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Challenging dogmas in pancreatic surgery: biliary drainage, outcome and beyond

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Publication date
2012

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Citation for published version (APA):

van der Gaag, N. A. (2012). *Challenging dogmas in pancreatic surgery: biliary drainage, outcome and beyond*. [Thesis, fully internal, Universiteit van Amsterdam].

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**Consensus
Definitions of
Complications
in Pancreatic
Surgery;
Comprehensive
Evaluation and
Future Prospects**



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ABSTRACT

Background

To enhance transparency in outcome registration the International Study Group of Pancreatic Surgery (ISGPS) has initiated consensus definitions and severity grading. In a large cohort we evaluated ISGPS definitions by comparison with our former system and investigated the grading in relation to relevant outcome variables.

Methods

Previous used definitions of complications and ISGPS definitions were applied to a consecutive series of 626 patients who underwent pancreatoduodenectomy between 1994 and 2006. Complication rates were compared and clinical outcomes (hospital stay, mortality) through all ISGPS grades were investigated.

Results

Postpancreatectomy hemorrhage (PPH) occurred in 19 patients (3%) according to former vs. 51 (8%) according to ISGPS definitions; postoperative pancreatic fistula (POPF) in 81 (13%) vs. 116 (18%); delayed gastric emptying (DGE) in 162 (26%) vs. 430 (69%). For POPF and PPH no major difference in clinical outcome and management was observed between patients without complication and grade A. For all three complications higher ISGPS grades (B,C) corresponded with prolonged hospital stay: for PPH 14 days for patients without complication/grade A vs. 17 days for grade B and 32 days for grade C ($P < 0.001$). For POPF: 13 vs. 22 and 36 days respectively ($P < 0.001$), and DGE 10 vs. 20 and 33 days respectively ($P < 0.001$). Each grade C complication, in resemblance to the former definition, was associated with highest mortality.

Conclusions

Application of ISGPS definitions increases complication registration significantly, but the clinical grading system correlates severity with relevant outcome. Minor modifications for POPF and PPH, and less restrictive criteria for DGE are required to prevent overdiagnosis. For DGE suggestions for revision of the current conceptual ISGPS criteria are provided.

INTRODUCTION

Current low mortality rates following pancreatoduodenectomy (PD) for pancreatic and periampullary cancer have been attributed to an increased experience with the procedure, the key reason for a plea for centralization of this complex surgical procedure.¹⁻⁶ Despite this recognized inverse relationship of institutional volume and mortality, high morbidity rates after PD persist with percentages up to 54% in recent reports.^{1,7-10} A debate over outcome is largely compromised by difference in employed definitions for the various complications, prohibiting conclusive comparisons between institutions. This lack of objective parameters has been observed by various groups and has led to initiatives for expert meetings to build consensus around definitions.^{11,12} The International Study Group of Pancreatic Surgery (ISGPS) has proposed definitions for three important postoperative complications: Postoperative pancreatic fistula (POPF), postpancreatectomy hemorrhage (PPH), and delayed gastric emptying (DGE).^{11,13,14}

Anastomotic leakage at the pancreaticojejunostomy resulting in POPF is regarded one of the most serious complications of PD with a reported incidence ranging from 2.1 to 22.6% in recent large series.^{7,15-22} Postpancreatectomy hemorrhage (PPH) is one of the most severe complications after pancreatic resection with life-threatening potential occurring up to 8.8%.²³⁻²⁷ PPH can occur in the early or late postoperative phase [delayed massive hemorrhage: DMH], for which different reports distinguish various intervals.^{26,27} Whereas, late PPH is often associated with a POPF or a local septic focus, early PPH is generally caused by technical failure.^{24,26,27} DGE is one of the most prevalent postoperative complications after PD, often in association with other complications, with an incidence up to 57%.²⁸⁻³⁰ Although not life-threatening, DGE is a bothersome complication that prolongs hospital stay, affects quality of life and delays adjuvant therapies.³¹

Lately studies that have addressed the implications of the ISGPF definitions for the respective complications have been published in short term.³²⁻³⁵ Wente et al. found the ISGPS classification scheme accurate in delineating POPF and evaluation of severity, but suggested further justification has to come from critical appraisal of the ISGPS criteria by other institutions. Evaluation of the ISGSP definition for PPH by one of the authors of the consensus definition showed that the ISGPS definition of PPH was feasible and applicable, but produced a high rate of false positive mild PPH cases for which minor modifications seem indicated.³³

The aim of the present study was to evaluate the incidence of POPF, PPH and DGE in patients undergoing PD, by applying both ISGPS definitions and definitions previously published by our group and currently used in our complication registration.^{15,27,36} Possible changes in registration were studied, as well as the value of the ISGPS grading system for each complication.

