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Duodenal Fistula after Elective Gastrectomy for Malignant Disease

An Italian Retrospective Multicenter Study

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Abstract

Background Duodenal fistula (DF) after gastrectomy continues to be a life-threatening problem. We performed a retrospective multicenter study analyzing the characteristics of DF after elective gastrectomy for malignant disease.
Methods Three thousand seven hundred eighty-five patients who had undergone gastrectomy with duodenal stump in 11 Italian surgical units were analyzed.
Results Sixty-eight DFs occurred, with a median frequency of 1.6% and a mortality rate of 16%. Complications were mainly septic but fistulas or bleeding of surrounding organs accounted for about 30%. Reoperation was performed in 40% of patients. We observed a correlation between mortality and age (hazard ratio 1.09; 95% CI 1.00–1.20) and serum albumin (hazard ratio 0.90; 95% CI 0.83–0.99). The appearance of further complications was associated with reoperation ($P<0.001$) and death ($P=0.054$), while the preservation of oral feeding was related to DF healing ($P<0.001$).
Conclusions This paper represents the largest series ever published on DF and shows that its features have changed in the last 20 years. DF alone no longer leads to death and some complications observed in the past have disappeared, while new ones are emerging. Nowadays, medical therapy is preferred and surgery is indicated only in cases of abdominal sepsis or bleeding.

Keywords Gastrectomy · Complications · Duodenal fistula

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Introduction

Duodenal fistula (DF) after gastrectomy has a low frequency, occurring in about 3% of cases, but continues to be a life-threatening problem with a high rate of complications and a very long period of hospitalization. Published studies dealing with postoperative DF were based on small series of patients; moreover, DFs were reported after different types of surgery for different causes and in many cases as an emergency, so the reported data are very heterogeneous and the clinical pictures are not comparable.[1–6] In fact, according to these data, the overall mortality ranges from 7% to 67%[1–3] and spontaneous fistula closure from 28% to 92%.[2,4,5]

Possible causes of postoperative DF include 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.

Patients affected by DF very often develop other complications, such as intraabdominal abscess, wound infection, necrosis or dehiscence, diffuse peritonitis, sepsis, malnutrition, fluid and electrolyte disturbances, dermatitis, acute cholecystitis, pancreatitis, abdominal bleeding, and pneumonia.[1]

Many surgical procedures have been proposed for the treatment of DF: from tube duodenostomy,[7] to repair with a rectus abdominis muscle flap,[8] from closure by a Roux-en-Y duodenojejunostomy[9] to pancreatoduodenectomy.[10]

Also percutaneous treatments are often used in the treatment of DF: abscess drainage; transhepatic biliary drainage;[11] and fistula obliteration by cyanoacrylate or prolamine.[12]

The management of DF remains controversial and is mainly based on the prevention or early detection and treatment of complications, as well as nutritional support by enteral nutrition (EN) or total parenteral nutrition (TPN) and use of somatostatin or its analogu octreotide.[13]

The aim of this paper is to report the characteristics of a homogeneous group of patients who developed DF after elective gastrectomy for malignant disease in an attempt to describe the natural history of this rare but fearful complication of gastric surgery.

Material and Methods

We performed a multicenter retrospective study involving 11 Italian surgical units. A diagnosis of DF was made on the basis of the presence of duodenal juice in the surgical drainage or its leakage through the abdominal wall, and confirmed by CT scan and/or fistulography. The frequency and characteristics of DF were analyzed after 3,785 elective gastrectomies with duodenal stump carried out from 1991 to 2006 for malignant diseases. The procedures included 1,613 total gastrectomies (TG) and 2,172 subtotal gastrectomies (SG). Surgical access was by laparotomy in most cases, with only 21 cases of laparoscopic or video-assisted gastrectomy. For each DF, we collected a series of clinical data regarding the patient and his/her outcome. All charts filled out at the different centers were validated by the main investigator (L.C.). In Table 1 the characteristics of the participating centers are reported. In our search for factors predicting the outcome of DF, we analyzed correlations with morbidity and mortality.

