



Original Research

Duodenal fistula: The most lethal surgical complication in a case series of radical gastrectomy



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ARTICLE INFO

Keywords:

Stomach neoplasms
Gastrectomy
Postoperative complications
Digestive system fistula

ABSTRACT

Background: Despite all advances regarding the surgical treatment of gastric cancer (GC), duodenal stump fistula (DF) continues to negatively affect postoperative outcomes. This study aimed to assess DF regarding its incidence, risk factors, management and impact on overall survival.

Methods: We retrospectively analyzed 562 consecutive patients who underwent gastrectomy for GC between 2009 and 2017. Clinicopathological characteristics analysis was performed comparing DF, other surgical fistulas and patients with uneventful postoperative course.

Results: DF occurred in 15 (2.7%) cases, and 51 (9%) patients had other surgical fistulas. Tumor located in the lower third of the stomach ($p = 0.021$) and subtotal gastrectomy ($p = 0.002$) were associated with occurrence of DF. The overall mortality rate was 40% for DF and 15.7% for others surgical fistulas ($p = 0.043$). The median time of DF onset was on postoperative day 9 (range 1–75). Conservative approach was performed in 8 patients and surgical intervention in 7 cases. Age (OR 7.41, $p = 0.012$) and DF (OR 9.06, $p = 0.020$) were found to be independent risk factors for surgical mortality. Furthermore, patients without fistula had better long-term survival outcomes comparing to patients with any type of fistulas ($p = 0.006$).

Conclusion: DF is related with distal tumors and patients submitted to subtotal gastrectomy. It affects not only the postoperative period with high morbidity and mortality rates, but may also have a negative impact on long-term survival.

1. Introduction

Surgery remains as the only curative option to treat gastric cancer (GC). Despite the recent advances in surgical techniques and devices, including staplers, duodenal stump fistula (DF), often called just duodenal fistula, continues to be a challenge and life-threatening complication. It has a high postoperative morbidity and mortality rate leading to long postoperative period of hospitalization due to DF-related complications such as wound infections, pancreatitis, intra-abdominal bleeding, abscesses and severe malnutrition [1].

The incidence of DF reported in the literature ranges from 1.6% to 5%. In a recent Italian multi-centric analysis, DF occurred in 1.8% of cases, with morbidity rate of 75% and mortality of 16%. However, the available data are very heterogeneous and the clinical scenarios sometimes are not comparable [2].

The aim of this study was to assess DF regarding its incidence, risk factors, management and impact on overall survival.

2. Methods

We retrospectively reviewed all consecutive patients submitted to gastrectomy due to gastric adenocarcinoma from 2009 to 2017 at Cancer Institute of the University Hospital. All clinical data came from our prospective collected database. Patients with gastric stump neoplasia, histological type different from adenocarcinoma and emergency surgeries were excluded from the analyses.

Patients were staged preoperatively through abdominal and pelvis computed tomography, endoscopy and laboratory tests. Extension of gastric resection (total vs subtotal) was based on the location of the tumor to obtain free proximal margin [3]. TNM staging was performed according to TNM 7th edition [4].

Clinical characteristics evaluated included American Society of Anesthesiologists (ASA) classification [5], Charlson Comorbidity Index (CCI) [6], Neutrophil-to-lymphocyte ratio (NLR) and laboratory tests. CCI was considered without inclusion of gastric cancer neoplasm as

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comorbidity.

Duodenal Fistula was defined as the presence of fluid through the abdominal drain or after radiologic drainage with a concentration of bilirubin and amylase at least three times higher than serum value. Other surgical fistulas evaluated were pancreatic, esophagojejunal, gastrojejunal, jejunoojejunal, colonic and the remaining types were labeled as others. Patients who had no postoperative complications were labeled as the no complication group and served as control.

Surgical complications were graded according to Clavien-Dindo's classification [7]. Major complications were considered Clavien III-V. The hospitalization period and the number of retrieved lymph nodes were evaluated. Surgical mortality was considered when it occurred within the first 30 days after surgery or during hospital stay after the procedure.

The postoperative follow-up was performed on a quarterly basis in the first year and every 6 months in the following years. Follow-up tests for relapse detection were performed based on the presence of symptoms. Absence in consultations for more than 12 months was considered as loss of follow-up.

