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Risk factors for esophago-jejunal anastomosis leakage after total gastrectomy for cancer. A multicenter retrospective study of the Italian research group for gastric cancer

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ABSTRACT

Background: Many Eastern reports attempted to identify predictive variables for esophago-jejunal anastomosis leakage (EJAL) after total gastrectomy for cancer. There are no definitive answers about reliable risk factors for EJAL. This retrospective study shows the largest Western series focused on this topic.

Methods: This is a multicenter retrospective study analyzing patients' datasets collected by 18 Italian referral Centres of the Italian Research Group for Gastric Cancer (GIRCG) from 2000 to 2018. The inclusion criteria were pathological diagnosis of gastric and esophageal (Siewert III) carcinoma requiring total gastrectomy. The primary end point of risk analysis was the occurrence of EJAL; secondary end points were post-operative (30-day) morbidity and mortality, length of stay (LoS), and survival.

Results: Data of 1750 patients submitted to total gastrectomy were collected. EJAL developed in 116 (6.6%) patients and represented the 26.3% of all the 441 observed post-operative surgical complications. EJAL diagnosis was followed by a reoperation in 39 (33.6%) patients and by an endoscopic/radiological procedure in 30 cases (25.9%). In 47 patients (40.5%) EJAL was managed with conservative approach. Post-operative LoS and mortality were significantly higher after EJAL occurrence (27 days versus 12 days and 8.6% versus 1.6%, respectively). At risk analysis, comorbidities (particularly, if respiratory), minimally invasive surgery, extended lymphadenectomy, and anastomotic technique resulted significant predictive factors for EJAL. EJAL did not significantly affect survival.

Conclusions: These results were consistent with Asian experiences: the frequency of EJAL and its higher rate observed in patients with comorbidities or after minimally invasive approach were confirmed.

Introduction

Surgery is the mainstay for the curative treatment of gastric cancer and total gastrectomy with D2 lymphadenectomy represents the standard of care for tumors of the esophagogastric junction-Siewert type III and of the upper third of the stomach [1].

Despite constant improvements in perioperative management and care in gastric surgery, some post-operative complications still seem unavoidable. Post-operative morbidity increases hospital stay with a significant delay of any effective adjuvant therapy and, potentially, with negative prognostic impact [2].

Among surgical complications after total gastrectomy, esophago-jejunal anastomosis leakage (EJAL) is a well-known determinant factor for severe morbidity and mortality [3,4].

EJAL can be directly suspected by clinical presentation (fever, abdominal pain, signs of sepsis) and confirmed by a radiological examination with oral contrast, or, indirectly, by detection of salivary fluid or (orally administered) vital dye in abdominal drain output, or by CT scan imaging showing any fluid-air collection near the anastomosis [5].

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Literature data report reduction of EJAL incidence after introduction of stapling devices and after appropriate surgical learning curve [6]. At the moment, minimally invasive surgery certainly did not show to decrease the risk of EJAL [7]. However, the absolute prevention of anastomotic leakage remains a real challenge after total gastrectomy. According to the most recent studies EJAL incidence is reported as ranging between 1.7 and 15% (average incidence 4.4%) [4,5,8,9] with a related post-operative mortality up to 30% [10,11]. At the moment no clear and definitive specific risk factors for EJAL have been reported in Literature.

The aim of this study is to analyze the potential determinants of EJAL and its survival impact in a large nationwide multicenter series of patients collected in the Italian Research Group for Gastric Cancer (GIRCG) network.

Methods

This is a multicenter retrospective study analyzing patients' datasets provided by 18 Italian referral Centres of the Italian Research Group for Gastric Cancer (GIRCG), coordinated by the Surgical Oncology and Digestive Surgery Unit of the Department of Oncology of San Luigi University Hospital (Orbassano, Turin, Italy).

Data and outcomes of all the patients who underwent total gastrectomy from 2000 to 2018 were considered.

The inclusion criteria were pathological diagnosis of gastric and esophageal (Siewert III) carcinoma requiring total gastrectomy, age between 18 and 85 years, ASA I-III score, and surgery with curative intent.

EJAL occurrence was defined according to criteria established by a recent international consensus [12].

