to delay the decision to perform surgery in patients with sepsis persisting after conservative treatment. In patients who need surgery when extensive necrosis of the tube is found and/or when the patient's general condition is critical, removal of the gastric tube by cervical esophagostomy and delayed reconstruction should be an option. The anastomosis can be reconstructed only when the gastric tube is well vascularized.

Similar to what has been reported in other studies^[16], the mortality rate was higher among patients with leaks treated surgically than among patients with leaks treated endoscopically; this is likely a selection effect because the medical conditions of patients with surgical indications are more severe and patients undergoing surgery have more severe local conditions. We acknowledge that, like other retrospective analyses of prospectively collected data, our study has limitations. In addition, the ML treatment strategies differed among the seven surgical centers, which makes it difficult to recommend a specific treatment strategy for this severe complication. However, the MuMeLe study group is a representative sample of Italian surgical centers with expertise in esophageal resection and, as such, can serve as an important benchmark for future studies. It is also noteworthy that the reported mortality rates in our series are definitely low, which means that the therapeutic choices were overall quite effective despite differing among centers.

In summary, our series shows that the incidence of ML after esophagectomy was high. ML occurred mainly in the group of patients undergoing TMIE, suggesting that technical problems during the initial phase of the learning curve are likely the main drivers behind the occurrence of ML. General and specific (leak-related) mortality rates were, however, low, demonstrating that the therapeutic choices were correct. Based on our experience and the analysis of our series, we strongly believe that the early treatment (surgical or endoscopic) of severe leaks, presenting either directly as severe or causing persistent sepsis after initial conservative treatment, is mandatory, and that there should be no hesitation before reoperation if the first attempt of conservative management fails.

Table 4 Mediastinal leakage rate by surgical technique

	Surgical technique			Total	P value
	Open IL	Hybrid IL	MIIL ¹		
Number of TEG	152	244	105	501	
Number of leaks	16	22	21	59	
Leakage rate (%)	10.5	9.0	20.0	11.8	
Necrosis - type I	1	4	0	5	
Necrosis - type II	9	10	11	30	
Necrosis - type III	6	8	10	24	
Hybrid <i>vs</i> MI					0.0072
Open <i>vs</i> MI					0.0520
Open + hybrid <i>vs</i> MI					0.0560

¹Minimally invasive Ivor Lewis (MIIL) procedure performed in 4 of the 7 surgical centers. Anastomoses in MIIL are mainly semi-mechanical (highest leaking rate compared to manual and mechanical). TEG: Transthoracic esophagectomy with intrathoracic anastomosis; MIIL: Minimally invasive Ivor Lewis; IL: Ivor Lewis; MI: Minimally invasive.

Table 5 Treatment of mediastinal leaks

	Conservative		Endoscopic		Surgical		
	NGT antibiotics	NED	ES	Other	Deb	Redo A	Dem
Primary, <i>n</i>	8 ¹	11	12	6 ²	6	10	6
Primary, %	13.6		49.2			37.3	
Retreat, <i>n</i>	1	2	1	2	2		
Retreat, %	12.5		17.2			9.1	
Secondary	1 stent	2 end stent	1 restent	1 surg+stent; 1 stent	1 redo A 1 restent		
Tertiary		1 reanast		1 reanast; 1 restent	1 dem		
Total leaks	7		26			26	
Mortality	2		2			3	2
Mortality (%)	25		6.9			22.7	

¹Eight patients: radiologically guided drainage (pleural/mediastinal collections).

²One patient transferred to another hospital. NED: Naso-esophageal extraluminal drainage. ES: Endoscopic stent; Other: Other endoscopic treatment (clip, glue); Deb: Surgical debridement with or without stent; Redo A: Redo anastomosis; Dem: Demontage.

Table 6 Mediastinal leakage and mortality rates: Multicenter study on mediastinal leaks and other studies

	Patients	Mortality rates		Leakage rates	Leak-related mortality rates	
		30-d	90-d		30-d	90-d
Price's in 2013	268		3.7 ¹	5.9		
Dent <i>et al</i> ^[28] 2016	377		0 ¹	7.2	0	
Van Daele <i>et al</i> ^[9] 2016	412			2.9		
Guo <i>et al</i> ^[15] 2014	1867			1.8	18.2	
Rutegård <i>et al</i> ^[8] 2012 ²	559		6.2	7.9		
Kassis <i>et al</i> ^[16] 2013 ³	1559		3.6	9.3		
MuMeLe study ⁴	501		3.2	11.8	5.0	15.3

¹Operative mortality rate;

²Multicenter prospective study;

³Multicenter retrospective study;

⁴Multicenter retrospective study. MuMeLe: Multicenter study on mediastinal leaks.