METHODS

Patients and Surgical Technique

Between January 1994 and December 2006, a consecutive series of 626 patients underwent PD, or the pylorus preserving modification (PPPD), for a suspected pancreatic or periampullary malignancy at the Academic Medical Center (AMC). The clinicopathological data were prospectively collected in a database. Operations were performed with curative intent, i.e. in the absence of extensive local invasion and/or distant metastases. In short, the standard surgical procedure consisted of a pylorus preserving PD, as previously described, with concomitant dissection of the regional lymph nodes at the anterior and posterior face of the head, around the common and proper hepatic artery, in the hepatoduodenal ligament and lymph nodes to the right of the superior mesenteric vein.³⁷⁻³⁹ In case of suspicion on tumor ingrowth in the proximal duodenum a classical Whipple procedure was performed. In case intraoperatively (minimal) tumor ingrowth of the portal or superior mesenteric vein was found, a segmental or wedge resection was carried out.^{40;41} Reconstruction consisted of a retrocolic jejunal loop with end-to-side pancreaticojejunostomy, hepaticojejunostomy and gastro- or duodenojejunosomy. Pancreaticogastrostomy was not performed. Biliary T-drains or transhepatic biliary drainage were not used routinely. Drain management consisted of leaving a subhepatic silicone drain extending to the pancreatic anastomosis, of which the output in the postoperative course was measured daily. Routine application of a feeding jejunostomy was abandoned in the year 2000, because a prospective study could not demonstrate any benefit.⁴² Up to 2004 prophylactic somatostatin was administered routinely (three times daily for 7 days) to prevent pancreatic leakage. Thereafter administration of somatostatin was confined to patients with a pancreas of soft texture as encountered during surgery, or in the presence of a non-dilated pancreatic duct (<3mm). At the start of surgery antibiotics were administered for 24 hours as prophylaxis.

Postoperative Course

The drain near the anastomosis was removed when output had fallen below 100mL/day without signs of anastomotic leakage, i.e. drain amylase activity lower than 3 times serum amylase activity and no bilirubin in drain output. Incidence, time of onset and type of complication were recorded for both surgical (POPF, PPH, DGE, biliary leakage, wound infection, intra-abdominal abscess) and non-surgical (pulmonary, cardiac, urological and other) complications. Nutritional support, nasogastric tube (NGT) management and (recovery of) gastrointestinal function were recorded. Initial hospital stay, intensive care unit (ICU) stay, reoperations and 30-day readmissions were recorded. Mortality was defined as death due to any cause during hospitalization.

Pancreatic Fistula

Criteria from Johns Hopkins, and adapted and previously published by our group, define POPF by a high amylase level in the abdominal drain effluent (more than 3 times serum level), leakage proven at imaging or relaparotomy, in combination with one or more clinical signs such as peritoneal tenderness, progressive abdominal pain, fever or leucocytosis.⁴³ The ISGPS defines POPF as any measurable drainage from an intraoperatively placed drain (or a subsequently placed percutaneous drain) on or after postoperative day 3, with an amylase content greater than 3 times the upper limit of normal serum amylase level.¹¹ ISGPS grade A depicts transient, asymptomatic fistulas, grade B fistulas require further evaluation and (minimal invasive) therapeutic measures, grade C fistulas lead to major deviations in management (Table 1).

