

## Risk Factors for Complications after Duodenopancreatectomy. Initial Results after Implementing a Standardized Perioperative Protocol

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### Rezumat

#### **Factorii de risc pentru apariția complicațiilor după duodenopancreatectomie cefalică. Rezultate inițiale după implementarea unei conduite perioperatorii standardizate**

**Introducere:** În perioada 1993-2008, în cadrul Clinicii Chirurgie III s-au efectuat mai multe studii retrospective, cu scopul de a identifica factorii de risc pentru apariția complicațiilor după duodenopancreatectomie cefalică (DPC). În urma rezultatelor acestor studii, s-a elaborat un protocol de pregătire preoperatorie a pacienților propuși pentru DPC precum și o serie de modificări tehnice intraoperatorii, cu scopul de a ameliora morbiditatea și mortalitatea postoperatorie. Implementarea protocolului s-a făcut treptat și a fost inomogenă la nivelul serviciului nostru.

**Material și metodă:** Studiul este prospectiv, efectuat în perioada 2009-2012, pe un lot de 180 de pacienți și are ca scop analiza rezultatelor imediate după DPC efectuat pentru tumori maligne periampulare, cu scopul de a analiza efectele implementării protocolului menționat mai sus. S-au urmărit ratele de apariție a complicațiilor (fistula pancreatică, pancreatita de bont, hemoragia din bontul pancreatic, staza gastrică), precum și factorii ce ar putea influența apariția acestora.

**Rezultate și concluzii:** Din totalul de 180 de pacienți, 10 (5.5%) au dezvoltat fistulă pancreatică și 24 (13.3%) au prezentat stază gastrică. Dintre factorii ce au fost asociați semnificativ cu prezența acestor complicații, amintim: utilizarea montajului pancreato-jejunal și montajul gastro-jejunal transmezocolic. Odată cu implementarea protocolului, factorii de risc identifi-

cați anterior în studiile retrospective efectuate în serviciul nostru (valori crescute ale transaminazelor, experiență echipă chirurgicală, etc) și-au pierdut din semnificație, dar nu au dispărut în totalitate, datorită nerespectării în totalitate a conduitei propuse. Rezultatele studiului nostru indică faptul că aplicarea omogenă a unui ghid perioperator, împreună cu o tehnică chirurgicală standardizată poate duce la îmbunătățirea semnificativă a rezultatelor imediate după DPC.

**Cuvinte cheie:** duodenopancreatectomie cefalică, complicații, factori de risc, protocol perioperator

### Abstract

**Introduction:** During 1993-2008 period, in the Surgical Clinic III were conducted several retrospective studies, in order to identify risk factors for complications after cephalic duodenopancreatectomy (DP). As a result of these studies, a preoperative protocol was developed for preparation of patients proposed for DPC, as well as a number of intraoperative technical changes in order to improve postoperative morbidity and mortality. Implementation of the protocol was gradually and inhomogeneous done in our service.

**Methods:** The study is prospective, conducted in 2009-2012, in a group of 180 patients and aims to evaluate immediate results after DPC for periampular malignancy, looking to analyze the effects of implementation of the protocol mentioned above. We analyzed the rates of complications (pancreatic fistula, bluntpancreatitis, bleeding from the pancreatic blunt, delayed gastric emptiness), and the factors that might influence their occurrence.

**Results and conclusions:** of the 180 patients, 10 (5.5%) developed pancreatic fistula and 24 (13.3%) had delayed gastric emptiness.

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Among the factors that have been significant associated with these complications we mention: the pancreatico-jejunal anastomosis and gastro-jejunal transmesocolic assembly. With the implementation of the protocol, the risk factors previously identified in retrospective studies performed in our service (elevated transaminases, experienced surgical team, etc.) have lost significance, but they have not disappeared entirely, due to fact that the conduit proposed was not entirely followed. We believe that the homogeneous application of a perioperative guide, together with a standardized surgical technique, will lead to improve immediate results after DP.

