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ORIGINAL ARTICLE

Duodenal stump fistula after gastric surgery for malignancies: a retrospective analysis of risk factors in a single centre experience

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Abstract
Background Duodenal stump fistula (DSF) is the most severe surgical complication after gastrectomy. This study was designed to assess the incidence, to observe the consequences, and to identify the risk factors associated with DSF after gastrectomy.
Methods All procedures involving total or sub-total gastrectomy for cancer, performed between January 1987 and June 2012 in a single institution, were prospectively entered into a computerized database. Risk factors analysis was performed between DSF patients, patients with complete uneventful postoperative course and patients with other major surgical complications.
Results Over this 25 years period, 1287 gastrectomies were performed. DSF was present in 32 cases (2.5 %). Mean post-operative onset was 6.6 days. 19 patients were treated conservatively and 13 surgically. Mean DSF healing time was 31.2 and 45.2 days in the two groups, respectively. Mortality was registered in 3 cases (9.37 %), due to septic shock (2 cases) and bleeding (1 case). In monovariate analysis, heart disease ($p < 0.001$), pre-operative lymphocytes number ($p = 0.003$) and absence of manual reinforcement over duodenal stump ($p < 0.001$) were found to be DSF-specific risk factors, whereas liver cirrhosis ($p = 0.002$), pre-operative albumin levels ($p < 0.001$) and blood losses ($p = 0.002$) were found to be non-DSF-specific risk factors. In multivariate analysis heart disease (OR 5.18; $p < 0.001$), liver cirrhosis (OR 13.2; $p < 0.001$), bio-humoral nutritional status impairment (OR 2.29; $p = 0.05$), blood losses >300 mL (OR 4.47; $p = 0.001$) and absence of manual reinforcement over duodenal stump (OR 30.47; $p < 0.001$) were found to be independent risk factors for DSF development.
Conclusions Duodenal stump fistula still remains a life-threatening complication after gastric surgery. Co-morbidity factors, nutritional status impairment and surgical technical difficulties should be considered as important risk factors in developing this awful complication.

Keywords Gastric cancer · Surgery · Duodenal stump fistula · Gastrectomy · Risk factors

Introduction

Duodenal stump fistula (DSF) is one of the most frightful complications after total or sub-total gastrectomy. Even if its incidence reported in Literature is low, it is correlated with high post-operative morbidity and mortality rate, and prolonged post-operative period of hospitalization.

In fact, in a recent Italian multi-centric retrospective analysis [1] of 3785 cases, DSF was observed in only 68 cases (1.8 %), but DSF-correlated morbidity rate was 75 % and mortality rate was 16 %; moreover, 40 % of patients needed 1 or more re-operations and overall median healing time was 19 days (range 1–1035 days). Most common reported complications were intra-abdominal abscess, wound infection, necrosis or dehiscence, diffuse peritonitis, sepsis, malnutrition, fluid and electrolytes disturbances, dermatitis, acute cholecystitis, pancreatitis, abdominal bleeding, and pneumonia [2].

Therefore, DSF is considered one of the dangerous and life-threatening events in the post-operative course after gastrectomy.

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In the years, different strategies have been proposed for DSF treatment: from surgical procedures (such as tube duodenostomy [3, 4], repair with a rectus abdominis muscle flap [5], closure by a Roux-en-Y duodenojejunostomy [6, 7] or pancreatoduodenectomy [8]) to percutaneous approach, (such as abscess drainage, transhepatic biliary drainage [9, 10], fistuloscopy [11] and fistula obliteration by cyanoacrylate or prolamine [12], or, more recently, percutaneous transhepatic biliary drainage and occlusion balloon [13]).

Furthermore, administration of enteral and/or total parenteral nutrition according to nutritional guide-lines [14, 15], allows a faster fistula healing and a lower morbidity rate [16–19]. Finally, the use of somatostatin and its analogues are proved to reduce fistula output and to shorten healing times [20, 21].

Concerning DSF pathogenesis, many possible causes of post-operative DSF have been proposed in the past, such as 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; however, few studies are reported in literature about that, a no risk-factors analysis has ever been conducted.

Therefore, the aim of this study is to identify the risk-factors associated with post-operative DSF development, by retrospectively analyzing the data registered from our experience, in order to better comprehend and, if possible, avoid such a fearful complication after gastric surgery.

Materials and methods

This study was approved by the Institutional Review Board at San Raffaele Scientific Institute.

We retrospectively analyzed our case record from 1987 to present. Only patients underwent elective total or sub-total gastrectomy, with excluded duodenum, for malignant diseases were included in this study.

Duodenal stump fistula was defined as the presence of duodenal juice in surgical drainage(s), or its leakage through the abdominal wall, irrespective of clinical impact or symptoms, and confirmed by CT scan and/or fistulography.

DSF patients group was compared with 2 control groups of patients:

a. A group of 506 patients underwent the same surgical procedures in the same time span, with complete uneventful post-operative course (UPC), defined as the complete absence of both medical and surgical post-operative complications. We decide to use UPC patients as control group in order to minimize any statistical bias related to other post-operative complications.
b. A group of 268 patients that presented any other major surgical complications after gastric surgery (OSC) different from duodenal stump fistula, in order to verify if analyzed parameters could be considered as specific risk factors for DSF development or if they are generic risk factors for any surgical complications after gastric surgery.

Clinical parameters collected and analyzed were divided in three categories: demographic characteristics, co-morbidity factors and surgical variables.

Demographical characteristics analyzed were age, sex, type of disease, disease stage (only for adenocarcinoma), tumor site, ASA score and BMI.