Statistical Analysis

Categorical data are presented as absolute frequency and percent proportion; their confidence intervals were computed by the exact method based on binomial distribution. Continuous data are presented as median and range because the corresponding variables were asymmetrically distributed. Parametric and nonparametric tests were used as appropriate in order to evaluate the significance of differences in the distribution of the variables (t test, Fisher's exact test, Wilcoxon's rank-sum test, and Pearson's chi-square). Survival analysis was carried out according to the Kaplan–Meier method and the Cox regression model to evaluate prognostic factors. The heterogeneity test was used to explore differences in DF incidence among centers.

Results

Out of 3,785 gastrectomies for malignant disease a total of 68 DFs were observed (1.8%); histology was carcinomas in 66 patients, lymphoma in one, and GIST in one. The median age of the patients was 66 years (range 42–83 years). In Table 2, the frequency of DF for a single center is reported. The variability in the frequency of DF between centers

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Table 1 Characteristics of the Centers Participating in the Study

Centers	Gastrectomies performed	TG	TG Roux	TG Omega loop	SG	SG Roux	SG BII
1	905	355	355	0	550	11	539
2	89	55	55	0	34	28	6
3	675	358	345	13	317	7	310
4	108	93	93	0	15	0	15
5	163	59	55	4	104	104	0
6	287	111	111	0	176	176	0
7	236	81	76	5	155	42	113
8	250	140	140	0	110	0	110
9	417	137	137	0	280	3	277
10	346	115	115	0	231	172	59
11	309	109	109	0	200	200	0
Total	**3,785**	**1,613**	**1,591**	**22**	**2,172**	**743**	**1,429**
Median	287	111	111	0	176	28	59
Range	89–905	55–358	55–355	0–13	15–550	0–200	0–539

TG total gastrectomy, *SG* subtotal gastrectomy, *Roux* Roux-en-Y reconstruction, *BII* Billroth II reconstruction

(Table 2) was statistically significant ($P<0.001$), but no correlation was found among the 11 centers between DF frequency and total number of gastrectomies performed.

The extent of gastrectomy did not affect the frequency of DF (1.7% after TG and 1.9% after SG). Concerning the method of reconstruction of the digestive tract after TG, we did not observe any difference in DF frequency between patients with Roux-en-Y or omega loop reconstructions, but SG patients with Roux-en-Y reconstruction had a higher frequency of DF than patients with Billroth II reconstruction (3.4% versus 1.1%, respectively; $P<0.001$). The median time of DF onset was on postoperative day 7 (range 0–22), and the median daily output was 290 mL

(range 40–2,200 mL). The DF healing rate was 84% (57 patients) after a median of 19 days (range 1–1,035 days). In our series DF onset and daily output did not affect DF time to healing or mortality. The overall mortality rate was 16% (11 patients) due to multiple organ failure in ten patients and in one case to pulmonary embolism, after a median of 18 days (range 4–60 days). Complications occurred in 51 patients (75%; Table 3), most of them were septic, but more than 30% of patients developed a new fistula, acute inflammation or bleeding at surrounding abdominal organs.

Reoperation was performed in 27 patients (40%) for abdominal sepsis in all but one, in whom the indication was

Table 2 Duodenal Fistulas

Centers	Gastrectomies performed	Duodenal fistulas	Frequency of duodenal fistulas (%)
1	905	4	0.4
2	89	2	2.2
3	675	7	1.0
4	108	1	0.9
5	163	5	3.1
6	287	17	5.9
7	236	15	6.3
8	250	4	1.6
9	417	8	1.9
10	346	1	0.3
11	309	4	1.3
Total	3,785	68	
Median	287	4	1.6
Range	89–905	1–17	0.3–6.3