Treatment was generally started by restriction of oral intake and maintenance of drain placement.¹⁵ In case diagnostic imaging revealed a concomitant intra-abdominal abscess or fluid collection percutaneous drainage was performed, while relaparotomy was reserved for clinical deterioration of the patient or failure to improve. In case of confined anastomotic leakage found at relaparotomy only selective drainage was performed, completion pancreatectomy was restricted to patients with anastomotic dehiscence and partial necrosis of the pancreatic remnant. From 1997 to 2004 a more organ-sparing approach was followed with the intention to prevent 'brittle diabetes': disconnection of the pancreatic anastomosis with preservation of a small pancreatic remnant, shortening of the blind jejunal limb and closure of the pancreatic duct of the remnant.¹⁵ Due to poor results this technique has been discontinued after 2004.

Postpancreatectomy Hemorrhage

Our previously published criteria for DMH are a postoperative bleeding occurring 24 hours after the index operation and a transfusion need of at least 4 packed cells within 24 hours.²⁷ The ISGPS definition of PPH includes all bleeding complications with division in *mild* and *severe*. Mild is defined as a decrease of hemoglobin concentration less than 3 g/dL without or with discrete clinical impairment (tachycardia, decrease of mean arterial blood pressure), requiring (minimal) transfusion (Table 2).¹⁴ Severe PPH comprises a serum hemoglobin decrease of ≥ 3 g/dL with clinical impairment and requiring invasive (non-) surgical treatment. Onset of PPH occurs either *early* (≤ 24 hours after end of index operation) or *late* (>24 hours).

Conservative treatment of PPH consisted of supportive therapy; nasogastric suction, antibiotics and blood products. For anastomotic bleeding sclerotherapy was performed using adrenaline 0.01% or ethoxysclerol 1%. Surgical interventions consisted generally of exploration and ligation of the bleeding vessel, removal of the intra-abdominal hematoma and, if associated with PJ leakage, the anastomosis was dismantled. Recently embolization is increasingly used at time of angiography with visualization of the celiac trunk (including hepatic and splenic artery) and the superior mesenteric artery.⁴⁴ Depending on the localization of the bleeding coil occlusion for side branches of arteries, or placement of a covered stent-graft (hepatic or splenic artery) is performed.

Table 1 Selected criteria for POPF according to former definition and ISGPS definition by grade of severity.

Criteria	Former definition	ISGPS Grade A	ISGPS Grade B	ISGPS Grade C
Drain amylase	>3 times serum amylase	>3 times upper normal serum amylase on, after POD 3	>3 times upper normal serum amylase on, after POD 3	>3 times upper normal serum amylase on, after POD 3
Persistent drainage (>3 wks)	n/a	No	Usually yes	Yes
Signs of infection	Yes	No	Yes	Yes
Readmission	n/a	No	Yes/No	Yes/No
Reoperation	n/a	No	No	Yes

Table 2 Selected criteria for PPH according to former definition and ISGPS definition by grade of severity.

Criteria	Former definition	ISGPS Grade A	ISGPS Grade B	ISGPS Grade C
Time of onset*	Late	Early	Early or Late	Late
Hemoglobin decrease*	n/a	<3 g/dl	≥3 g/dl (early) or <3 g/dl (late)	≥3 g/dl
Clinical condition	n/a	Well	Intermediate	Life-threatening
Blood transfusion (PC's)	≥4 units [†]	2-3 units	>3 units (early) or 1-3 units (late)	>3 units
Embolization/relaparotomy	n/a	No	Yes (early), No (late)	Yes
ICU admission	n/a	No	Yes/No	Yes
Prolongation of hospital stay	n/a	No	Yes/No	Yes

Table 3 Selected criteria for DGE according to former definition and ISGPS definition by grade of severity.

Criteria	Former definition	ISGPS Grade A	ISGPS Grade B	ISGPS Grade C
Nasogastric tube required	≥10th POD	POD 4-7, reinsertion POD 3	POD 8-14, reinsertion POD 7	POD >14, reinsertion POD 14
Solid intake unable by	POD 14	POD 7	POD 14	POD 21
Clinical condition	n/a	Well	Well/minor discomfort	Ill
Co-morbidities [‡]	n/a	No	Yes/No	Yes
Specific treatment [§]	n/a	Yes/No	Yes	Yes
Diagnostic evaluation [¶]	n/a	No	Yes/No	Yes
Prolongation of hospital stay	n/a	No	Yes	Yes

LEGEND TABLE 1-3

* Early onset defined as ≤24 hrs, late onset >24 hrs.

† administered within 24 hrs.