Co-morbidity factors analyzed were: hypertension, diabetes mellitus, chronic renal failure, heart disease, COPD, liver cirrhosis, pre-operative weight loss >10 % and >20 % of usual body weight, pre-operative serum albumin level and pre-operative lymphocytes number.

Surgical variables analyzed were: intra-operative blood losses, duration of surgery, distal margin involvement by cancer, surgical access, type of gastrectomy, type of reconstruction, level of lymphadenectomy, duodenal stump closure (manual/mechanical), type of stapler device used for duodenal closure, confection of manual reinforcement over duodenal stump.

Categorical data are presented as percent proportion; continuous data are presented as mean and standard deviation. Groups were compared simultaneously using one-way ANOVA followed by post hoc comparisons (Tukey's test) or Pearson's χ^2 test, depending on the nature of the data. For multiple comparisons of categorical variables, Bonferroni's adjustment was used, in order to prevent multiple testing bias. For incomplete data, a dummy variable classified as "missing" was included in the analysis to allow for inclusion of all available cases. All variables with $p < 0.05$ in the univariate analysis between DSF and UPC group were subsequently included in a multivariate binary logistic regression model, in order to determine risk factors associated with DSF. Analyses were performed by the use SPSS software for Microsoft Windows 22.0th Edition. Variables were considered significantly different if two-tailed p value was <0.05.

Results

From 1987 to present, 1287 patients underwent total or sub-total gastrectomy with excluded duodenum for malignant disease. Demographic characteristics of the patients are reported in Table 1.

Table 1 Demographic characteristic in patients with duodenal stump fistula underwent total or sub-total gastrectomy

Variable	N. of patients (percent) or mean ± standard deviation
Age	69.5 ± 10.8 years
Sex	M: 22 (69 %)
	F: 10 (31 %)
ASA score	ASA 0: 23 %
	ASA 1: 7 %
	ASA 2: 47 %
	ASA 3: 23 %
	ASA 4: 0 %
BMI	24.9 ± 3.5

Duodenal stump fistula was observed in 32 patients (2.5 %). Mean age of patients was 69.5 ± 10.8 years, male/female ratio 2.2. In all 32 cases, patients underwent surgery for gastric adenocarcinoma: intestinal type in 19 cases (59 %), infiltrating with signet-ring cells type in 10 cases (32 %), mucinous type in 1 case (3 %) and both infiltrating and mucinous type in 2 cases (6 %).

According to UICC TNM Classification of Malignant tumors 7th Edition, stage I was present in 22 % of cases, stage II was present in 28 % of cases, stage III was present in 28 % of cases and stage IV was present in 22 % of cases. None of 32 DSF patients underwent pre-operative neo-adjuvant chemotherapy, despite 25 cases of advanced neoplasms. In fact, according to recent developments in gastric cancer oncological management [22], in our Institute nowadays all advanced cases undergo peri-operative chemotherapy; however, all DSF cases recorded in our database predate the introduction on neo-adjuvant schemes. Duodenal resection margin involved by the tumor (R1) was present in 6 % of patients. All oncological characteristics are reported in Table 2.

Mean post-operative DSF onset day was 6.6 ± 4.7 days and mean fistula maximum daily output was 246 ± 266 mL. Nineteen patients were treated conservatively and 13 patients were treated with 1 or more surgical revision(s). Conservative treatments consisted in percutaneous abdominal abscess drainage/trans-shepatic biliary drainage, total parenteral/enteral nutrition and/or somatostatine/octreotide administration. Surgical treatments consisted in direct stump closure (with or without external duodenal drainage) in 4 cases, duodenal stump resection and closure (with or without external bile diversion via trans-cystic drainage) in 6 cases, external duodenal drainage in 2 cases and surgical placement of abdominal drainages in 1 case (see Table 3).

Table 2 Oncological characteristics in patients with duodenal stump fistula underwent total or sub-total gastrectomy

Oncological parameters	N. of patients (%)
Histological type	
Adenocarcinoma	32 (100)
Intestinal type	19 (59)
Infiltrating with signet-ring cell type	10 (32)
Mixed type (mucinous and infiltrating)	2 (6)
Mucinous type	1 (3)
Disease stage	
Stage I	7 (22)
Stage Ia	4 (13)
Stage Ib	3 (9)
Stage II	9 (28)
Stage IIa	3 (9)
Stage IIb	6 (19)
Stage III	9 (28)
Stage IIIa	5 (16)
Stage IIIb	2 (6)
Stage IIIc	2 (6)
Stage IV	7 (22)
Tumor site	
Proximal	7 (23)
Middle	4 (11)
Distal	21 (65)
Early and Advanced gastric cancer	
Early gastric cancer	7 (22)
Advanced gastric cancer	25 (78)
Resection margin status	
R0	30 (94)
R1	2 (6)

Mean DSF healing time was 31.2 ± 19.7 days in conservatively-treated patients, and 45.2 ± 57.4 days in surgical-treated patients. Overall DSF-correlated morbidity was 84 %. Most common DSF-correlated complications were sepsis (75 %), abdominal abscess (69 %), pneumonia (34 %), wound infection (28 %) and bleeding (22 %) (see Table 4). Mortality was registered in 3 cases (9.37 %), due to septic shock in 2 cases and bleeding in 1 case. All fatal outcomes occurred in the surgical-treated group.

For what concern DSF incidence over the 25 years analyzed in this study, 3 cases were observed between 1987 and 1991 (2.3 %), 6 cases between 1992 and 1996 (2.1 %), 4 cases between 1997 and 2001 (1.2 %), 12 cases between 2002 and 2006 (5.1 %) and 7 cases from 2007 to present (2.1 %) (see Fig. 1). Incidence of DSF in the period 2002–2006 was found to be significantly higher than in the other periods observed ($p = 0.049$).

