

Predictors of anastomotic leak after total gastrectomy in patients with adenocarcinoma

Predictores de fuga anastomótica después de gastrectomía total en pacientes con adenocarcinoma

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Abstract

Background: Esophagojejunal anastomotic leakage (EJAL) is among the most feared complications after gastric cancer surgery; they entail an uncertain prognosis and relate with increased morbidity and mortality. Factors associated with their development are not well determined, and their diagnosis and treatment vary between institutions. **Material and methods:** Retrospective case-control study of patients operated of total gastrectomy with Roux-en-Y esophagojejunostomy from January 2002 to December 2018. We divided our sample into two groups based on the presence of EJAL, and compared demographic, clinical, and histologic variables. We performed a logistic regression model to search risk factors associated with EJAL and described the management offered in our center. **Results:** We included 58 patients of which 8 (13.7%) presented clinically relevant EJAL. On the comparative analysis, albumin levels and diffuse histology presented a statistically significant difference between groups and presented association with EJAL in the logistic regression model. Regarding treatment of EJAL, ten patients (55.5%) required only conservative measures, whereas eight patients (44.4%) warranted an endoscopic or surgical intervention. **Conclusion:** Our retrospective analysis identified some factors that may be associated with the development of EJAL after gastric cancer surgery. High suspicion and prompt identification of this complication is essential to improve postoperative outcomes in this group.

Keywords: Total gastrectomy. Gastric cancer. Gastric adenocarcinoma. Esophagojejunal anastomotic leak. Postoperative leak.

Resumen

Introducción: Las fugas de la anastomosis esófago-yeyunal se encuentran entre las más temidas complicaciones de la cirugía para cáncer gástrico. Estas conllevan un mal pronóstico con una alta mortalidad y morbilidad. Los factores asociados a su desarrollo no están bien determinados y su diagnóstico, y tratamiento varían ampliamente entre instituciones. **Material y métodos:** Estudio retrospectivo de casos y controles en pacientes operados de gastrectomía total con esófago-yeyuno anastomosis en Y de Roux en el periodo de enero 2002 a diciembre 2018. Nuestra muestra fue dividida en dos grupos con base al desarrollo de fuga de anastomosis en el postoperatorio. Se realizó un análisis comparativo de características demográficas, clínicas y histológicas. Se realizó además una regresión logística para identificar factores de riesgo asociados al desarrollo de fuga de anastomosis en nuestra serie. **Resultados:** Incluimos a 58 pacientes de los cuales 8 (13.7%)

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presentaron fuga de anastomosis clínicamente relevante. En el estudio comparativo: Niveles disminuidos de albúmina e histología difusa fueron significativamente mayores en el grupo de fuga y se asociaron en el modelo de regresión logística. En cuanto al tratamiento, diez pacientes (55%) requirieron únicamente tratamiento conservador, mientras que ocho pacientes (44.4%) fueron sometidos a maniobras endoscópicas o quirúrgicas. Conclusión: Nuestro análisis retrospectivo identifico factores asociados al desarrollo de fuga de anastomosis posterior a cirugía de cáncer gástrico. Una alta sospecha diagnóstica es esencial para mejorar el pronóstico de estos pacientes.

Palabras clave: Gastrectomía Total. Cáncer Gástrico. Adenocarcinoma Gástrico. Fuga anastomótica. Fuga postoperatoria

Introduction

According to GLOBOCAN 2018, gastric cancer is considered the sixth most common cause of cancer worldwide¹. It is, currently, the fifth cause of cancer death and is considered one of the main contributors to the disability-adjusted life year burden among all types of malignancy². Its incidence is especially high in Asia, Latin America, and the center and east of Europe³.

Several different classifications have been utilized for this entity^{4,5}. However, the most used divides it in two main types depending on its histologic characteristics, diffuse, and intestinal⁶.