‡ postoperative pancreatic fistula, intra-abdominal abscess.

§ prokinetic drugs, potential reinsertion of nasogastric tube, partial/total parenteral nutrition.

¶ endoscopy, X-ray passage, CT scan.

n/a, not applicable; US, ultrasound; CT, computed tomography; POD, postoperative day; PC, packed cell; ICU, intensive care unit

Delayed Gastric Emptying

The previously published criteria for registration of DGE in our institution are defined as gastric stasis requiring nasogastric suction for ≥ 10 days, or inability to tolerate a regular (solid) diet on or before postoperative day (POD) 14.⁴⁵ The ISGPS definition states that DGE is present when the NGT remains in place for >3 days or has to be reinserted (for persistent nausea and/or vomiting) after POD 3, or when there is inability to tolerate a solid diet by POD 7.¹³ Higher grades correspond to increased duration of nasogastric drainage and inability to have a normal diet (Table 3). In the application of the grading system, patients were appointed to the highest grade for which one of the parameters was positive.

Besides a comparison of these two definitions, we performed a subanalysis to discern two classes of DGE; primary DGE, when not associated with intra-abdominal complications (POPF, PPH, biliary leakage, intra-abdominal abscess, relaparotomy any cause), and secondary DGE (associated with these complications). Treatment of DGE consisted generally of prolonged NGT placement or reinsertion, in combination with administration of prokinetics such as erythromycin or metoclopramide. Prolonged inadequate nutritional intake was an indication for starting supportive enteral nutrition via a postoperatively placed duodenal feeding catheter, initiated at the surgeon's discretion, or ultimately by administration of total parenteral nutrition (TPN).

Analysis

The clinical and diagnostic parameters required for complication registration of POPF, PPH and DGE, according to our previously used system and according to the new ISGPS definitions are summarized in Table 1a-c. A complication meeting the ISGPS definition is categorized to a particular grade of severity when most but at least one parameter for that particular grade is positive. The clinical course and follow-up 30 days after discharge were analyzed for all patients by two assessors (NAG, KH) individually, both from the information readily available in the prospectively maintained database, as well as by reviewing medical charts of each patient. Application of former definitions as well as ISGPS definitions with subsequent grading was applied to every patient. Disagreements over registration or grading were solved by discussion. No pre-modifications were made to each of the ISGPS definitions or grades. SPSS statistical software, version 14.0 (SPSS Inc, Chicago, Ill, USA), was used for statistical analysis. A mean \pm SD, or median with range if not normally distributed, described continuous parameters. Factors associated with ISGPS severity grades were compared using the χ^2 statistic and Pearson correlation test. The Student's t-test, the Mann-Whitney U test, the χ^2 statistic or the Fisher's exact test, used where appropriate, analyzed the differences in the various parameters across grades. A P-value of <0.05 was considered statistically significant.

Table 4 Characteristics of 626 patients who underwent PD.

Characteristic	
Mean (SD) age (years)	63 (11)
Gender [no.(%)]	
Male	352 (56)
Female	274 (44)
ASA classification	
I, II	517 (83)
III	109 (17)
Surgical technique [no.(%)]	
PPPD	566 (90)
Classic PD (distal gastrectomy)	60 (10)
Pathological diagnosis [no.(%)]	
Adenocarcinoma	465 (74)
Cystic tumor	46 (7)
Chronic pancreatitis	60 (10)
Other	55 (9)
Median hospital stay (days) [range (10th-90th percentiles)]	14 (9-33)
Overall hospital deaths [no.(%)]	12 (1.9)