Table 3 Comparison of conservative and surgical treatment for patients with duodenal stump fistula, and post-operative outcome

	Conservative treatment (19 pts.)	Surgical treatment (13 pts.)
Treatment	Observation: 11 pts.	Direct stump closure: 4 pts.
	PTBD: 3 pts.	Stump resection and closure: 3 pts.
	PAD: 5 pts.	External duodenal drainage: 2 pts.
		Surgical abdominal drainages: 1 pt.
Drugs		
Somatostatine	1 pt.	0 pts.
Octreotide	10 pts.	3 pts.
Nutrition		
TPN	13 pts.	13 pts.
EN	11 pts.	8 pts.
Per os	8 pts.	0 pts.
Outcome		
Healing	19 pts.	10 pts.
Death	0 pts.	3 pts.
		Cause of death
		Septic shock 2 pts.
		Bleeding 1 pt.
Mean healing time	31.2 ± 19.7 days	45.2 ± 57.4 days

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

Table 4 Post-operative complications correlated with duodenal stump fistula in patients underwent total or sub-total gastrectomy

Type of complication in patients with DSF	N. of patients (%)
Sepsis	24 (75)
Abdominal abscess	22 (69)
Pneumonia	11 (34)
Wound infection	9 (28)
Bleeding	7 (22)
Acute renal failure	5 (16)
Colonic fistula	4 (12)
Gastro-jejunal anastomosis leakage	2 (6)
Central line infection	2 (6)
Pneumothorax	2 (6)
Pulmonary embolism	1 (3)
Anastomotic stenosis	1 (3)
Abdominal wall cellulitis	1 (3)
Acute urinary retention	1 (3)
Acute liver failure	1 (3)
Cholecystitis	1 (3)
Urinary tract infection	1 (3)
Myocardial infarction	1 (3)
Respiratory failure	1 (3)
Overall	27 (84)

Demographic and oncological characteristics univariate analysis

Results from comparison of demographic and oncological characteristics are reported in Table 5. In particular, no significant difference was found between the three groups concerning age, sex, type of disease, adenocarcinoma disease stage, tumor site, ASA score and BMI.

Co-morbidity factors univariate analysis

Comparison for single co-morbidity factors are reported in Table 6 and depicted in Fig. 2.

Heart disease was found present in 34 % of patients who developed DSF in post-operative course, whereas it was present in only 10 % of patients with UPC and in 11 % of patients with other major surgical complications, with a significant difference between the three groups ($p = 0.001$).In one-to-one analysis, heart disease was significantly higher in DSF group in comparison with both UPC and OSC groups ($p = 0.001$ and 0.004, respectively), whereas no difference was found between UPC and OSC groups. About 13 % of patients with DSF and 12 % of OSC patients presented liver cirrhosis at surgery time, whereas it was present in only 3 % of patients with UPC ($p = 0.002$).The incidence was significantly higher in both DSF and OSC groups in comparison with UPC group ($p = 0.022$ and 0.041, respectively); instead, no statistical difference was found between DSF and OSC groups.

For what concerns pre-operative albumin levels, there was a statistically significant difference between groups as determined by one-way ANOVA ($p < 0.001$). Post-hoc test revealed that albumin levels were statistically significantly lower in DSF (37.2 ± 3.2 g/L, $p = 0.028$) and OSC (36.8 ± 3.1 g/L, $p = 0.002$) group compared to UPC group (42.2 ± 3.1 g/L). There were no statistically significant differences between DSF and OSC groups. Moreover, incidence of patients with serum albumin <35 g/L was significantly higher in DSF (35 %) and OSC (33 %) groups, than in UPC group (19 %; $p = 0.035$).

Finally, a statistically significant difference between groups was found also in pre-operative lymphocytes number, as determined by one-way ANOVA ($p = 0.003$). Post-hoc test revealed that lymphocytes number was significantly lower in DSF group (1,940 ± 634.2/mm^3) compared to UPC (3,860.2 ± 2,787/mm^3, $p = 0.003$) and