Nowadays, surgical resection remains the only curative approach in the treatment of gastric cancer. The objective of such operation is the complete excision of the tumor aiming for a free 5 cm margin and proper lymph node dissection (D1 + D2 with a goal of examining at least 15 lymph nodes) with subsequent gastrointestinal reconstruction, which is usually achieved with a Roux en Y esophagojejunostomy (EJ). An R0 resection is accomplished in 45-60% of the cases subjected to surgical treatment. Most of those cases usually require a total gastrectomy (TG) due to the characteristics of the tumor and its relation with adjacent structures. Those cases with pre-operative evidence of invasion to distant or adjacent structures are not considered surgical candidates on an initial basis and benefit from neoadjuvant chemoradiotherapy and subsequent re-staging of the disease to assess for the most convenient approach^{7,8}.

Esophagojejunal anastomotic leakage (EJAL) is among the most feared complications after gastric cancer surgery; both subclinical and symptomatic cases entail an uncertain prognosis and relate with increased morbidity and mortality. The reported incidence of this complication is quite variable worldwide⁹; this has a strict correlation with the heterogeneity of their operative definition, which has further complicated the development of generalized algorithms for their treatment and early recognition. Studies have demonstrated that

the presence of EJAL is associated to prolonged hospitalization and a significant risk of death¹⁰. Furthermore, there is evidence suggesting that infectious complications after gastric cancer surgery are associated with increased rates of cancer recurrence¹¹.

Factors associated with the development of EJAL after gastric cancer surgery are not well determined. A large retrospective study from Asia, suggest that older age (> 65 years), increased intraoperative blood loss and comorbidities may be related¹². However, such findings have not been reproduced consistently by others¹³⁻¹⁵. EJAL can present in two different clinical scenarios. The first and most indolent, is in asymptomatic patients that undergo either routine imaging studies before starting oral feeding or an imaging study requested for another reason; and in symptomatic patients who frequently present with abdominal pain, fever, peritoneal irritation, and saliva or intestinal content in perianastomotic drains after the procedure or when the start of oral intake is attempted. The diagnostic approach and treatment varies depending on the particular case. However, there is marked diversity between institutions^{9,10}.

The purpose of this study was to identify risk factors for the development of EJAL in patients subjected to TG in a third level university based oncologic center and describe the treatment algorithm utilized to manage this complication in our hospital.

Materials and methods

We performed a retrospective analysis of our hospital registry to identify the subjects of this study. All patients over 18 years old with the diagnosis of gastric cancer, who were subjected to TG with Roux en Y EJ at our third level academic center between January 2002 and December 2018, were included in the study. Patients with incomplete data were excluded from the analysis. This study received approval of the local Institutional review board. All patients were approached by laparotomy and operated by a board-certified surgical oncologist.

EJAL was defined as any clinical or imaging evidence of luminal spillage adjacent to the EJ; Including evidence of intestinal contents or saliva in perianastomotic drains, evidence of extraluminal contrast material in imaging studies (esophagogram and contrast-enhanced Computed tomography [CT] scan) or fluid collections adjacent to the EJ in CT scan or ultrasound. All post-operative imaging studies of analyzed patients were reviewed for the purpose of this study to decrease risk of bias, some of which were requested for an alternate diagnostic suspicion.

The variables age, gender, comorbidities (Type 2 diabetes, high blood pressure, hypothyroidism, or dyslipidemia) perioperative chemotherapy, histologic type, and presence of signet ring cells were recorded. Relevant routine preoperative laboratory values, obtained at admission 1 day previous to the operation, were also registered, including hemoglobin, total leukocytes, total neutrophils, total lymphocytes, neutrophil to lymphocyte ratio platelets, and albumin levels. Variables related to the surgical procedure such as surgical technique (hand sewn vs. stapled anastomosis), operative time and operative bleeding were included in the study.

Our sample was divided in two groups for statistical analysis, based on the presence of EJAL during their post operative period. Variables were compared between these two groups.