The primary end point was the occurrence of EJAL; secondary end points were post-operative (30-day) morbidity and mortality, post-operative length of stay (LoS), and, for survival analysis, death during follow-up.

Complications were classified according to the Clavien-Dindo score [13].

Risk analysis considers several potential factors which have been evaluated in the meta-analyses published in the last 10 years [7,9–11,14,15]. All data were analyzed anonymously; all patients signed an informed consent for total gastrectomy with particular specifications about EJAL occurrence. The study protocol was approved by the local ethics committee of each participating center. No preregistration exists for the reported studies reported in this article.

Statistical analysis

Continuous variables are reported as median and range, whereas categorical variables are reported as frequencies and percentages. Normality distribution has been tested by the Shapiro-Wilk normality test.

Univariate analysis of the differences between the two subgroups (EJAL 0 versus EJAL 1) was performed with the chi-square test for categorical data (with Fisher correction when needed) and with the non-parametric Mann-Whitney test for continuous variables.

In order to identify potential predictors of end points, a multivariate analysis using logistic regression models was then performed. The covariates included in the final model were those with a univariate p-value < 0.05. Results are expressed as Odds Ratio (OR) with 95% Confidence Intervals (95% CI).

Survival was defined with the number of months elapsed from discharge date to the death or last follow-up date. Overall survival was analyzed by the Kaplan-Meier analysis.

For all the used test, statistical significance level was set at the conventional $p \leq 0.05$.

The results were analyzed using the StataSE 15 statistical software (Stata Corp., College Station, TX).

Table 1
Surgical complications according to Clavien-Dindo classification12. In case of synchronous complications, only most severe event was considered.

Complication	Clavien-Dindo score							# (%)
	1	2	3a	3b	4a	4b	5	441
Bleeding	13	81	12	12	1	1	3	123 (27.8)
EJAL	**10**	**34**	**27**	**30**	**4**	**1**	**10**	**116 (26.3)**
Fluid collection	8	32	16	6	0	0	5	67 (15.2)
Ileus	12	10	3	4	0	0	2	31 (7.0)
Pancreatic fistula	4	18	4	1	0	0	2	29 (6.6)
Wound dehiscence	10	6	3	2	1	0	0	22 (5.0)
Duodenal fistula	4	2	4	4	1	0	2	17 (3.8)
Other	14	10	9	3	0	0	0	36 (8.1)

Results

Data of 1750 patients submitted to total gastrectomy accordingly with inclusion criteria were collected (for a median of 97 patients per center). For most patients (1 074, 61.3%) all the considered data were available. EJAL developed in 116 (6.6%) patients and represented the 15.8% of all the 736 observed post-operative complications. Surgical-related complications rate was 25.2% (441 patients) (Table 1).

EJAL diagnosis was obtained in 42 cases by CT scan, in 40 cases by upper gastrointestinal contrast swallow, and in 5 cases through oral administration of methylene blue. In 29 patients, diagnosis was obtained by multiple modalities, including endoscopy. EJAL was detected in median on 7th post-operative (5th-10th).

EJAL diagnosis was followed by a reoperation in 39 (39/116, 33.6%) patients and by an endoscopic/radiological procedure in 30 cases (25.9%). In 47 patients (40.5%) EJAL was managed with conservative approach, including antibiotics, fasting, total parenteral nutrition or enteral feeding (through the jejunostomy performed during gastrectomy). Post-operative LoS was significantly longer after EJAL occurrence (27 days versus 12 days, $p < 0.001$). Similarly, post-operative mortality was 8.6% (10 patients) in EJAL group compared with 1.6% (26 patients) in patients without EJAL ($p = 0.01$).

The results of the univariate and multivariate analysis of risk factors for EJAL are summarized in Table 2.

After a median follow-up of 61 months, 5-year overall survival (OS) rate was 66.9% (SE 0.020). EJAL did not significantly affect 5-year patients' survival (67.2%, SE 0.085 versus 66.4%, SE 0.020; $p = 0.929$; Fig. 1).