Table 7 Mediastinal leakage and mortality rates by minimally invasive technique: Multicenter study on mediastinal leaks and other studies

Technique	Study	Patients	Operative mortality rate	Mediastinal leakage rate
MIIL	van Workum <i>et al</i> ^[23] 2019	646	2.3	14.4
	Schmidt <i>et al</i> ^[13] 2017	49	6.1	6.1
	Zhang's in 2017	15		0.0
	Mungo <i>et al</i> ^[25] 2016	52	3.8	14.0
	MuMeLe study	105	5.9	20.0
Hybrid	Woodard's in 2017	143	2.5	2.5
	MuMeLe study	244	1.8	9.0

MIIL: Minimally invasive Ivor Lewis; Hybrid: Hybrid Ivor Lewis; MuMeLe: Multicenter study on mediastinal leaks.

ARTICLE HIGHLIGHTS

Research background

Cancer of the esophagus is a highly malignant disease with a poor prognosis. Esophagectomy is still a highly invasive surgical procedure, with significant morbidity rates and mortality rates. Minimally invasive esophagectomy was introduced with the aim of improving postoperative morbidity rates, yet possibly affecting the leakage rate. In fact, anastomotic mediastinal leakage (ML) represents one of the most feared complications of esophageal resection, being associated with mediastinitis, sepsis, acute respiratory distress syndrome, prolonged hospitalization, decreased quality of life, and reduced life expectancy.

Research motivation

A standard strategy for both the diagnosis and treatment of MLs remains difficult to establish because the incidence, the underlying risk factors, the associated mortality rates, and the treatment strategies of MLs reported in the literature vary widely. This heterogeneity in the reported findings is partly explained by the fact that different series and studies use different definitions of ML, which make it difficult to compare their findings, and, hence, to derive clear indications regarding the best strategy for the diagnosis and treatment of MLs.

Research objectives

The aim of our retrospective study was to evaluate the incidence, predictive factors, treatments, and associated mortality rates of ML after transthoracic esophagectomy using a standardized and commonly agreed upon definition of ML recently proposed by the Esophagectomy Complications Consensus Group (ECCG) and relying on a large, multicenter and comprehensive dataset of esophagectomies.

Research methods

The data include all transthoracic esophagectomies intrathoracic esophagogastric anastomosis performed from 2014 to 2017 in seven Italian surgical centers (5 high-volume and 2 low-volume), which form a representative sample of Italian centers with surgical teams having significant expertise in esophageal resection. A total of 501 patients were identified by retrospective review of the prospectively maintained medical databases. MLs, patient ASA score and body mass index (BMI), tumor histology and stage, use of neoadjuvant treatment, pyloric procedure, duration of surgery, surgical approach, and anastomotic technique were coded. The Mann-Whitney *U* test was used to compare continuous variables not normally distributed [presented as the median and interquartile range (IQR)]. The normality of the distribution of variables was determined using the D'Agostino-Pearson test. Chi-square or Fisher's exact tests, when appropriate, were used to compare categorical variables.

Research results

The overall incidence of ML was 11.8%, with a leakage rate varying across centers from 1.6% to 20%. Leakage incidence did not correlate with center volume. The 30- and 90-d total mortality rates were 1.4% and 3.2%. Meanwhile, the 30- and 90-d leak-related mortality rates were 0.6% and 1.8%. The ASA score, tumor histology and stage, use of preoperative (neoadjuvant) treatment, and duration of surgery did not correlate with the occurrence of ML. BMI was significantly correlated with an increased risk of ML ($P = 0.032$). The surgical approach significantly influenced the incidence rate of ML: the proportion of leakages was 10.5% and 9% after open Ivor Lewis esophagectomy and hybrid esophagectomy, respectively, and doubled (20%) after total minimally invasive esophagectomy ($P = 0.016$). Conservative treatment was the first-line treatment in 13.6% of ML cases. Endoscopy was the first-line treatment in 49% of ML cases. Surgery, as a first-line treatment, consisting of surgical debridement with or without stent placement, re-anastomosis or demontage, was performed in 37.3% of patients. Endoscopy had the highest rate of retreatment (17.2%) but the lowest mortality rate (6.9%).

Research conclusions

The main novel finding from the analysis of our series is that technical aspects of esophageal resection, more specifically the use of a minimally invasive approach, seem to be one of the two predictive factors for the occurrence of ML (BMI being the other). In contrast, other factors, such as tumor histology and stage, multimodality treatment, and duration of surgery, did not seem to influence the occurrence of this postoperative surgical complication.

Research perspectives

Our series shows that ML occurred mainly in the group of patients undergoing totally minimally invasive esophagectomy, suggesting that technical problems during the initial phase of the learning curve are likely the main drivers behind the occurrence of ML. The take-home message of our study is that early treatment of severe leaks, presenting either directly as severe or causing persistent sepsis after initial conservative treatment, is mandatory, and that there should be no hesitation before reoperation if the first attempt of conservative management fails. Further studies using large and comprehensive datasets from other countries yet relying on the same standardized definition of ML recently proposed through international consensus by the ECCG will enable to compare different series in a meaningful way. This in turn will significantly improve the understanding of the risk factors, incidence and treatment strategies for mediastinal leaks after esophageal resection.

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