**Key words:** cephalic duodenopancreatectomy, complications, risk factors, perioperative protocol

## Introduction

Duodenopancreatectomy (DP) has its indication of radical intent in the treatment of periampullary malignant tumors: cephalopancreatic neoplasia, distal cholangiocarcinoma or ampuloma. Of these, cephalopancreatic adenocarcinoma has the worst prognosis, DP managing to provide a 5-year survival of 31.4% for tumors diagnosed in stage I and only 2.8% for stage IV tumors, with a median of 24.1 months for stage I and 4.5 months for stage IV (1). In patients with unresectable tumors, 5-year survival is only 0.6% for stage IV (with a median of 2.5 months) and 3.8% for stage I (with a median of 6.8 months) (1,2). Given this grim prognosis, radical surgery is the only chance for patients with this pathology; unfortunately, only 15-20% of them are suitable for it.

Although perioperative mortality after DP has significantly decreased in excellence centers, from 15-20% in the 70s to under 5% at present, morbidity remains high: 31-47% (3).

Pancreatic fistula is the most feared complication after DP, being considered the Achilles' heel of this procedure (4). The incidence of this complication varies between 2% and 12%, noting that in the presence of a low consistency pancreatic parenchyma (ampuloma), the occurrence rate of this complication can reach up to 20-30% (3,5). The management of pancreatic fistula may be conservative: drainage, administration of Sandostatin, nutritional support. In situations with important anastomotic dehiscence, reintervention is required, with pancreatic stump revision and redo of the anastomosis or total pancreatectomy (6).

Delayed gastric emptying occurs at a rate of 7-16% of patients who underwent DP and has an important impact on their quality of life, significantly increasing the number of hospitalization days (7). The treatment is conservative and consists of: maintaining a nasogastric tube, nutritional support, administration of prokinetics (metoclopramide) and motilin agonists (erythromycin) (8).

Other specific postoperative complications after DP are bleeding from the pancreatic stump with an incidence of 5-10% and pancreatitis at the level of the pancreatic stump, with

a rate of occurrence of 1-2% (9). Biliary fistula, gastrointestinal fistula, intra-abdominal abscess or biliary-digestive anastomotic stenosis are possible but nonspecific complications for this surgery, being common in the field of biliary-digestive interventions.

## Methodology

The present study is a prospective one and includes 180 patients who underwent DP in our service, for periampullary malignant disease, from year 2009 to 2012.

We considered a high experience surgeon the one with over 50 DP conducted, a medium experience surgeon the one with 10-30 DP done and a low experience one with less than 10 DP.

We have set the difference between specific complications after DP (pancreatic fistula, delayed gastric emptying, bleeding from the pancreatic stump, pancreatitis of the pancreatic stump) and nonspecific common complications after surgeries performed within the biliary-gastrointestinal field (biliary-digestive anastomotic fistula, gastrointestinal anastomotic fistula, intraperitoneal hemorrhage, wound infection, intra-abdominal abscesses, decompensation of other associated pathologies, cardiovascular complications, pulmonary complications).

We took into consideration as being a pancreatic fistula the situations when the secretions from the abdominal drainage tubes totalled more than 30 ml/day, and their amylase content was at least 3 times the normal serum value; these values should be maintained over a period of at least 3 days (5).

Delayed gastric emptying is defined as food intolerance or the need of maintaining or of reinstalling the nasogastric tube after the 3rd postoperative day (3).

In this study we followed the general morbidity and the rate of occurrence of each specific complication after DP: pancreatic fistula, delayed gastric emptying, hemorrhage from the pancreatic stump and pancreatitis of the pancreatic stump. We also tried to identify factors that could influence this complication's occurrence. In consequence, we took in consideration as being factors related to the patient status: age, diabetes or other malignancies association, hemoglobin level less than 10 mg%, leucocytosis  $> 12000/\text{mm}^3$ , elevated transaminase levels  $> 200 \text{ U/l}$ , the amylase levels  $> 200 \text{ IU}$ , serum glucose level above 200 mg / dl, total protein of  $< 6 \text{ g}$ , Wirsung duct diameter  $< 3 \text{ mm}$  and soft pancreatic parenchyma. From the factors related to preoperative and surgical management, we analysed the impact of surgeon's experience, preoperative stenting, pancreatico-digestive anastomosis type, length of surgery time  $> 240 \text{ min}$  and blood loss  $> 500 \text{ ml}$ , over the incidence of complications. Laboratory tests considered were those taken the day before surgery.