All patients were assessed by a multidisciplinary team, and were operated by a certified surgical oncologist. The pre-operative assessment and post-operative routine were according current international practice guidelines. The standard protocol was early feeding as tolerated, total parenteral nutrition (when required and progression of analgesia to achieve early discharge.

Patients with identified EJAL were defined as asymptomatic when no clinical symptoms suggestive of secondary abdominal sepsis (such as pain, oral intolerance, or peritonitis) were present during serial examinations and were treated with supportive treatment including nothing by mouth, intravenous hydration, analgesia, and antibiotics and fluid collection drainage with interventional approaches when appropriate. Such patients were followed closely with clinical examinations and serial imaging. None of these patients required invasive interventions.

Symptomatic patients were assessed and treated according their particular presentation. Our general approach included nothing by mouth, early nutritional support, intravenous antibiotics, drainage of fluid

collections, and depending on the nature of the case either endoscopic revision with fibrin glue, clip, or stent placement over defect or surgical management. All such procedures were considered emergency interventions.

We also included the variables hospital stay, perioperative mortality, and overall survival for descriptive purposes.

Statistical analysis

Categorical variables were presented as total frequencies (n), proportions and percentages (%). Continuous variables were analyzed for normal distribution. Variables with normal distribution were presented as means and standard deviations ($\pm$ SD) and those with non-normal distribution were presented as medians and ranges. Categorical variables were compared within groups using Chi-square test or Fischer's exact test, whereas continuous variables were compared using Student's t-test or Mann-Whitney U test. All tests were two sided and utilized an alpha of 0.05.

Univariate logistic regression analysis was performed utilizing the included variables. Odds ratios and 95% confidence intervals were calculated. All values were two tailed in this analysis and $p < 0.05$ was considered to be statistically significant. The analysis was performed employing SPSS Version 22.0 (IBM Corporation, Armonk, New York, NY).

Results

We included a total of 58 patients subjected to TG in our sample. No patients were excluded due to lack of available data after our review. All included patients were analyzed.

A total of 18 patients (31.03%) fulfilled our definition of EJAL during their post operative period. All patients were diagnosed within 1 week of their operation and were still hospitalized when the EJAL was identified. Ten cases (55.5% of the anastomotic leaks) were classified as asymptomatic and were identified during the post-operative period through either routine imaging (contrast-enhanced esophagogram) requested before starting oral intake, or imaging studies pursuing alternate diagnostic suspicion.

The remaining eight patients with EJAL, were considered symptomatic and presented with fever (100%), diffuse abdominal pain (25%), peritonitis (25%), oral intolerance (75%), leukocytosis $> 12.500 \times 10^9/L$, 75%),

Table 1. Clinical and histologic variables

	All patients (n = 58)	EJAL (n = 18)	No EJAL (n = 40)	p < 0.05
Age (years)	61.5	63.8	60.5	0.21
Gender				
Male	22 (37.9%)	12 (66.6%)	20 (50%)	0.268
Female	26 (44.8%)	6 (33.3%)	20 (50%)	
Comorbidities				
With	33 (56.89%)	10 (55.5%)	23 (57.5%)	1.0
Type 2 diabetes	17 (29.3%)	8 (44%)	9 (22.5%)	
Dyslipidemia	7 (12%)	3 (16.6%)	4 (10%)	
High blood pressure	19 (32.7%)	6 (33.3%)	13 (32.5%)	
Hypothyroidism	2 (0.1%)	2 (11.1%)	0 (0%)	
Others	10 (17.4%)	4 (22.2%)	6 (15%)	
Without	25 (43.10%)	8 (44.4%)	17 (42.5%)	
Perioperative Chemotherapy				
No	19 (32.7%)	6 (33.3%)	13 (32.5%)	0.17
Neoadjuvant	11 (18.9%)	6 (33.3%)	5 (12.5%)	
Adjuvant	10 (17.24%)	1 (5.55%)	9 (22.5%)	
Perioperative	18 (31.03%)	5 (27.77%)	13 (32.5%)	
Histologic Type				
Intestinal	19 (32.7%)	4 (22.2%)	15 (37.5%)	0.05
Diffuse	29 (50%)	9 (50%)	20 (50%)	
Mixed	10 (12%)	5 (27.7%)	5 (12.5%)	
Presence of Signet ring cells				
With	35 (60.3%)	9 (50%)	26 (65%)	0.385
Without	23 (39.6%)	9 (50%)	14 (35%)	