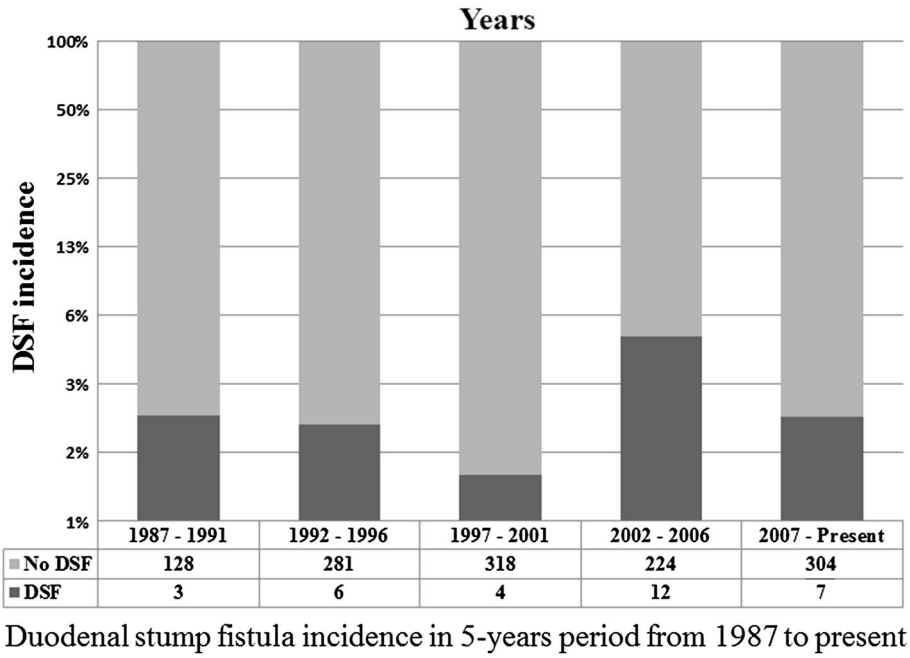

Fig. 1 Duodenal stump fistula incidence in 5-years periods from 1987 to present

Table 5 Univariate analysis of demographic and oncological characteristics between patients who developed DSF, patients with uneventful post-operative course and patients who developed other surgical complications different from DSF after total or sub-total gastrectomy

Variable	DSF patients (32 pts.)	UPC patients (506 pts.)	OSC patients (268 pts.)	Overall *p*	DSF-UPC *p*	DSF-OSC *p*	UPC-OSC *p*
Age	69.5 ± 10.8 years	66.4 ± 12.2 years	67.3 ± 11.6 years	0.23	0.29	0.54	1
Sex	M: 69 %	M: 52 %	M: 54 %	0.14	/	/	/
	F: 31 %	F: 48 %	F: 46 %				
Type of disease	ACA: 100 %	ACA: 95 %	ACA: 90 %	0.16	/	/	/
	Others: 0 %	Others: 5 %	Others: 10 %				
Disease stage (only for adenocarcinoma)	Stage I: 22 %	Stage I: 38 %	Stage I: 28 %	0.09	/	/	/
	Stage II: 28 %	Stage II: 18 %	Stage II: 19 %				
	Stage III: 28 %	Stage III: 22 %	Stage III: 33 %				
	Stage IV: 22 %	Stage IV: 22 %	Stage IV: 20 %				
Tumor site	Proximal: 23 %	Proximal:11 %	Proximal:13 %	0.15	/	/	/
	Middle: 11 %	Middle: 28 %	Middle: 29 %				
	Distal: 65 %	Distal: 61 %	Distal: 58 %				
ASA score	ASA 0: 23 %	ASA 0: 14 %	ASA 0: 18 %	0.23	/	/	/
	ASA 1: 7 %	ASA 1: 14 %	ASA 1: 18 %				
	ASA 2: 47 %	ASA 2: 57 %	ASA 2: 53 %				
	ASA 3: 23 %	ASA 3: 14 %	ASA 3: 10 %				
	ASA 4: 0 %	ASA 4: 1 %	ASA 4: 1 %				
BMI	24.9 ± 3.5	24.6 ± 4.3	25.2 ± 3.8	0.73	0.99	0.98	0.71

DSF Duodenal stump fistula patients, *UPC* uneventful post-operative course patients, *OSC* other surgical complications patients

OSC (3,458.3 ± 2,753/mm^3, $p = 0.002$) groups, whereas there were no statistically significant differences between DSF and OSC groups. Furthermore, incidence of patients with lymphocytes count <2,000/mm^3 was significantly higher in DSF group than in both UPC and OSC groups (62, 34, 33 %, respectively; $p = 0.006$).

Surgical variables univariate analysis

Results from comparison of surgical specific parameters are reported in Table 7 and depicted in Fig. 3.

One-way ANOVA revealed a significant difference between groups in intra-operative blood losses

Table 6 Univariate analysis of co-morbidities factors between patients who developed DSF, patients with uneventful post-operative course and patients who developed other surgical complications different from DSF after total or sub-total gastrectomy

Variable	DSF patients (32 pts.)	UPC patients (506 pts.)	OSC patients (268 pts.)	Overall *p*	DSF-UPC *p*	DSF-OSC *p*	UPC-OSC *p*
Hypertension	Presence: 41 %	Presence: 36 %	Presence: 31 %	0.54	/	/	/
	Absence: 59 %	Absence: 64 %	Absence: 69 %				
Diabetes mellitus	Presence: 6 %	Presence: 7 %	Presence: 9 %	0.79	/	/	/
	Absence: 94 %	Absence: 93 %	Absence: 91 %				
Chronic renal failure	Presence: 3 %	Presence: 3 %	Presence: 3 %	0.99	/	/	/
	Absence: 97 %	Absence: 97 %	Absence: 97 %				
Heart disease	Presence: 34 %	Presence: 10 %	Presence: 11 %	<0.001	0.001	0.004	0.52
	Absence: 64 %	Absence: 90 %	Absence: 89 %				
COPD	Presence: 3 %	Presence: 4 %	Presence: 4 %	0.98	/	/	/
	Absence: 97 %	Absence: 96 %	Absence: 96 %				
Liver cirrhosis	Presence: 13 %	Presence: 3 %	Presence: 12 %	0.002	0.022	0.75	0.041
	Absence: 87 %	Absence: 97 %	Absence: 88 %				
Pre-op. weight loss >10 % of usual body weight	Yes: 28 %	Yes: 19 %	Yes: 27 %	0.39	/	/	/
	No: 72 %	No: 81 %	No: 72 %				
Pre-op. weight loss >10 % of usual body weight	Yes: 6 %	Yes: 4 %	Yes: 6 %	0.63	/	/	/
	No: 94 %	No: 96 %	No: 94 %				
Pre-operative albumin	37.2 ± 3.2 g/L	42.2 ± 9.6 g/L	36.8 ± 3.1 g/L	<0.001	0.028	1	0.002
Pre-operative lymphocytes	1,940 ± 634.2/mm^3	3,860.2 ± 2,787/mm^3	3,458.3 ± 2,753/mm^3	0.003	0.003	0.002	0.47