ASA: American Society of Anesthesiologists

PD: pancreatoduodenectomy; PPPD: pylorus preserving PD

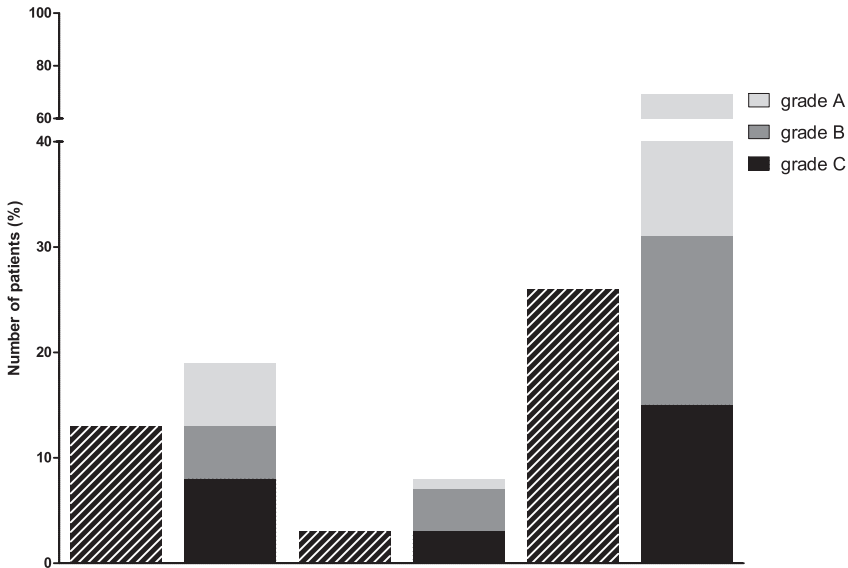


Figure 1 Prevalence of postoperative pancreatic fistula (POPF), postpancreatectomy hemorrhage (PPH) and delayed gastric emptying (DGE) when registering according to the former and the current ISGPS complication registration.

RESULTS

Table 4 shows the patient characteristics of the entire cohort. Figure 1 shows that application of the ISGPS definitions resulted in a higher registration for every complication compared to former definitions.

Prevalence of POPF

The overall prevalence of POPF according to the former definition was 13% (81 patients), whereas the ISGPS definition identified 116 patients (18%). Patients with ISGPS grade B or C POPF were all registered by the former definition. Previously, ISGPS grade A fistulas were not registered as complication, exclusively due to the requisite ‘sign(s) of infection’ in the former definition and absence of it in the new definition. The higher median drain amylase in grade B (37657 IU/L) compared to grade C (20959 IU/L) might be explained by relaparotomy preventing further augmentation of amylase level in the latter group, while grade B was treated with persistent or percutaneous drainage only.

Grading of POPF and Outcome

Grade A, 30% (35/116) of all POPF cases, did not require any therapeutic interventions for fistula management, whereas grade B, 29% (34/116) of POPF cases, was treated with administration of antibiotics or (continuous) drainage (Table 5). For grade C, 41% (47/116) of POPF cases, reoperation was performed in 68%. Four grade C patients suffered from pancreatic leakage before POD 3, as apparent during emergency laparotomy, and strictly would not have been identified by the ISGPS definition. Higher grades were significantly associated with increased resource use (antibiotics, continued or additional drainage, reoperation, length of stay, and readmission) ($P < 0.001$). The longer hospital stay for grade A compared to patients without POPF (median 13 days; IQR 10-17) was possibly due to a significantly higher incidence of concomitant hepaticojejunostomy leakage, intra-abdominal abscess formation and wound infection in patients with grade A fistula (data not shown).

Prevalence of PPH

Applying our former definition PPH occurred in 3% (19 patients), while according to the ISGPS definition this increased to 8% (51 patients). For the 51 patients meeting the ISGPS definition grades, based on time of onset and severity of bleeding, were: grade A 1% (7/626), grade B 4% (25/626), grade C 3% (19/626).

Grading of PPH and Outcome

Grade C PPH cases were equal to those identified by the former definition, whereas the sharper delineation of grade of severity, with allowed blood transfusion, and strict distinction by time of onset resulted in the additional registration of grade A and grade B (Table 6). Also for PPH higher grades correlated to increased resource use (transfusion need, invasive treatment and duration of stay). With respect to the

correlation between PPH and POPF analysis revealed that severity of PPH had a close relation with POPF; The majority of grade C PPH occurred in adjunction to preceding POPF (Table 7). None of the grade A PPH patients suffered from POPF.

Table 5 Clinical outcomes related to POPF according to former definition and ISGPS definition and severity grade.