Discussion

Treatment of Siewert III or upper-third gastric cancer includes total gastrectomy with free resection margins together with extended lymphadenectomy (D2), producing a relevant surgical trauma and a consequent risks of post-operative complications [3,16]. Nowadays, improvements in surgical technique and perioperative management generally decreased overall morbidity, but esophago-jejunal anastomotic leakage (EJAL) still represents one of the most serious and life-threatening occurrence.

It could be clinically outstanding to define specific risk factors for EJAL, particularly in this surgical era with a large proportion of frail patients due to advanced age and/or comorbidities. Many reports (mostly from Eastern world) attempted to identify and classify predictive variables for EJAL after total gastrectomy and a lot of potential risk factors have been suggested [16]. This study shows

Table 2
Univariate and multivariate analysis of risk factors for EJAL occurrence.

Variables	EJAL		Univariate analysis (p value)	Multivariate analysis	
	Yes (116) # (%) or median (range)	No (1634) # (%) or median (range)		OR	p value
Gender			0.124		
M (1185)	86 (7.3)	1099 (92.7)			
F (565)	30 (5.3)	535 (94.7)			
Age	67 (40–85)	70 (18–84)	0.135		
BMI	24.4 (15.6–40.2)	24.1 (14.7–60.3)	0.405		
Smoke [a]			0.002	2.20 reference	0.192
Smoker or ex smoker (333)	40 (12.0)	293 (88.0)			
Non smoker (795)	47 (5.9)	748 (94.1)			
Respiratory disease			0.010	2.27 reference	0.048
Yes (201)	22 (10.9)	179 (89.1)			
No (1549)	94 (6.1)	1455 (93.9)			
Heart disease			0.041	1.49 reference	0.309
Yes (324)	31 (9.6)	293 (90.4)			
No (1426)	85 (6.0)	1341 (94.0)			
ASA score [a]			0.815		
I-II (674)	54 (8.1)	620 (91.9)			
III-IV (400)	36 (9.0)	364 (91.0)			
Preoperative serum albumin (g/dl)	3.8 (3.4–4.2)	3.7 (3.3–4.1)	0.107		
Surgical approach			0.003	reference 1.03	0.967
Open (1664)	103 (6.2)	1561 (93.8)			
Minimally invasive (86)	13 (15.1)	73 (84.9)			
Laparoscopic (73)	*11(15.1)*	*62 (84.9)*			
Robotic (13)	*2 (15.4)*	*11 (84.6)*			
Tumor stage [a]			0.001	reference −0.51	0.997
I-II (725)	52 (7.2)	673 (92.8)			
III-IV (981)	62 (6.3)	919 (93.7)			
Neoadjuvant therapy			0.148		
Yes (394)	23 (5.8)	371 (94.2)			
No (1356)	93 (6.9)	1263 (93.1)			
Chemotherapy (374)	*20 (5.3)*	*354 (94.7)*			
Radiotherapy (20)	*3 (15.0)*	*17 (85.0)*			
Operation time (min)	290 (230–330)	275 (220–324)	0.076		
Lymphadenectomy [a]			0.014	reference 18.43	0.997
D1 (324)	11 (3.4)	313 (96.6)			
D2 or more (1398)	103 (7.4)	1295 (92.6)			
Anastomotic technique [a]			<0.001	1.76 reference	0.221
Partially mechanical (312)	42 (13.5)	270 (86.5)			
Totally mechanical (1142)	72 (6.3)	1070 (93.7)			
End-to-side (1195)	89 (7.4)	1106 (92.6)	0.335		
Side-to-side (44)	5 (11.4)	39 (88.6)			
Combined resection			0.064		
Yes (919)	64 (7.0)	855 (93.0)			
No (831)	52 (6.3)	779 (93.7)			
Residual tumor [a]			0.297		
R0 (1461)	105 (7.2)	1356 (92.8)			
R1 (108)	4 (3.7)	104 (96.3)			

[a] Some data are missing.

the largest Western series focused on this topic.