DSF duodenal stump fistula patients, *UPC* uneventful post-operative course patients, *OSC* other surgical complications patients

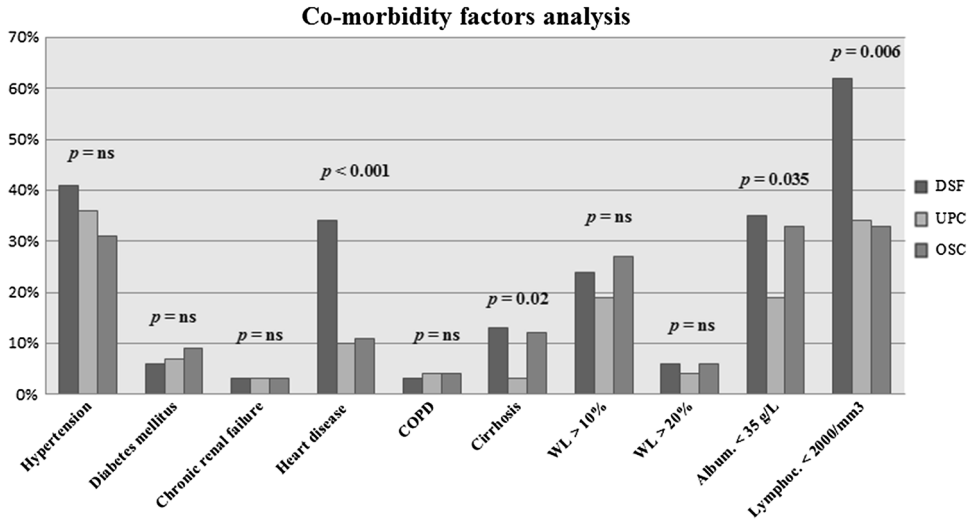

Fig. 2 Co-morbidity factors analysis

($p = 0.002$). Post-hoc analysis showed that blood losses were significantly higher in DSF (425.8 ± 425.2 mL, $p = 0.05$) and OSC (400.6 ± 359.0 mL, $p = 0.016$) groups compared to UPC group (301.5 ± 304.8 mL). There were no statistically significant differences between DSF and OSC groups. Moreover, incidence of patients with blood losses >300 mL was significantly higher in DSF (63 %) and OSC (51 %) groups than in UPC (37 %, $p = 0.01$), whereas no statistical significance was found between UPC and OSC groups.

For what concern the type of operation performed, the percentage of total gastrectomies was significantly higher in OSC group (42 %) compared to UPC group (29 %, $p < 0.001$), whereas no differences were found between DSF (34 %) and UPC groups, and between DSF and OSC groups.

The absence of manual reinforcement over duodenal stump closure was found to be significantly higher in DSF group (48 %) compared to both UPC (3 %, $p < 0.001$) and OSC (0 %, $p < 0.001$) groups, while

Table 7 Univariate analysis of surgical variables between patients who developed DSF, patients with uneventful post-operative course and patients who developed other surgical complications different from DSF after total or sub-total gastrectomy

Variable	DSF patients (32 pts.)	UPC patients (506 pts.)	OSC patients (268 pts.)	Overall *p*	DSF-UPC *p*	DSF-OSC *p*	UPC-OSC *p*
Intra-operative blood losses	425.8 ± 425.2 mL	301.5 ± 304.8 mL	400.6 ± 359.0 mL	0.002	0.05	1	0.016
Duration of surgery	241 ± 69.6 min	220.9 ± 76.4 min	239.1 ± 112.2 min	0.15	1	1	0.21
Distal margin involvement	Yes: 6 %	Yes: 3 %	Yes: 4 %	0.41	/	/	/
	No: 94 %	No: 96 %	No: 96 %				
Surgical access	LPT: 69 %	LPT: 82 %	LPT: 83 %	0.17	0.06	0.06	0.7
	LPS: 31 %	LPS: 18 %	LPS: 17 %				
Type of gastrectomy	Total: 34 %	Total: 29 %	Total: 42 %	<0.001	0.54	0.45	<0.001
	Subtotal: 66 %	Subtotal: 71 %	Subtotal: 58 %				
Type of reconstruction	B2: 12 %	B2: 9 %	B2: 8 %	0.65	/	/	/
	Roux: 88 %	Roux: 91 %	Roux: 92 %				
Lymphoadenectomy	D1: 26 %	D1: 26 %	D1: 24 %	0.96	/	/	/
	D2: 74 %	D2: 74 %	D2: 76 %				
Duodenal stump closure	Manual: 0 %	Manual: 2 %	Manual: 0 %	0.47	/	/	/
	Mechanical: 100 %	Mechanical: 98 %	Mechanical: 100 %				
Type of stapler device	GIA: 47 %	GIA: 46 %	GIA: 47 %	0.35	/	/	/
	TA: 22 %	TA: 36 %	TA: 34 %				
	EndoGIA: 31 %	EndoGIA: 18 %	EndoGIA: 19 %				
Manual reinforcement	Yes: 52 %	Yes: 97 %	Yes: 99 %	<0.001	<0.001	<0.001	0.2
	No: 48 %	No: 3 %	No: 0 %				

DSF duodenal stump fistula patients, *UPC* uneventful post-operative course patients, *OSC* other surgical complications patients