Table 3 Complications in Patients with Duodenal Fistula

Complications	51/68 patients (75%)
Abdominal abscess	26 (38%)
Wound infection	19 (28%)
Sepsis	18 (26%)
Central line infection	10 (15%)
Pneumonia	9 (13%)
Acute renal failure	7 (10%)
Colonic fistula	5 (7%)
Pancreatic fistula	4 (6%)
Acute pancreatitis	4 (6%)
Intraabdominal bleeding	4 (6%)
Abdominal wall necrosis	3 (4%)
Pulmonary embolism	2 (3%)
Jejunal fistula	2 (3%)
Roux-en-Y syndrome	2 (3%)
Esophagojejunal fistula	2 (3%)
Heart failure	2 (3%)
Others	11 (16%)

Others cholecystitis, septic arthritis, deep venous thrombophlebitis, bilateral pleuritis, dermatitis, fascitis, cerebral ischemia, urinary tract infection, respiratory failure, bowel occlusion, and hypertensive attacks

failure to DF heal. Surgery was performed once, twice, and three times in 18, six, and three patients, respectively; and it consisted of peritoneal drainage, duodenal suture, and tube duodenostomy; a Roux-en-Y duodenojejunostomy was performed in only one patient. In Table 4 are also reported the frequency and types of percutaneous treatment and medical therapy; among them nutritional support was the main therapy, especially TPN. No TPN-related death occurred in the 51 patients receiving this type of nutrition, but the rate of related complications was high (20%), including ten central line infections; thrombosis or liver failure, on the other hand, were never reported. Twenty patients (29%) received EN, but only three as the sole nutrition, while 12 in addition received TPN, two oral feeding, and three both. Thirty-three patients (48%) maintained oral feeding despite the presence of DF: 19 as the only source of food, two combined with EN, nine with TPN, and three with both. Among the 33 patients maintaining oral feeding, only one death occurred (3%) versus ten deaths among 35 fasting patients (29%; $P<0.001$). Higher daily DF output was often treated by octreotide or somatostatin; the median output in treated patients was 375 mL (range 80–1,500 mL) versus 180 mL (40–220 mL) in untreated patients, but this difference was not statistically significant.

Treatment with octreotide or somatostatin did not affect outcome, time of DF healing, or development of other complications.

About one third of patients (23 cases) were malnourished with a weight loss greater than 10%, and or a serum albumin level <35 g/L (21 cases), and a lymphocyte count <1,500/mL (11 cases). Over two thirds of patients (52) had comorbidities mainly involving the cardiovascular system. Two patients had received preoperative chemotherapy and 12 (17.5%) had duodenal resection line involvement.

In an attempt to detect prognostic factors for DF outcome, we analyzed the influence on mortality of all the variables reported in Tables 1, 2, 3, and 4, nutritional status, and associated comorbidities. Using univariate Cox regression, we found a correlation between mortality and age: the median age of deceased patients was 71 years, range 60–83, versus 64.5 years, range 42–81, for surviving patients; $P=0.017$; hazard ratio per 1 year increase in age is 1.09, 95% CI 1.00–1.20, $P=0.036$. Correlations with mortality were also found for serum albumin level (hazard ratio per 1 g/L increase in serum albumin level is 0.90; 95% CI 0.83–0.99, $P=0.040$), development of further complications, and the need for surgery or TPN in DF management.

In the 11 patients who died, the median number of further complications was 3.5 (range 1–6), and only two patients had only one complication (pulmonary embolism and sepsis, respectively). While in the 57 patients who fully recovered from DF, the median number of further complications was 1.5 (range 0–4), and 17 patients had none at all. No patient without further complications died, while the presence of further complications caused death in over 20% of patients (11/51; $P=0.054$). The recovery time was shorter in patients without complications (median 21 days, range 7–65 days) than in those with complications (median 31 days, range 1–1,035 days), but the difference was not statistically significant.