Outcome	Former Definition N=81	ISGPS Grade A N=35	ISGPS Grade B N=34	ISGPS Grade C N=47	P-value
Day of diagnosis, median POD	7	4	7	7	.025
Highest drain amylase, median IU/L	33601	2170	37657	20959	<0.001
Drain removal, median POD*	25	11	22	34	<0.001
Antibiotics, n (%)	68 (84)	0	21 (62)	47 (100)	<0.001
Percutaneous drainage, n (%)	33 (41)	0	13 (38)	20 (43)	<0.001
Reoperation, n (%)	32 (40)	-	-	32 (68)	<0.001
Duration of stay, days, median (IQR)	30	15 (12-25)	22 (16-32)	36 (27-63)	<0.001
Readmission, n (%)	19 (23)	0	13 (38)	6 (13)	<0.001
In-hospital mortality, n (%)†	9 (11)	0	1 (3)	8 (17)	<0.001

* based on high amylase in drain output on/after POD 3, or proven at laparotomy.

† any cause. POD, postoperative day; IQR, interquartile range.

Table 6 Clinical outcomes related to PPH according to former definition and ISGPS definition and severity grade.

Outcome	Former Definition N=19	ISGPS Grade A N=7	ISGPS Grade B N=25	ISGPS Grade C N=19	P-value
Early PPH, n (%)*	n/a	7 (100)	12 (48)	0	<0.001
Late PPH, n (%)†	n/a	0	13 (52)	19 (100)	<0.001
Mild PPH, n (%)‡	n/a	7 (100)	13 (52)	0	<0.001
Severe PPH, n (%)§	n/a	0	12 (48)	19 (100)	<0.001
Transfusion need, PCs, median (IQR)	9 (6-16)	2 (2-3)	3 (2-8)	9 (6-17)	<0.001
Embolization, n (%)	8 (42)	0	2 (8)	8 (42)	<0.001
Reoperation, n (%)	9 (47)	0	8 (32)	9 (47)	<0.001
Duration of stay, days, median (IQR)	32	13 (10-22)	22 (16-32)	32 (19-41)	<0.001
In-hospital mortality, n (%)¶	5 (26)	0	1 (4)	5 (26)	<0.001

* within 24hrs.

† after 24hrs.

‡ mild = decrease in hemoglobin concentration <3 g/dl, need of volume resuscitation/blood transfusion 2-3 units (early) or 1-3 (late).

§ severe = decrease in hemoglobin concentration ≥3 g/dl, need for >3 units.

¶ any cause. POD, postoperative day; IQR, interquartile range; PC, packed cell; n/a, not applicable.

Prevalence of Delayed Gastric Emptying

Application of our former definition diagnosed 162 patients (26%) with DGE. According to the ISGPS definition 430 patients (69%) had DGE: grade A 239 patients (38%), grade B 97 patients (16%), and grade C 94 patients (15%). Primary DGE, i.e. DGE in absence of other abdominal complications, occurred in 273 (44%) patients, secondary DGE in 157 (25%) patients.

Grading of DGE and Outcome

Grade A DGE, 56% (239/430) of DGE cases, occurred for 34 patients (14%) in association with POPF, 22 patients (9%) had an intra-abdominal abscess (Table 8). Grade B DGE, 23% (97/430) of DGE cases, occurred for 26 patients (27%) in association with POPF and for 13 patients (13%) with an intra-abdominal abscess, whereas for grade C DGE, 22% (94/430) of DGE cases, figures were 42 patients (45%) and 32 patients (34%) respectively. Higher DGE grades all were correlated with increased use of supportive treatment and increased hospital stay.

Table 7 Sequential relation between the presence of Postoperative Pancreatectomy Hemorrhage (PPH) and the occurrence of Postoperative Pancreatic Fistula (POPF), graded by severity of PPH according to ISGPS criteria.

	Total PPH	PPH Grade A	ISGPS Grade B	ISGPS Grade C	P-value
Timing POPF	N=51	N=7	N=25	N=19	
POPF after PPH, n (%)	10 (20)	0	4 (16)	6 (31)	<0.001
POPF before PPH, n (%)	11 (21)	0	1 (4)	10 (53)	<0.001
No POPF	30 (59)	7 (100)	20 (80)	3 (16)	<0.001

Table 8 Clinical outcomes related to DGE according to former definition and ISGPS definition and severity grade.