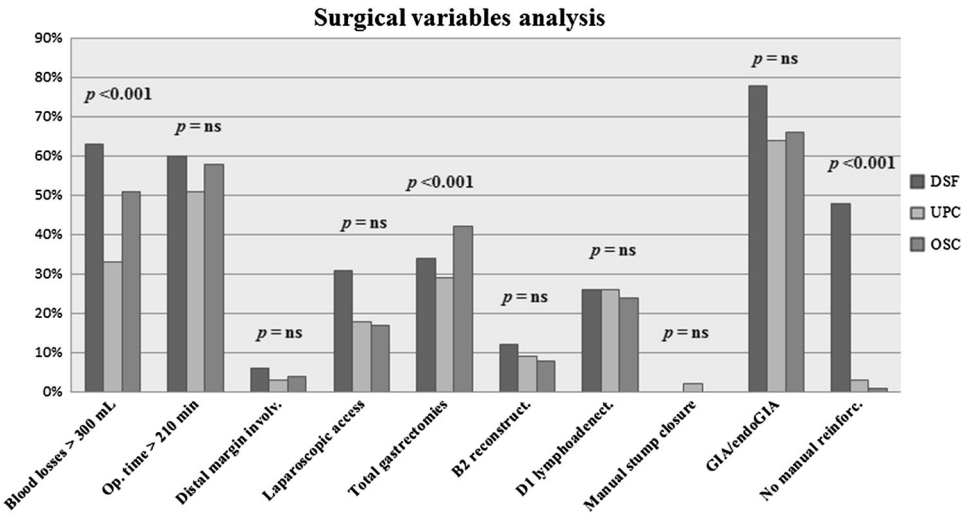

Fig. 3 Surgical variables analysis

no differences were found between UPC and OSC groups.

Finally, even if the overall comparison did not show a statistical significance ($p = 0.17$), we found that laparoscopic approach was more common in DSF group (31 %) compared to both UPC (18 %) and OSC (17 %) groups, with a p value close to statistical significance ($p = 0.06$) in both one-to-one analyses. No differences were found between UPC and OSC groups.

Multivariate logistic regression model analysis

All variables identified in monovarite analyses with $p \leq 0.05$ between DSF and UPC groups were subsequently

Table 8 Results of multivariate binary logistic regression analysis between patients who developed DSF and patients with uneventful post-operative course, for duodenal stump fistula risk factors identified in monovariate analysis with $p < 0.05$

Variable	DSF patients (32 pts.) (%)	UPC patients (506 pts.) (%)	Monovariate p value	OR	95 % CI	p
Heart disease			0.001			
Absence	64	90		Reference		
Presence	34	10		5.182	2.150–12.489	<0.001
Cirrhosis			0.022			
Absence	87	97		Reference		
Presence	13	3		13.203	3.201–54.453	<0.001
Bio-humoral nutrit. status			0.001			
Normal	34	64		Reference		
Impaired[a]	66	36		2.291	0.994–5.277	0.05
Intra-operative blood losses			0.001			
≤300 mL	37	67		Reference		
>300 mL	63	33		4.469	1.838–10.864	0.001
Manual reinforcement			<0.001			
Presence	52	97		Reference		
Absence	48	3		30.469	12.605–73.650	<0.001

DSF duodenal stump fistula patients, *UPC* uneventful post-operative course patients

[a] If pre-operative albumin level was <35 g/L and/or pre-operative lymphocytes number was <2,000/mm^3

included in multivariate analysis, in order to identify independent risks factor for DSF development.

In order to minimize the number of variables inserted in the multivariate equation, because of the small number of patients in DSF group (32), a new variable called "bio-humoral nutritional status" was created and used in logistic regression analysis. Patients were considered with a bio-humoral nutritional status impairment if pre-operative albumin level was <35 g/L and/or pre-operative lymphocytes number was <2,000/mm^3. A preliminary Fisher's exact test showed that the percentage of patients with bio-humoral nutritional status impairment was significantly higher in DSF group compared to UPC group (66 vs. 36 %, $p = 0.001$).

Presence of heart disease (OR 5.18) and liver cirrhosis (OR 13.2), bio-humoral nutritional status impairment (OR 2.29), blood losses >300 mL (OR 4.47) and absence of manual reinforcement over duodenal stump (OR 30.47) were all found to be independent risk factors for DSF development.

All variables entered into the multivariate logistic regression model, their odds ratios, 95 % confidence intervals, and p values are shown in Table 8.

Discussion

Duodenal stump fistula is an uncommon but extremely dangerous complication after gastric surgery for malignancy, and represents one of the most challenging and life-threatening post-operative events that the surgeon must deal with.

Unfortunately, few and not recent data are available in literature about that. In fact, published studies dealing with DFS are based on small series of patients and DFS are reported after different types of surgery and for different causes (in many cases as an emergency), so the reported data are very heterogeneous and the clinical pictures are not comparable [1, 2, 19, 23–25].

According to those data, DSF incidence was about 3 %, overall mortality ranges from 7 to 67 % [2, 23, 24], and spontaneous fistula closure ranges from 28 to 92 % [18, 23, 25].

In a recent multi-centric Italian study [1] DFS was found to be present in 1.8 % of 3,785 gastrectomies for malignant disease, with a mortality and morbidity rate of 16 and 75 %, respectively. DSF healing rate was 84 % (57 patients) after a median of 19 days (range 1–1,035 days). Exitus was 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).

In our series, DSF incidence was 2.5 %, overall mortality was 9.37 % and DSF-related morbidity was 84 %. Infections (pneumonia, abdominal abscess, surgical site) and sub-sequent sepsis were the most common morbidity and mortality causes observed. Also intra-abdominal bleeding was found to be an important and frequent complication.