Table 4 Therapies and Procedures for 68 Duodenal Fistulas

Surgery	27 (39.7%)
One operation	18 (26.5%)
Two operations	6 (8.8%)
Three operations	3 (4.4%)
Percutaneous treatments	
Percutaneous abdominal drainage	15 (22%)
PTBD	4 (6%)
Percutaneous duodenostomy	2 (3%)
Medical therapies	
TPN	51 (75%)
EN	20 (29.4%)
Somatostatin	15 (22%)
Octreotide	14 (20.6%)
Gabexate mesylate	1 (1.5%)

PTBD percutaneous transhepatic biliary drainage, *TPN* total parenteral nutrition, *EN* enteral nutrition

The need for repeat surgery was related to the development of further complications ($P<0.001$), and prolonged the recovery time to 58 days (range 1–1,035 days), versus 25 days (range 7–65 days) ($P=0.004$) in no surgical patients. Furthermore, eight of the 11 (73%) patients who died had undergone repeat surgery versus 19 of the 57 (33%) survivors ($P=0.020$).

The need for intensive management in seriously ill patients was demonstrated also by the use of TPN; in fact, all patients who subsequently died received TPN versus 70% (40) of surviving patients ($P=0.054$).

Discussion

The series of DF after gastrectomy reported in the literature are small and not homogeneous,[1–5] so an accurate description of the natural history and management of this complication is still lacking. In order to reduce the background variability and collect a large number of DFs, the present retrospective multicenter study was performed in 11 Italian centers and was focused on elective gastrectomies for malignancies. Hence the largest series published up to now was collected. Out of 3,785 gastrectomies for malignant diseases 68 DF (1.8%; median 1.6%; range 0.3–6.3) were recorded, confirming data of frequency reported in literature.[1–7] Regarding the causes of DF, it seems that duodenal resection line involvement facilitates the development of this complication. Resection line involvement was reported in the literature in about 1–10% of patients,[14,15] and is generally considered as a cause of high surgical morbidity;[16] in our series of DF patients its frequency was 17.5%.

Concerning technical causes, some authors maintain that DF after SG is more frequently associated with Billroth II reconstruction due to difficult emptying of the afferent jejunal loop.[17] Our data do not support this hypothesis and even suggest the opposite, i.e., that the risk of DF is higher after Roux-en-Y than after Billroth II reconstruction (3.4% vs. 1.1%, respectively). This observation must be interpreted with caution because almost all the participating centers performed only one type of reconstruction without an internal control submitted to the other technique (Table 1).

DF onset is usually delayed (median postoperative day 7), but the variability is very large (range 0–22 days); the occurrence of this complication must therefore be suspected also in outpatients who have recently undergone a gastrectomy if fever or right abdominal pain is present.

In contrast to what was previously reported by other authors,[1] daily fistula output did not affect DF duration or mortality. In our series, DF with abundant output was commonly treated with octreotide or somatostatin but, in contrast with other experiences on other gastrointestinal fistulas,[13] its use did not affect DF closure time or outcome; so we can conclude that this therapy is not indicated for DF.

Many factors can influence the mortality rates, and our study confirms reports by other authors that age, a low serum albumin level, complications, and multiple reoperations are correlated with death.[1,4,7]

The treatment of patients with DF should be aimed at facilitating spontaneous fistula closure. Nowadays, the presence of DF alone no longer leads to death, but the problem is the development of new complications. Since the risk of death is linked to the number of complications arising, particularly sepsis, maximum effort to prevent and promptly treat septic complications is mandatory.[6] Only if sepsis has been adequately managed can spontaneous closure of a fistula take place.[4]