All cases were operated in a high-volume center by surgeons with extensive experience in the surgical management of GC. The surgical technique, extension of resection and dissected lymph node chains followed the recommendations of the Japanese Gastric Cancer Association guidelines [8]. The extent of nodal dissection (D1 or D2 lymphadenectomy) was defined accordingly to the lymph node chains removed. In all cases, the duodenum was closed and sectioned with linear stapler Autosuture™ DST Series GIA™ 80-3.8 mm (U.S. Surgical, Norwalk, CT) or Proximate™ TLC™ 75 blue 3.85 mm (Ethicon, Inc., Somerville, NJ). Roux-en-Y alimentary tract reconstruction was performed in all cases.

The study was approved by the hospital ethics committee (NP993/16) and registered in the “Plataforma Brasil” (CAAE: 2915516.2.0000.0065) that collects all research projects that involve human beings in the country. It was also registered in the international research registry database (www.researchregistry.com). The study was designed and reported in line with the PROCESS criteria [9].

2.1. Statistical analysis

The Chi-square tests were used for categorical variables and ANOVA for continuous variables. Overall survival (OS) was estimated using the method of Kaplan-Meier, and differences in survival were examined using the Log Rank Test. The factors associated with surgical mortality (Clavien V complications) were determined by binary logistic regression analysis by the backward elimination with a stay level of 0.20. Survival time, in months, was calculated from the date of surgery until the date of death/recurrence. The patients alive were censored at the date of last contact. All tests were two-sided and $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS software, version 18.0 (SPSS Inc, Chicago, IL).

3. Results

Six hundred and thirty-six patients surgically treated for GC in that period were initially evaluated. Of these, 74 did not meet inclusion criteria and were excluded from the analysis. The remaining 562 patients were enrolled in the study. Of these, 15 (2.7%) patients had DF, 51 (9%) patients had other surgical fistulas and 390 patients (69.3%) had no postoperative complications and labeled as the no complication group – and served as control group.

The mean age of total population was 62.5 years (range 37–77), with a male preponderance (73.3% vs. 26.7%). Most tumors were located at the distal part of the stomach (66.7%) and therefore subtotal gastrectomy was the most frequent type of resection performed (80% of cases).

Clinical characteristics of patients with DF, other fistulas and no

Table 1

Clinical characteristics of patients with DF, other fistulas and no complication group.

Variables	No complication	Other fistulas	Duodenal fistula	<i>p</i>
	n = 390 (%)	n = 51 (%)	n = 15 (%)	
Gender				0.462
Female	158 (40.5)	18 (35.3)	4 (26.7)	
Male	232 (59.5)	33 (64.7)	11 (73.3)	
Age (years)				0.187
Mean	61.8	65.2	62.5	
BMI (Kg/cm ²)				0.758
Mean	24.4	24.3	23.4	
Hemoglobin (g/dL)				0.173
Mean	12.3	11.7	12.9	
Albumin (mg/dL)				0.421
Mean	4.1	3.7	3.9	
Neutrophil lymphocyte ratio (NLR)				
Mean	2.64	2.96	3.10	
Neoadjuvant therapy				0.401
Yes	48 (12.3)	10 (19.6)	2 (13.3)	
No	342 (87.7)	41 (80.4)	13 (86.7)	
Charlson Comorbidity Index (CCI)				0.687
0–1	341 (89.5)	44 (86.3)	14 (93.3)	
> 1	40 (10.5)	7 (13.7)	1 (6.7)	
ASA Classification				0.742
I/II	305 (80.1)	42 (82.4)	11 (63.3)	
III/IV	76 (19.9)	9 (17.6)	4 (26.7)	

complication groups are summarized in Table 1.

The median time of DF diagnosis was on postoperative day 9 (range 1–75). Surgery with curative intention was performed in more than 90% of cases, and 78.5% of patients underwent D2 lymphadenectomy. Type of surgery and extent of lymphadenectomy were not related to the occurrence of DF nor to other fistulas ($p = 0.558$ and $p = 0.809$, respectively). Tumors located in the lower third of the stomach ($p = 0.021$) and subtotal gastrectomy ($p = 0.002$) were associated with DF (Table 2). Adjuvant therapy were administered in 71.2%, 59.5% and 45.5% of no complication, others fistulas and DF stage pTNM II/III patients, respectively ($p = 0.081$).

A binary logistic regression was performed to identify risk factors associated to surgical death (Clavien V). Variables entered on step 1 were age, gender, NLR, Charlson, ASA, pTNM, type of resection, type of lymphadenectomy and the occurrence of DF. After the multivariate analysis using the “steps forward” option, age > 70 years and DF were independent risk factors for surgical death (Table 3).