	Former Definition	ISGPS Grade A	ISGPS Grade B	ISGPS Grade C	P-value
Outcome	N=162	N=239	N=97	N=94	
Co-morbidities					
POPF, n (%)	59 (36)	34 (14)	26 (27)	42 (45)	<0.001
Intra-abdominal abscess, n (%)	42 (26)	22 (9)	13 (13)	32 (34)	<0.001
Diagnostic X-ray passage	26 (16)	0	3 (3)	25 (27)	<0.001
Supportive treatment*					
Enteral nutrition via NGT, n (%)	83 (51)	35 (15)	45 (46)	49 (52)	<0.001
Parenteral nutrition, n (%)	43 (27)	15 (6)	19 (20)	27 (29)	<0.001
Prokinetic drugs, n (%)	68 (42)	31 (13)	29 (30)	48 (51)	<0.001
Duration of stay, days, median (IQR)	32	13 (11-16)	20 (16-25)	33 (26-44)	<0.001

* nutritional support not specifically for DGE

POPF, postoperative pancreatic fistula; NGT, nasogastric tube

DISCUSSION

The present study demonstrates that application of ISGPS definitions for POPF, PPH and DGE following PD resulted in a higher incidence of these complications in the same cohort, compared to formerly used definitions. This is mainly due to identification of not clinically significant grade A. Discerning severity of complications in grade B and C provides a better understanding of impact and consequences. Transparency in evaluating outcome between centers is to be expected with wide-spread use of the new definitions, however, necessary adaptations and extensive validation should precede implementation.

POPF is the most feared complication following PD with a central role in the discussion around proper definition and grading. The aim of our study was complication registration, we did not focus on risk factors for development of pancreatic fistulas. To define POPF biochemically on or after POD 3 has limitations and the initiators of the ISGPS definition for POPF have already stated that the current definition should undergo revision based on a recent study, demonstrating the predictive value of height of drain amylase on POD 1.⁴⁶ Patients with POD 1 drain amylase levels >5000 U/L are prone for leakage and might benefit from an anticipated treatment of prolonged fasting and postponed drain removal. This would imply a deviated clinical course from normal and should be scored at least as grade A. Strasberg et al have pointed out that registration of POPF depends on the frequency of drain amylase measurement and it is very likely that patients without postoperative drain placement might suffer from small volume transient leakage (grade A), but can never be identified on that basis.⁴⁷ On the other hand, we in our series had 4 patients that had proven pancreatic leakage at emergency laparotomy on POD 1 and 2, and, therefore, lack the requirement of a drain amylase of three times upper normal serum value on POD 3. We would suggest to add leakage that is directly proven by imaging or relaparotomy to the definition.

The diversity in underlying pathophysiologic mechanisms renders PPH a difficult complication to assess. The distinction between ‘early’ (within 24 hours after the index surgery) and ‘late’ is probably most commonly used, since this provides an insight in cause and prognosis. We found that late, severe PPH (grade C) developed for the majority in close association with POPF and had the worse clinical outcome. This is in accordance with a recent large study evaluating PPH in pancreatic surgery after various procedures.²⁶ Remarkably, the authors of this study claimed to use the ISGPS definition, but modified the interval for early PPH from 24 hours postoperatively to five days, again making ultimate comparison complicated.

Another problem arises when grading of complications are linked to outcome measures (duration of hospital stay or specific therapeutic measures), since this requires a direct cause-effect relationship. Frequently multiple complications occur in the same patient, mostly as a sequel of events after an ‘index’ complication. Whenever possible a clear distinction has to be made whether a patient suffers from more complications than the one of interest, with determination whether therapeutic con-

sequences and final outcome are directly related to this specific complication. Especially DGE, which is defined by duration of nasogastric intubation and/or first day of solid food intake, suffers from the association with other complications. A severely ill patient with grade C POPF undergoing a relaparotomy will inevitably have either a prolonged nasogastric intubation or NGT reinsertion with a delayed first day of solid intake. Theoretically the stomach emptying rate might be normal, but the patient will still be classified as having DGE when the definition is strictly applied. A distinction between primary DGE, i.e. no other intra-abdominal complications, and secondary DGE is necessary.