To treat DF and prevent complications, several surgical procedures have been proposed: tube duodenostomy alone or coupled with continuous intraluminal infusion and aspiration,[7] fistula repair with a rectus abdominis muscle flap,[8] or Roux-en-Y duodenojejunostomy to close a large duodenal defect not controlled for more than 6 weeks;[9] occasionally, pancreaticoduodenectomy may be necessary and can be lifesaving.[10] In the present series, Roux-en-Y duodenojejunostomy was performed only in one patient; the other 26 patients were submitted to drainage of peritoneal abscess, duodenal suture, and tube duodenostomy with a 30% of recurrence rate of abdominal sepsis with the need of another surgical procedure. Therefore, surgery is indicated only if necessary to drain an abscess or close a DF that is very large, persistent or otherwise difficult to manage. In the surgical treatment of DFs the main questions are the choice of operative versus non-operative treatment and the timing and type of surgery.[18] It is advisable to avoid surgery on fistulas occurring within 10 days to 6 weeks of the initial operation, although an undrainable abscess, bacteremia, peritonitis, and intestinal bleeding always require emergency surgery. Careful attention must be paid to the choice and management of abdominal drainage in order to avoid its possible migration into the fistula, which hinders spontaneous closure,[19] and to prevent bleeding and formation of new fistulas in neighboring abdominal organs. In the present study, we observed an approximately 20% frequency of new fistulas. Such a high frequency had not been reported previously and is perhaps attributable to the fact that better patient management leads to longer survival associated with a long recovery time; in other words, while healing DF, patients may be at risk of developing new fistulas.

Rossi et al. suggested prophylactic cholecystectomy in cases of surgery for DF because of the high frequency of cholecystitis.[1] Our results do not justify this management, as only one case of cholecystitis was observed in our series.

In the past, many authors suggested nasogastric suction and withholding oral intake,[20] but more recent data demonstrated a better outcome in patients in whom oral intake was maintained.[21] In our series, about half of the patients were able to maintain an oral diet, plus or less combined with EN and/or TPN, and their outcome was better than that of fasting patients, confirming that nasogastric suction and bowel rest are indicated only in the presence of diffuse peritonitis and ileus, whereas oral feeding should always be encouraged. Furthermore, the low rate of cholecystitis in our study might be linked to the preservation of oral feeding.

Several complications of DF commonly reported in the past, such as water and electrolyte loss, acid/base imbalance, and dermatitis, were not observed in our study, probably owing to improved techniques and patient care.

The role of TPN in the treatment of DF is well established, and TPN is routinely used in all cases of high-output and many cases of low-output fistulas. EN could be a good and cheap alternative to TPN, but data reported in the literature show that less than 50% of DF patients tolerate adequate amounts of EN.[5] In our series, about 30% of the patients received EN, but only 25% of them did not need any other nutritional support. Prolonged starvation without careful nutritional support results in severe malnutrition, sometimes leading to superior mesenteric artery syndrome with duodenal obstruction inhibiting DF closure.[20]

Conclusions

In conclusion, our study shows that the features of DF have partially changed with respect to the latest data reported in the literature, which date back about 30 years. Some new characteristics have been acquired and others lost. In general, we can confirm that DF is a rare but serious complication of gastrectomy with a high mortality rate, and improved surgical techniques or the use of staplers have not decreased its frequency; however, newly available therapies such as nutritional support and percutaneous drainage have dramatically reduced the mortality (from 40% to 16% since 1980), and today the presence of DF alone no longer causes death. In fact, some complications, such as fluid, electrolyte, and acid/base imbalance or dermatitis, typically observed in patients with DF in the past, no longer occur. Also the incidence of cholecystitis has decreased, probably because patients are encouraged to eat or have EN, and the practice of fasting or nasogastric suction has been abandoned. Moreover, we demonstrated with this study that oral feeding is related to DF healing.

The onset of DF varies greatly in terms of timing, output, and clinical presentation, and surgeons must always beware the possibility of a DF after gastrectomy because of the high risk associated with a delay in DF diagnosis coupled with the appearance of other complications. The main complication remains sepsis, often requiring repeated surgery and still burdened by a very high mortality. Mortality is highest in the first weeks (median 18 days, range 4–60 days), despite a very long healing time with recurrences also after several months, necessitating the maximum medical effort at an early stage.

Nowadays, medical therapy is preferred to surgery, the latter being indicated only for abdominal sepsis, bleeding, or fistulas in neighboring organs.

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