Regarding the management of these patients, eight were treated conservatively and seven patients required surgical intervention. All interventions were performed by open approach with extensive lavage of the abdominal cavity followed by drainage. Closure of the duodenal fistula orifice with suture was performed in all cases. In addition, in one case fibrin glue was used. The mortality rate was 37.5% (three patients) and 42.8% (three patients) in conservative and surgical treatment, respectively ($p = 0.833$).

Compared with other fistulas, the mortality of DF was the highest along with that of jejunoojejunal anastomosis fistula (both 40%) (Table 4). The mortality of the other fistulas grouped as a single category was 15.7%. It was significantly lower compared to the 40% rate of DF group ($p = 0.043$).

The median follow-up of the study population was 24.3 months. Overall survival of patients with no complications and patients with any type of fistula, after exclusion of surgical deaths, are represented in Fig. 1. Patients who had any kind of fistula had a negative impact on survival outcome comparing to patients without any surgical complication ($p = 0.006$).

Table 2

Surgical and pathological characteristics of patients with DF, other fistulas and no complication group.

Variables	No complication	Other fistulas	Duodenal fistula	<i>P</i>
	n = 390 (%)	n = 51 (%)	n = 15 (%)	
Type of surgery				0.558
Curative	348 (89.2)	48 (94.1)	14 (93.3)	
Palliative	42 (10.8)	3 (5.9)	1 (6.7)	
Type of resection				0.002
Subtotal	259 (66.4)	22 (43.1)	12 (80)	
Total	131 (33.6)	29 (56.9)	3 (20)	
Surgical approach				
Open surgery	342 (87.7)	46 (90.2)	14 (93.3)	
Laparoscopic	48 (12.3)	5 (9.8)	1 (6.7)	
Type of lymphadenectomy				0.809
D2	304 (77.9)	42 (82.4)	12 (80)	
D1	86 (22.1)	9 (17.6)	3 (20)	
Tumor site				0.021
Lower	273 (71.8)	23 (47.9)	10 (71.4)	
Middle	75 (19.7)	17 (35.4)	3 (21.4)	
Upper	23 (6.1)	8 (16.7)	1 (7.1)	
Others	9 (2.4)	0 (0)	0 (0)	
Tumor size (cm)	mean	5.1	5.7	0.389
Lauren				0.674
Intestinal	192 (49.2)	23 (45.1)	7 (46.7)	
Diffuse/mixed	174 (44.6)	23 (45.1)	8 (53.3)	
undetermined	24 (6.2)	5 (9.8)	0 (0)	
PTNM stage				0.238
I/II	2016 (52.8)	21 (41.2)	9 (60)	
III/IV	184 (47.2)	30 (58.8)	6 (40)	

Table 3

Risk factors for surgical death (Clavien V) in gastric cancer: results of multivariate analysis.

Variables ^a	Odds Ratio	95% CI	<i>P</i>
Age 0–69 vs > 70 years	7.41	1.56–35.14	0.012
Charlson 0–1 vs. Charlson > 1	6.56	0.82–52.3	0.076
Total vs. subtotal gastrectomy	4.89	0.76–31.6	0.095
D2 vs. D1 gastrectomy	6.27	0.92–42.72	0.061
Stage I/II vs. stage III/IV	0.34	0.073–1.58	0.168
Other fistulas vs. duodenal fistula	9.06	1.41–58.3	0.020

^a The first variable represents the reference category.

Table 4

All fistulas incidence and mortality in patients treated for GC with surgery.

Type of Fistula	Total cases (n)	Incidence (%)	Deaths (n)	Lethality (%)
Esophagojejun ^b	9	4.5	2	22.2
Gastrojejun ^c	9	2.5	3	33.3
Jejunojenunal	5	0.9	2	40
Duodenal	15	2.7	6	40
Pancreatic	17	3	0	0
Colonic	11	2	1	9.1
Others	4	0.7	0	0
Total ^d	70 ^a	11.7	14	21.2

^a 4 of 66 patients had 2 types of fistulas simultaneously.

^b Considering only patients submitted to total gastrectomy (n = 200).

^c Considering only patients submitted to distal gastrectomy (n = 362).

^d Calculation of the remaining fistulas performed on total gastrectomy (n = 562).

4. Discussion

Despite its low incidence, DF represents one of the most challenging and life-threatening postoperative events that surgeon must deal with.