These reference values correspond to the values found in similar studies in the literature, also designed to assess their impact on postoperative outcome (10-15).

For statistical analysis we used parametric and non-parametric tests of significance. The association between non-

parametric variables was tested using Chi Square Test, Fisher's exact test and odds ratios (OR). OR was calculated for contingency table with cell frequency less than 5.

The study of the differences in the values of quantitative variables in two independent groups was performed by Student T-test with equal variances; the variances were tested in advance with Levene test.

In all the tests that were used, the confidence interval was 95% ( $p$ -value  $< 0.05$ ); also the bilateral  $p$ -value was taken into consideration, where tests provided it. For statistical processing we used statistical calculations and graphics environment R version 2.15.0, with graphic interface Rcmdr version 1.8-3.

The results obtained between 2009 and 2012 were compared with those obtained before 2009, in an attempt to see if the introduction of a standardized attitude imposed by the continued growth of our service addressability regarding DP led to an improvement in morbidity rate. Data on morbidity after DP obtained before 2009 were collected from the works carried out by staff members as a result of retrospective studies (16-18).

Perioperative protocol for DP was developed and implemented gradually; it was achieved with the contribution of surgical team members concerned for pancreatic surgery. Below we briefly outline the required elements that are part of the guide, as reached today (2013).

Abdominal CT or MRI examination with contrast should not be missing from the diagnostic algorithm, endoscopic ultrasound being indicated when the other examinations are without sufficient information to determine the indication of surgery (19).

Preoperatively, the compensation of the related diseases is mandatory, multidisciplinary approach being important: surgeon - gastroenterologist - intensive care doctor.

Rebalancing nutrition by enteral and/or parenteral administration is necessary in patients with weight loss  $> 10\%$  or a body mass index  $< 18.5$ , in the absence of any diets. Also, nutritional support is recommended for patients at risk of malnutrition, which were not adequately fed for at least 5 days prior to surgery, or it is considered that they will not be fed properly for at least the next 5 days (20). Nutrition is established and maintained for 7 to 14 days before surgery, in order to achieve total protein values above 6 g/l. Regardless of nutritional status, a high protein diet is recommended to be administered orally for 5-7 days before surgery.

Biliary drainage, made by endoscopic or surgical approach is required when the total bilirubin level is  $> 10$  mg%, this procedure being followed by radical surgery in 7-10 days apart. Where appropriate, an endoscopic common bile duct (CBD) stenting or laparoscopic cholecystostomy is performed.

Improvement of liver function in terms of effective biliary drainage will be made with the support of hepatoprotective, hepatotropic drugs (Silymarin, Aspatofort) and hepatocyte's membrane stabilizers (Dexamethasone). Timing of surgery will be at a value of transaminases under 200 U / L.

The treatment of angiolcolitis, often present in patients with periampullary tumors, with prolonged jaundice, with or without a stent in the CBD, involves the administration of

cephalosporins with biliary tropism.

Anemic patients will be transfused, preoperative accepted hemoglobin values being  $> 10$  g/dl.

Before surgery, it is recommended to install an epidural catheter, being proved that the postoperative analgesia administered this way, in addition to increased comfort provided to patients, decreases postoperative dynamic ileus period (21).

Importantly, in terms of surgery, we recommend the presence in the team that will carry out the DP of at least one surgeon with medium experience in pancreatic surgery. The dissection will be performed by standard techniques; approach of the porto-mesenteric vascular axis will be done as the surgeon prefers: posterior approach, artery "first" or classic (22-24). Pancreatic division will be done with a "cold" knife after placing the hemostatic sutures to the upper and lower edge of the pancreas. The completion of the hemostasis at the level of the pancreatic stump will be done after the Wirsung duct is identified, using monofilament, slow absorbable, 4-0, "U" stitches. The resected jejunal loop will be as short as possible, being demonstrated that at this level motilin receptors are still located, their absence having a role in the occurrence of delayed gastric emptying after DP (7).