Concerning DSF treatment, data available in literature suggest that, when possible, conservative approach should be preferred, along with artificial nutrition and somatostatin/octreotide administration. Surgery should be considered only when conservative management does not allow the control of the fistula and correlated complication (i.e. bleeding, sepsis, etc.…) [10].

Unfortunately, unlikely many studies concerning DSF management and treatment, no data are available in literature analyzing specific causes and risk factors for DSF onset; therefore, the results presented in this study cannot be compared with similar ones.

In our series, patients with DSF were basically older than other patients, even if this difference was not statistically significant. It is still controversial if considering age as an independent risk factor for post-operative morbidity and mortality in gastric cancer surgery. Hsu [26] found a higher postoperative morbidity and in-hospital mortality rates in patients ≥80 years old underwent gastric resections; similar results were found by Pisanu [27] in patients 75 years or older with an overall morbidity and mortality rate of 27.9 and 8.5 %, respectively. Moreover, age was found to correlate with a higher mortality in patients with post-operative DFS [1], and the mortality hazard ratio per 1 year increase in age is 1.09. On the other hand, in a retrospective analysis of more than 1110 cases [28], we found that age does not affect post-operative morbidity and mortality (27 and 7 % in patients ≥75 years old; 23 and 3 % in <75 years old, respectively), and thus cannot be considered as an independent risk factor. These findings are confirmed by the results of this study, in which age seems not to increase surgical complications different from DSF after gastric surgery. In any case, elder patients tend to present more co-morbidities than younger ones, and therefore any considerations about surgical risk should be taken considering the global conditions and performance status of the patients and not only their age.

In co-morbidity analysis, we found that a higher percentage of DSF patients presented heart diseases. In literature, few data are reported concerning correlation between cardiovascular diseases and complications after gastric surgery, or abdominal surgery in general. Cozzaglio [1] found that, in their series of 68 duodenal stump fistulas, over two-thirds of patients presented comorbidities mainly involving the cardiovascular system. Moreover, Jeong [29] found that patients with heart diseases presented a higher rate of both medical and surgical post-operative morbidities (history without medication OR 4.0; history with medication OR 6.7).

Furthermore, also liver cirrhosis was found to be an independent, but non-DSF specific, risk factor, as reported also in literature. In fact, in the previously mentioned study [29], Jeong reported that the presence of chronic liver disease effects the development of post-operative complications (chronic hepatitis OR 2.4; liver cirrhosis class A OR 8.4; liver cirrhosis class B OR 9.38). Similar results were found by Neef [30] in recent retrospective series of 138 non-hepatic abdominal operations in patients with liver cirrhosis: overall and surgical morbidity rate were 64 and 47 % even in elective surgery, therefore liver cirrhosis must be considered as a high impact risk factor for all kind of abdominal surgery.

Finally, nutritional status and, in particular, low pre-operative serum albumin level and lymphocytes number seems to correlate with an higher risk of post-operative DSF. It is well known, in fact, that nutritional status has a great impact over post-operative course and over development of both medical and surgical complications, and therefore, administration of enteral or parenteral nutrition is vital for those patients [31–33]. Wu [32] reported high morbidity and mortality rate after gastrectomy in undernourished patients (29.7 and 8.6 %, respectively). Moreover, Ryan [33] found that patients with >10 % weight loss had a significantly higher rate of complications and a significantly higher mortality rate than other patients. Weight loss at diagnosis was found to be the only predictive factor of post-operative complications (OR 3.1). In our study we did not find this kind of correlation with percentage of weight loss, but nutritional status in general and nutritional bio-humoral markers impairment are strictly correlated with surgical complication and, specifically, with DSF onset. In particular, low pre-operative lymphocytes number was found to be a specific DSF-correlated risk factor, whereas low pre-operative albumin level is associated with surgical complications in general. Concerning this topic, Hennessey [34], in a large multi-centric retrospective study, found that in patients who developed a surgical site infection had a lower preoperative serum albumin. Furthermore, hypoalbuminemia was an independent risk factor for surgical site infection development (RR 5.68), and albumin level <30 mg/dL was associated with an increased rate of deep vs. superficial SSI. In the study reported by Cozzaglio [1], about one-third of patients with DSF were malnourished, with a weight loss greater than 10 %, and or a serum albumin level <35 g/L, and a lymphocyte count <1,500/mL. Moreover, correlations with mortality were found for serum albumin level (hazard ratio per 1 g/L increase in serum albumin level is 0.90), development of further complications, and the need for surgery or TPN in DF management. Therefore, nutritional status impairment should be considered as one the most important factors, not only for DFS development, but also for its prognosis.

In surgical variables analysis, we found a statistically relevant non-specific correlation between intra-operative blood losses and DSF onset. Increased blood losses during surgery are referred to be a risk factor for complications in

general after abdominal surgery, not only for DSF [35]. In particular, for what concern gastric surgery, no studies were found in literature describing direct correlation between intra-operative blood losses and post-operative complications. Nevertheless, high blood losses [36, 37] and subsequent transfusions [38] are anyhow associated with a higher rate of recurrence, especially peritoneal, and therefore poor prognosis.

Resection line involvement was reported in literature in about 1–10 % of patients [39, 40] and is generally considered as a cause of high surgical morbidity [41]. In our series, despite of what is referred in literature, we found no correlation between resection line involvement and DSF development. However, it is important to underline that our resection line involvement rate was lower compared to 17.5 % reported in Cozzaglio's study [1].