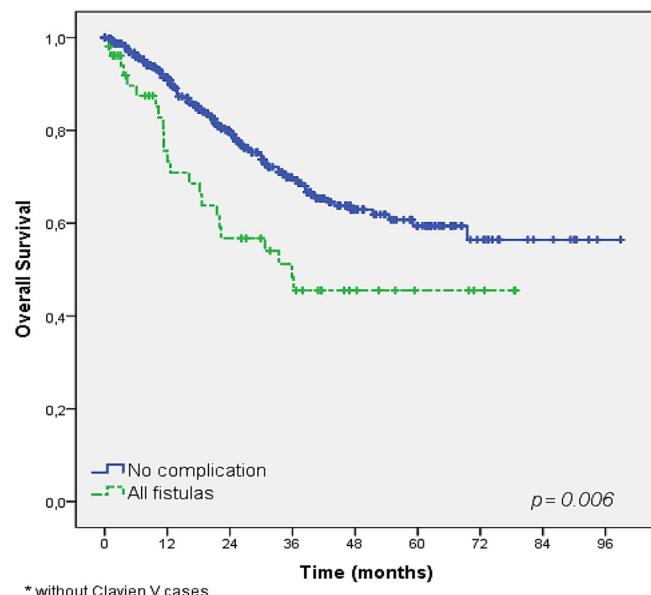


Fig. 1. Overall Survival of patients operated for GC in relation to fistula occurrence.

According to the present study, DF incidence was 2.7%. This frequency is consistent with those reported in the literature, corresponding to 1.6%–5% [2].

Concerning its pathogenesis, many possible factors have been proposed. For instance, inadequate closure of the duodenal stump, devascularization, cancer involvement of resection line, inflamed duodenal wall, local hematoma, incorrect drain position and postoperative distension of the duodenum due to distal obstruction [2].

According to our results, DF was associated to distal tumors submitted to distal subtotal gastrectomy. This might be explained by the need of major dissection of the duodenal stump to obtain free distal margins of neoplasia, which could lead to devascularization and therefore leakage.

When performed in high-volume centers, morbidity of gastrectomy with lymphadenectomy for GC are acceptable but not negligible. Thus, the extension of lymphadenectomy (D1 vs. D2) has been reported as independent prognostic factors for higher rates of complications [10]. However, in both techniques the lymph nodes around suprapyloric (number 5) and infrapyloric (number 6) are included in the dissection. Thereby, manipulation of the duodenal stump is similar and, as expected, we did not find an association between the occurrence of DF and the extension of lymphadenectomy.

It also has been reported that patient's clinical conditions such as heart disease, cirrhosis, diabetes mellitus and malnutrition are associated with DF [11,12]. Nevertheless, this association was not found in the present study.

The time of its occurrence may vary. Ali et al. reported a mean time of DF diagnosis of 10 days [1–20] [13]. Our data suggests that this period could be even longer. The median time of DF diagnosis was on the 9th postoperative day, but three patients had the diagnosis after the 20th day. Low output fistulas associated with local block may delay the diagnosis and in these cases it is impossible to precise the day of fistula occurrence. Therefore, possibility of late manifestation should be considered.

Regarding the treatment, conservative treatment based on proper drainage, infection control and nutritional support, are the cornerstone of the management of DF [1,14]. Surgery should be considered only when conservative management fails to adequately drain the fistula as well as its correlated complications such as bleeding, sepsis, bowel obstruction and other fistulas.

It is well known that nutritional status has a great impact over the

incidence and management of surgical complications. Therefore, aggressive administration of enteral and parenteral nutrition must be started as soon as possible, as well as broad spectrum antibiotics. Yet, hydroelectrolytic disorders are common and should be carefully monitored and corrected.

The use of routine postoperative drains in GC surgery has been the subject of much debate recently. In our institution, we routinely use external drains for all patients. Its use does not avoid the leakage; notwithstanding, it allows early diagnosis and, in many times, avoids other invasive procedures. Patients who are not drained, or whom the appearance of the fistula occurs after its removal, might be treated with percutaneous drainage. Oh et al. reported 10 cases of DF which were successfully treated with fluoroscopy-guide percutaneous Foley's catheter placement [15]. Another option is percutaneous drainage through computer tomography or ultrasound and placement of pigtail catheter [13].

Surgical intervention is pivotal to drain multiple abscesses or whenever diffuse peritonitis manifests itself. Efforts to close the fistula orifice during the procedure may be attempted through simple suture, biological glue or even with duodenojejunostomy. The effectiveness of these procedures is low and a duodenostomy for better drainage of the fistula is sometimes indicated [16].

Alternative procedures including biliary diversion with choledochojejunostomy [17] or percutaneous transhepatic biliary drainage and occlusion balloon (PTBD-OB) can also be used in high volume output fistulas. Cozzaglio et al. reported an efficacy to access the biliary tree with PTBD-OB and reduction of the output from 500 to 100 ml/day in six patients. Nonetheless, total resolution of DF was achieved in 50% of the cases [18].