Furthermore, a drawback of using criteria derived from the clinical condition of the patient lies in its subjectivity and local treatment policies, as has been brought up by others.⁴⁸ First, qualification of a postoperative course as 'normal' depends on the surgeon's intuition and his experience, for which objective criteria are lacking.⁴⁹ This observation has rendered Clavien et al. in their classification system to redefine a complication from 'any deviation from the normal postoperative course' to 'ideal postoperative course'.⁵⁰ This is less subject to subjective interpretation and might be regarded as a point of revision in the ISGPS classification scheme. Second, from our own experience application of ISGPS definition for DGE resulted in a dramatic overall increase of DGE prevalence, but this appeared to be mostly due to a policy in earlier days of late removal of the NGT (once bowel movement had returned), then considered normal. This underlines that, rather than a therapeutic consequence defining a complication, an objective criterion such as a laboratory or imaging study should diagnose a complication.⁴⁸ Furthermore, the definition of 'solid oral intake' is prone to subjective interpretation. Even in the ISGPS definition proposal, terms like 'tolerance of solid oral intake' and 'unlimited oral intake' are alternately used.^{13:33} We believe that these terms have different meanings and that unlimited oral intake is usually not to be expected within the first two months after PD. Other drawbacks of this definition are the fact that nasogastric production is not taken into account and that there are no strict criteria for removal of the NGT.

The registration of a complication without clear clinical impact (ISGPS grade A) is subject of debate. Following the definition of the National Surgical Complication Registry in The Netherlands "A complication is an unintended and undesirable event or condition following medical treatment, that is harmful for the patient and necessitates adjustment of medical treatment, or that leads to permanent harm" recognition of grade A could be considered superfluous. However, the further a definition is specified, the more restrictive it will be and as such prohibit insight and tools for quality improvement.⁵¹ In effect the registration of grade A is a consequence of the broad definition of the different complications. The present study clearly shows that application of the broad ISGPS definitions will lead to a higher percentage of complications, for which the grading system provides a means of appreciating the severity of each complication. In a recent paper from Massachusetts General Hospital the authors have also recognized that not all POPF have the same clinical impact and a distinction should be made in low and high (clinical) impact fistulas.⁵²

Although it is relatively simple to discern grade A from significant complications, we found the distinction between grade B and C sometimes difficult to accomplish. In general grade B requires minimal invasive treatment and C invasive treatment, but in our series 8 patients with grade B PPH underwent relaparotomy. It is hard to consider this a minimal invasive treatment of a complication, nevertheless, the current ISGPS definition of PPH allows both for grade B and C embolization and surgery as required treatment. Whereas in former days we held a low threshold for relaparotomy for PPH, we are now highly in favor of embolization and/or stenting by the intervention radiologist as a first-line treatment, which at the least can be considered less invasive than surgery.⁴⁴ This underlines the fact that appointing a certain grade of severity to a complication in a registration system based upon employed therapeutic measures, requires standardized treatment protocols for ultimate objectivity and appreciation of results. Local policies dictating specific treatment might influence classification and this should be a factor to be dealt with in a revised version of the classification scheme.

DeOliveira and coworkers have proposed a classification scheme of complications following pancreatic surgery, with seven categories in five grades, based on a revised, previously reported grading system.^{12,53} They found their grading system to be effective in analyzing incidence and severity of complications, by directly correlating initiated therapy to the specific complication. General definitions of therapeutic based grades allow application of the same system to different complications and appreciate the impact of severity of the different complications, not in the last place from the patient's perspective. As mentioned this requires standardized treatment protocols if one is interested in comparison of outcome between centers. An advantage of the ISGPS classification over the classification scheme of DeOliveira et al. is the understanding, next to required treatment, of specific characteristics of a single complication and its grade, e.g. length of duration of NGT placement for DGE and amount and onset of PPH.

The initiative to create transparency in outcome by defining universal definitions of complications is sorely needed considering the wide variety of complication rates reported in literature, and the impossibility to draw conclusive comparisons between institutions. A prerequisite for such comparison is a wide no-compromise acceptance of the new ISGPS definitions. Pre-modifications should be avoided, since this would only recreate the same problem. Nevertheless the modifications are understandable, while also the results of the present study show evident limitations and inconsistencies of the current definitions. Validation and necessary fine-tuning of the definitions should precede ultimate implementation.

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