Although several prospectic randomized clinical trials [42, 43] and meta-analyses [44–46] reported no statistical differences in post-operative complications incidence between LPS and open access, we found a near significant higher incidence of DSF in patients who underwent laparoscopic approach ($p = 0.06$). In fact, Kim [42] found no DSF incidence in both laparotomic and laparoscopic distal gastrectomy for early gastric cancer, even if more than 63 % of all patients had a Billroth 1 reconstruction, (therefore with no excluded duodenum). Also Usui [43], reported no statistical differences in post-operative surgical complication after laparoscopic vs. laparotomic total gastrectomy for early gastric cancer, but they do not but do not specify in more detail the type of complications occurred. More in-depth results are reported in Yacoub's meta-analysis [44], where no significant differences in DSF incidence were found in distal gastrectomy between open and laparoscopic approach for early gastric cancer. Also Martinez-Ramos, in his meta-analysis [45] on laparoscopic approach for advanced gastric cancer, found no differences in surgical complications too, but did not specify the type.

For what concern our results, two orders of explanations can be proposed: first, as was showed in per-period analysis, DSF incidence was significantly higher in the period 2002–2006, with a 5-years incidence of 5.1 % (more than twice that of other periods). This period corresponds with the beginning of the laparoscopic approach for the surgical treatment of gastric cancer in our Institute (that started in 2002). In fact, as we also reported in a recent article about our experience in laparoscopic gastric surgery [46], 80 % of DSF occurred after laparoscopic approach was registered in 2002–2006 period, significantly higher than in the subsequent 5-years period in comparison with DSF occurred after open approach ($p = 0.02$).

Therefore, the higher incidence of DSF in the laparoscopic approach should be interpreted as an effect of the normal learning curve in our experience, as it is also reported and well documented in several articles in literature [47–50].

Another possible explanation for the higher DSF in laparoscopic approach could be the relationship between laparoscopic approach and manual oversewing over duodenal stump. As we will discuss later, the absence of manual reinforcement was found to be a specific and independent risk factor for DSF onset. In the first years of our experience in laparoscopic gastrectomy, manual oversewing was not routinely performed by all surgeons, even when technically feasible. In fact, considering duodenal stump fistulas developed after laparoscopic surgery, almost 100 % of patients who did not have stump reinforcement was registered in the first 3 years of laparoscopic experience (2002–2005), a proportion significantly higher in comparison of those who had laparoscopic manual oversewing ($p = 0.035$).

No differences were found in DSF development concerning the type of gastrectomy (total vs. sub-total) and the method of reconstruction of the digestive tract after gastrectomy (Billroth II vs. Roux-en-Y). In literature reports, some authors maintain that DSF after sub-total gastrectomy is more frequently associated with Billroth II reconstruction due to difficult emptying of the afferent jejunal loop [51]. Different results were found in Cozzaglio's study [1], were they did not observe any difference in DSF frequency between patients with Roux-en-Y or omega loop reconstructions, but sub-total gastrectomy patients with Roux-en-Y reconstruction had a higher frequency of DSF than patients with Billroth II reconstruction (3.4 vs. 1.1 %, respectively). Nevertheless, these observations must be interpreted with caution because generally almost all the centers performed only one type of reconstruction, without an internal control submitted to the other technique.

Finally, for what concern duodenal stump closure, almost all the patients of our study have duodenal closed with mechanical devices, therefore no comparison could be made with direct manual closure, and no differences were found concerning the type of mechanical stapler used. Conversely, we found that the absence of manual reinforcement over duodenal stump closure is highly and specifically associated with the risk of DSF development. Reasons for which manual oversewing over duodenal stump closure was not performed are different from case to case, but mostly because of lack of sufficient free margins after extended ultra-pyloric resection or for difficult suture making in laparoscopic approach. In fact, among all the patients without manual oversewing who developed duodenal stump fistula, 60 % had distal located cancer, and none of them had distal margin involvement. Therefore, the necessity of an extended ultra-pyloric resection for achieving free resection margins, and the subsequent absence of free margin for oversewing confection, could be

considered in those cases the real risk factor for DSF onset. Moreover, as it was already been discussed previously, in laparoscopic procedures performed in the early years of experience in this field, manual reinforcement was not routinely performed, even when no technical difficulties were present. So far, no data available in literature about the correlation between the type of stapler device used and the risk of DFS development, nor about the necessity of manual reinforcement confection over duodenal closure as an additional measure for DSF prevention. Shao [52], in a retrospective study involving more than 2000 cases, found that in patients with manual purse-string closure, DFS incidence rate was significantly lower than in patients treated with the other types of closure. Moreover, surgical costs in direct manual closure were found to be significantly lower than in case of mechanical stapler employment, and operative time in two layers manual closure was significantly higher than in the other two groups.

Conclusions

Duodenal stump fistula still remains one of the most challenging and life-threatening complications after total and sub-total gastrectomy for gastric cancer. Early detection and conservative approach, along with nutritional management and somatostatin/octreotide administration, is the treatment of choice in most cases and allow a complete healing within 1 month from onset. Therefore, surgery should be reserved only for those cases in which conservative management does not allow the complete control of DFS-related complications (e.g. sepsis, bleeding or bowel perforation).

Co-morbidity factors, such as heart disease and liver cirrhosis, nutritional status impairment and technical difficulties during surgery (e.g. high blood losses or the impossibility of manual reinforcement confection over duodenal stump) seems to be correlated with DSF development and, thus, should be considered as significant risk factors.

Retrospective data from this study should be confirmed by larger, prospective and multi-centric analyses.

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Conflict of interest The authors declare no conflicts of interests.

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