elevated acute phase reactants (CRP > 1.5 mg/dl, 100%), or intestinal content on the perianastomotic drain (50%).

The mean age of our patients was 61.5 years with no statistically significant difference found between groups. In the initial comparative analysis, we found no significant difference in the clinical variables gender, comorbidities, perioperative chemotherapy, and presence of signet ring cells in histology. With the variable histologic type reaching $p = 0.5$ (Table 1).

Variables related to the surgical procedure and laboratory values were similar between groups with exception of serum albumin levels, which were significantly lower in the EJAL group (mean 3.9 mg/dl vs. 3.5 mg/dl $p = 0.02$) (Table 2).

On univariate analysis (Table 3), patients were more likely to develop EJAL if they presented diffuse gastric adenocarcinoma, according to the post-operative pathology report. The rest of the variables included in the analysis did not presented a significant association with the development of EJAL in our sample.

Table 2. Laboratory and procedure related variables

	EJAL (n = 18)	No EJAL (n = 40)	p < 0.05
Hemoglobin (g/dl)	12.4 (10.03-14.81)	12 (9.38-14.64)	0.56
Total Leukocyte count (cells/microL)~	7.5 (3.6-8.5)	6.7 (6.0-13.7)	0.14
Total Neutrophil count (cells/microL)~	4.9 (2.05-6.35)	4.0 (3.5-11.8)	0.31
T. Lymphocyte count (cells/microL)~	1.9 (0.78-2.7)	1.6 (0.18-8.54)	0.19
Total Neutrophil/Lymphocyte ratio~	2.3 (0.91-21.5)	2.3 (0.83-14.8)	0.65
Platelets ($\times 10^9/L$)	260.2 (126.9-393.4)	275.3 (211.2-339.2)	0.77
Serum albumin (mg/dl)	3.5 (2.66-4.34)	3.9 (3.38-4.44)	0.02
Operative time (min)	268.3 (223-313.6)	275.3 (211.2-339.2)	0.64
Operative Blood loss (ml)	498.9 (258.5-739.2)	530.5 (257.1-803.3)	0.66
Type of Anastomosis			
Mechanic (Stapled)	16 (88.8%)	29 (72.5%)	0.30
Manual (Hand Sewn)	2 (11.1%)	11 (27.5%)	

Variables with normal distribution were expressed as means $\pm$ STD. Non-normal variables (~) were expressed as median $\pm$ ranges.

Mean hospital stay was 29.5 days in the EJAL group and 12 days in the control. The mean overall survival in our entire sample was 26.97 months with no difference between groups.

Regarding treatment of the symptomatic EJAL, six patients required percutaneous drainage of fluid collections (10.3%). Four patients with symptomatic EJAL (6.8%) required an endoscopic intervention, involving application of fibrin glue in three patients and endoscopic clip in one patient. Two patients (3.4%) were treated with a primary operative intervention due to sepsis. Both were approached through laparotomy and were subjected to remodeling of the EJ and closed drain placement. One of such patients died in the post operative period secondary to severe sepsis and multiorgan failure. The rest of the EJAL identified were treated conservatively.

Discussion

This study aimed to identify the incidence of EJAL after gastric cancer surgery, as well as risk factors that were associated with their development in western population.