The occurrence of DF is related to high mortality rate. The 40% mortality rate reported in our series highlights the magnitude of such complication. DF and advanced age were independent factors associated to the risk of surgical death (Clavien V). In addition, we found that jejunojejunal fistula was also associated with dismal outcome (40% mortality rate). Other studies have reported mortality rates varying from 7 to 67% [19–21].

In a retrospective analysis, Park et al. reported 16 (2.2%) cases of DF in 716 patients submitted to gastrectomy for GC, with two deaths in this group (12.5%). According to their data, DF was associated to age > 60 years, clinical T stage, multiple comorbidities and gastric outlet obstruction as independent risk factors [12]. Aurello et al. published a systematic review regarding DF treatment after gastrectomy for malignant tumors with 145 cases. Seventeen (11.7%) patients died due to sepsis, abscess, peritonitis, bleeding, pneumonia and multiple organ failure [1].

According to our data, survival analysis demonstrated that patients who faced surgical fistulas had significantly lower long-term survival ($p = 0.006$). Similar results have been described in other studies encompassing colorectal, esophageal and pancreatic surgery [22]. It has been suggested that major complications, specially related to infection, could lead to long-standing suppressive effects on patient's immune system by the action of pro-inflammatory cytokines and thereby rendering them to be more susceptible to cancer recurrence. A recent meta-analysis reported a hazard ratio (HR) of 1.28 for decreased OS after any postoperative complication [23]. Surgical complications may also restrain patients to Return to Intended Oncologic Treatment (RIOT) and, therefore increase the risk of recurrence due to the lack of the benefits of adjuvant therapy [24].

In order to analyze OS in our study, we grouped all fistulas cases in the same category without evaluating the DF separately due to the small number of cases. However, there is no reason to believe that the impact on long-term survival would be different if only the analysis of DF cases could be performed.

One limitation and subject of great controversy is the lack of information regarding the reinforcement on the stapling line of the duodenal stump. Shao et al. retrospectively analyzed three different

techniques of duodenal stump closure in 2,034 patients operated for GC. There were 11 (0.53%) cases of DF. According to their results, purse-string suture had better outcomes regarding the presence of leakage when compared to duodenal stump treated with linear cutting stapler plus seromuscular layer reinforcement suture, and using full-thickness suture plus seromuscular layer reinforcement [25].

In our institution, all duodenums are divided with linear staplers and the stapling line reinforced with interrupted seromuscular stitches. Thus, no comparison could be made with direct manual closure. Orsenigo et al. found that the absence of manual reinforcement was an independent risk factor for DF onset [11]. However, it's important to emphasize that distal lesions invading the pylorus or duodenum require larger tumors-free margins, which could make manual reinforcement impossible to be properly achieved. Precisely, our results confirm that distal lesions are more often associated with DF. Analysis of retrospective data may lead to erroneously conclusion that not performing reinforcement of the stapler line is related to higher risk of developing this complication. Therefore, the necessity of an extended ultrapyloric resection for achieving free resection margins, and the subsequent absence of adequate duodenal wall for over sewing the stapler line may be the real risk factor for DF onset. Indeed, this needs to be investigated in a prospective randomized clinical trial, but a larger sample size will be required as the incidence of DF is very low.

5. Conclusions

Duodenal fistula has low incidence but is associated with high surgical mortality after radical gastrectomy. Tumors located in the distal third of the stomach undergoing distal gastrectomy are the main risk factors for its occurrence. It affects not only the postoperative period but may have a negative impact on long-term survival.

Disclosure

This study was not funded and the authors declare no conflict of interest.

Ethical approval

The study was approved by the hospital ethics committee (NP993/16) and registered in the "Plataforma Brasil" (CAAE: 2915516.2.0000.0065) that collects all research projects that involve human beings in the country.

Funding

This article received no financial support

Author's contribution

Marcus F.K.P. Ramos: study design, data retrieval, critical analysis, draft of the manuscript.

Marina A. Pereira: data retrieval, statistical analysis, draft of the manuscript.

Leandro C Barchi, Osmar K. Yagi, Andre R. Dias, Daniel J. Szor: data retrieval, review of the manuscript.

Bruno Zilberstein, Ulysses Ribeiro-Junior, Ivan Ceconello: critical analysis, review of the manuscript.

Conflicts of interest

Nothing to declare.

Research registration unique identifying number

researchregistry3414.

Guarantor

Marcus Fernando Kodama Pertille Ramos.
Ulysses Ribeiro-Júnior.

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