Its analysis considered 1750 patients with gastric cancer who underwent total gastrectomy in 18 Italian referral Centres of the Italian Research Group for Gastric Cancer (GIRCG) network. In the present population the EJAL rate (6.6%) was consistent with Literature data, particularly with Asian reports [4,5,8,9]. In fact, as supposed by Makuuchi et al. in a recent review, EJAL incidence (and mortality) tended to be lower in Asian countries than in Western ones [17]. Contrarily, these results demonstrate that the trend is discontinuing. Moreover, although EJAL represented the second surgical complication in this series (Table 1) and its negative effects on post-operative outcome were confirmed, its management in Italian referral centres for gastric cancer surgery resulted in keeping mortality rate much lower than 10%. However, with this specific regard, it is noteworthy that in almost two third of cases (69/116, 59.5%, Table 1) EJAL required an interventional approach, necessitating multidisciplinary competences and facilities.

Considering risk factors analysis of this study, the main role seems to be played by patient-related variables, as cardiologic and, particularly, respiratory conditions, probably strictly related to patients' smoking status (Table 2). This result is not so original. Actually, pulmonary problems (common in European latitudes and diagnosed in more than 11% of the present patients series) have been mentioned among determinants for the differences of EJAL incidence between Eastern and Western countries [11,17,18]. Consistently with these data, Schietroma et al. showed that the risk of EJAL was 49% lower in patients treated by supplemental oxygen administration during and 6 h after open total gastrectomy [19]. This aspect should furtherly focus the attention on pre-operative setting, aiming to optimize the respiratory work-up before total gastrectomy, according to ERAS recommendations [20] and recent further intriguing suggestions [21].

Tumor-related factors did not appear related to EJAL occurrence in this series: neoadjuvant treatment adopted for locally advanced disease did not affect its occurrence, and, paradoxically, early stages (I-II) were associated to a significantly higher EJAL rate (7.2% versus 6.3%) (Table 2).

Analyzing surgical data, this paradoxical result could find a

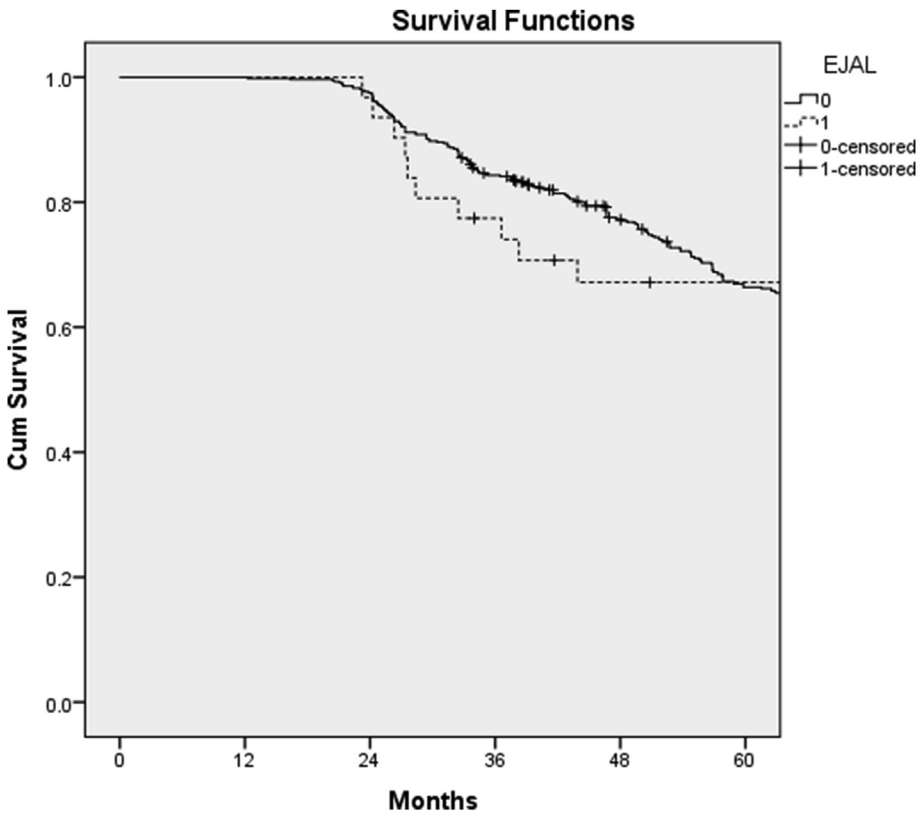

Fig. 1. Overall survival according to EJAL occurrence.