Table 3. Univariate logistic regression analysis of factors associated with EJAL

Risk factor for EJAL	Unadjusted OR (95% CI)	p < 0.05
Gender	0.50 (0.15-1.59)	0.241
Comorbidities	0.92 (0.30-2.83)	0.89
(+) Signet ring cells	0.53 (0.17-1.66)	0.28
Manual anastomosis vs. Mechanic	3.03 (0.59-15.41)	0.18
Chemotherapy	0.28 (0.02-2.90)	0.29
Histologic type		
Diffuse/Intestinal	9.32 (1.29-67.64)	0.02
Mixed/Intestinal	5.55 (0.90-34.24)	0.06
Hemoglobin (g/dl)	0.93 (1.29-67.64)	0.56
Leukocyte count (cells/microL)	1.13 (0.94-1.37)	0.17
Total Neutrophil count (cells/microL)	1.18 (0.9-1.37)	0.23
T. Lymphocyte count (cells/microL)	1.15 (0.91-1.46)	0.21
Total Neutrophil/Lymphocyte ratio	1.05 (0.89-1.23)	0.55
Platelets ($\times 10^9/L$)	0.99 (0.99-1.004)	0.76
Serum albumin (mg/dl)	0.82 (0.72-1.37)	0.07
Operative time (min)	0.99 (0.98-1.008)	0.67
Operative Blood loss (ml)	1 (0.99-1.002)	0.66

We realized that there is a very limited amount of research papers studying this complication in the context of gastric cancer, and that most of the studies are based on retrospective data, and focused mainly on Asian population¹¹⁻¹⁴. This is concerning because of the well-known differences in the perioperative approach paradigms and patient characteristics between western and eastern institutions¹⁵. The prevalence of EJAL following open gastrectomy for gastric cancer has been reported to range from 2.1 to 14.6%^{16,17}, with mortality associated with EJAL ranging from 0 to 50%^{17,18}. The differences in the literature may be explained by variations in study design, study cohort size, country, and study periods¹⁹. The EJAL incidence and mortality tend to be lower in Asian countries (including Japan) than in Western countries. The incidence of EJAL following open TG was 4.4% in a prospective cohort study from a Japanese nationwide registry²⁰, whereas the incidence ranged from 4 to 26% in phase III studies conducted in Western countries^{21,22}. This difference may be attributed to the higher incidence of cardiopulmonary comorbidities and intra-abdominal complications in patients with gastric

cancer from Western countries as well as the higher incidence of gastric cancer in Asian patients^{23,24}.

Identification of the risk factors of EJAL helps to decrease its incidence. The reported risk factors include patient and tumor characteristics and intraoperative factors. The impact of a challenging anastomosis on the occurrence of EJAL indicates that prevention is crucial to reduce this complication. Migita et al.²⁵ found that blood loss was significantly greater in gastrectomy with a complicated anastomosis (783 vs. 423 g, $p < 0.05$). Furthermore, gastrectomy with anastomotic complications tended to have a longer median duration of operation in comparison to that without it (351 vs. 290 min, $p = 0.0682$). These results indicate that more complicated gastrectomy is associated with higher incidence of the anastomotic complications. In our study, variables related to the surgical procedure were similar between groups.

On the other hand, anemia and malnutrition may result in insufficient blood and energy supplies to the anastomosis, which might affect the healing of the anastomosis and reduce the levels of inflammatory cells, inflammatory factors, and administered antibiotics, thereby increasing the risks of infection and of anastomotic leakage²⁶⁻²⁸. In our series, we demonstrated significantly lower albumin levels in patients who present EJAL, which is widely known as a predictor of EJAL, but has merely been described in this specific context^{29,30}. Furthermore, to the best of our knowledge, no previous study had determined diffuse histologic type to be related to EJAL; this could relate to a more increased local inflammatory reaction elicited by this aggressive type of neoplasm but again, more studies are needed to better understand this concept on a molecular basis.

Furthermore, we are aware that our series demonstrate a higher incidence of EJAL than other contemporary literature. However, we believe that this is due to the marked heterogeneity in the diagnostic approach and definition of EJAL. Most studies include only clinically significant EJAL and exclude perianastomotic fluid collections from their operative definition and thus describe higher rates of invasive interventions.

In comparison most of our EJAL were subclinical. The percentage of patients which required an intervention (either endoscopic or surgical) was 13.7%, which is similar to that reported in other series^{31,32}. We still decided to include all the patients with any evidence of contrast extravasation either clinical or subclinical for the comparison as even asymptomatic

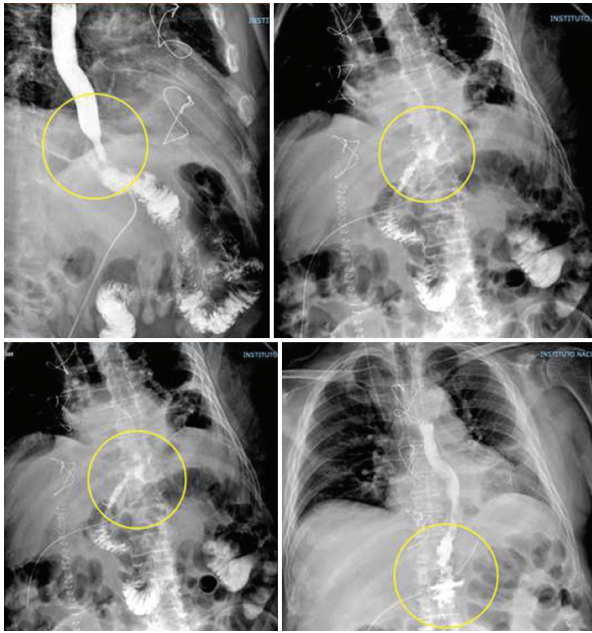


Figure 1. Contrast-enhanced esophagogram performed 4 days after total gastrectomy showing evidence of EJAL (yellow circle).

leaks resulted in a deviation from the conventional post operative management in our institution either because of increased hospital stay, medication regime and serial follow-up studies and allocation of resources.

Concerning the diagnostic approach of EJAL, some authors have proposed the performance of contrast-enhanced esophagogram previous to start oral feedings in their patients^{33,34} (Fig. 1).

However, further evidence has demonstrated that this practice has a low diagnostic yield and should not be done on a regular basis³⁵. On a study performed in our center, routine contrast enhanced esophagogram revealed to have a sensitivity of 86%, specificity 100%, positive predictive value 100%, and negative predictive value of 86% for detection of EJAL³⁶.

In our institution, perioperative practices have evolved through the years, showing a tendency to perform more imaging studies to our patients, attempting to identify complications earlier and improve prognosis.

As described earlier, all our patients received multidisciplinary expert care but still, the criteria to subject the patients to post operative imaging for different reasons, varied depending on the physician in charge; this variable criteria for the performance of imaging studies it is the main limitation of this retrospective review, in conjunction with its limited power.

Regarding the treatment of patients with EJAL, we usually perform a step up approach depending on the clinical presentation; our approach starts with nothing per mouth, naso-jejunal tube placement, intravenous hydration, early nutritional support, analgesia and antibiotics, followed by multidisciplinary consensus for the most appropriate invasive intervention which usually includes percutaneous treatment, endoscopic placement of sealants, clips or stents and surgical remodeling of the EJ, which is usually reserved for patients with large dehiscence of the anastomosis. This approach is similar to other current practices described in the literature.

Conclusions

EJAL is among the most feared complications after gastric cancer surgery; they entail an uncertain prognosis and relate with increased morbidity and mortality. Our retrospective analysis identified some factors that may be associated with the development of EJAL after gastric cancer surgery. High suspicion and prompt identification of this complication are essential to improve postoperative outcomes in this group.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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