statistical and technical explanation. Indeed, if the detrimental effect of the extended lymphadenectomy was quite predictable, it seemed surprising that early tumor stages, probably more often associated to a R0 resection, represented a risk factor for EJAL. What is more, this surprising result could justify the low impact of EJAL on overall survival in this series (Fig. 1): in fact, the prevalent distribution of this complication in early cases might have counterbalanced its negative prognostic implications. The negative effect of minimally invasive approach on postoperative complications could have influenced this result as well (Table 2), due to the fact that usually early stages represent an indication to laparoscopic or robotic techniques. Actually, compared with open conventional total gastrectomy, according to the present data these procedures seemed to increase the risk of EJAL (15.1% versus 6.4%). Additionally, the potential impact of a "manual" suture (during anastomotic procedures) on EJAL occurrence seems to be consistent with this suggestion. Indeed, current technical limitations of minimally invasive esophago-jejunal anastomosis still often induce surgeons to hand-suture enterotomies after mechanical anastomosis (i.e. partially mechanical anastomosis, see Table 2).

It is to be noted that in this series the minimally invasive surgery has been implemented only in 4 centres starting from 2009. Even considering only patients treated from 2009, the EJAL rate remained significantly higher in minimally invasive surgery than in open surgery group (15.1% versus 7.7%, 78/1016 patients; $p = 0.007$). This difference was not substantially affected by any learning curve effect during the last decade (data not showed).

Undoubtedly, these findings could be clearly affected by small figures of the present population in terms of early stages and, more specifically, minimally invasive procedures, but the warning released by Literature about this issue in minimally invasive surgery for gastric cancer cannot be underestimated [7,22–32]. The most recent contribution to this topic was published by Sakamoto et al. [30]. Analyzing the data of 58 689 patients collected in a nationwide retrospective cohort and with a propensity-score matching of 12 229 pairs, the authors reported an EJAL rate almost 2-fold-increased in laparoscopic group (2.9% versus 1.7%, $p < 0.001$). These numbers and these results were similar to those showed by Kodera et al. in a different large-scale, retrospective cohort study [31]. On the contrary, a recent prospective cohort study on a nationwide web-based database with 2494 patients (1024 propensity score-matched) documented no statistically significant differences in terms of EJAL incidence between laparoscopic and open procedures [32]. This inconsistency could be the result of selection biases in these studies, but meta-analyses and their methodological approximations [26–28] do not help to nullify all the concerns. In fact, the methodologically adequate evaluation of feasibility and safety of laparoscopic total gastrectomy for early cancer is still ongoing [33]. Meanwhile, hopefully in the future the higher rates of EJAL (if confirmed) could be lowered by the evolution of surgical devices and the increase of standardization and technical ease.

Clearly, this study presents some limitations. First, it is a retrospective analysis, with difficulties related to several missing data and a long period of observation (almost 20 years). Second, the sample is very non-homogeneous, due to the lack of a standardized protocol for neoadjuvant approach and/or surgical technique (with particular regard to lymphadenectomy and minimally invasive surgical approach).

In conclusion, anastomotic leakage is a fearsome event which can onset after total gastrectomy and that directly influences postoperative morbidity and mortality.

Despite its limitations, the results of this large retrospective Western study are consistent with observational data from far East,

in particular with the higher rate of EJAL reported in patients with comorbidities or after minimally invasive approach. Effectively, at the moment surgical approach could play a relevant role in EJAL onset. Therefore, waiting for the final results of large population-based randomized trials ongoing in Korea, China and Japan, minimally invasive surgery for total gastrectomy should be cautiously adopted in experimental settings.

Author contributions

Conceptualization: Trapani R, Degiuli M.
Data curation and Formal analysis: Trapani R, Reddavid R, Rausei S.
Methodology: Rausei S.
Supervision and Validation: Rausei S, Degiuli M.
Roles/Writing - original draft: Trapani R, Reddavid R.
Writing - review & editing: Rausei S, Degiuli M.

Declaration of competing interest

None.

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