Gastric resection will be prepiloric, this further facilitating the pancreatic-gastric anastomosis. The resection specimen will also contain the gastric antrum, being known that there is no evidence in the literature showing differences between results obtained in DP with or without pylorus preservation (25). As mentioned before, we recommend pancreatic-gastric anastomosis due to increased experience in our service regarding this technique. Hepatico-jejunal anastomosis will be made with separate stitches, with the jejunal loop ascended transmesocolic, passing near the space where the inferior duodenum knee was. Restoration of digestive continuity is achieved through the gastro-jejunal anastomosis, Hoffmeister-Finsterer type and by ascending the jejunal loop in the precolic area; data from the literature shows the benefits that this mounting brings to the incidence of delayed gastric emptying (7).

Supervision of patients will be done in the intensive care unit. Analgesia will be initially achieved through epidural catheter, which will be suppressed after 48-72 h. Antibiotic prophylaxis will be provided (intraoperatively), continued antibiotic treatment being dictated by the appearance of intraoperative bile aspect and postoperative culture results from this level. Also, the patients will receive anticoagulant agents and gastric antisecretory drugs for prophylaxis of venous thrombosis, stress ulcers or bleeding from the pancreatic stump. Suppression of the nasogastric tube is indicated immediately after surgery, the tube being reattached only when necessary (suspected upper gastrointestinal bleeding, delayed gastric emptying). Patients will be actively mobilized on the day of surgery.

Oral feeding should be started on the first day after surgery, by administration of fluids; following, the diversity will be installed based on tolerability. Depending on the risk of malnutrition, we indicate the use of drinkable protein concentrates, like Fresubin Protein Energy Drink, with an

energy intake of 1.5 kcal/ml and protein content of 10g% (26). The association of parenteral nutrition will be done for patients in whom we cannot provide more than 60% of energy needs with enteral intake (25 kcal/kg/day) (27). We do not recommend the administration of Sandostatin by principle, but only in the case of low consistency pancreatic parenchyma or when intra-operative handling of the pancreatic stump was more aggressive. We believe that these cases are associated with an increased risk of pancreatic fistula as indicated even in the specific literature (28).

## Results

Regarding age of patients undergoing DP between 2009-2012, we found statistically significant differences in the median age of patients with complications and without complications (Student test with equal variants,  $t=3.30$ ,  $df=178$ ,  $p=0.001$ ) (Table 1). Furthermore, statistically significant differences were found in median age of patients with and without delayed gastric emptying (Student test with unequal variances,  $t = 4.44$ ,  $df = 41.26$ ,  $p = 0.0001$ ).

30 patients (16.6%) had low levels of total protein; 20 of them developed complications, the association being statistically significant ( $p = 0.03$ , Fisher's Exact Test). In particular, we found an increased risk of digestive fistula in these patients (OR = 0.08) (4 of the 6 patients with gastrointestinal fistula had hypoproteinemia).

55 patients had low hemoglobin levels (30.5%); 33 of them developed postoperative complications, the association being statistically significant ( $p=0.023$ , Fisher's Exact Test). Moreover, the risk of developing gastrointestinal fistula is increased in patients with anemia (OR=0.08): of 6 patients with digestive fistula (3.33%), 5 had hemoglobin levels below normal.

Of the 180 DP, 46% ( $n = 83$ ) were performed by one surgeon with increased experience; 72 DP (39.5%) were done by three surgeons with limited experience and 25 DP (14.5%)

by seven surgeons with little experience. Obtained morbidity was 46% ( $n=84$ ), with an incidence of 5.5% pancreatic fistula and delayed gastric emptying of 13.3% (Table 2, Table 3). We have not found a statistically significant association between operator experience and the presence of complications (Chi-square test,  $\chi^2 = 1.26$ ,  $df = 2$ ,  $p = 0.533$ ).

In 10% of cases ( $n = 17$ ), pancreatico-jejunal anastomosis was preferred. We found an increased risk of stump pancreatitis appearance in these patients ( $n = 3$ , OR = 11.6). The same situation was found in the case of pancreatic fistula, a complication more common in patients with pancreatico-jejunostomy ( $n=5$ ,  $p=0.001$ , Fisher's Exact Test).

We found a much higher probability of reintervention in patients with complications, in general or in particular, in those who developed pancreatic fistula, pancreatic stump pancreatitis or intraperitoneal hemorrhage (Table 3). Bleeding from the pancreatic stump and biliary fistulas was significantly associated with a higher rate of reinterventions (Table 3).

## Discussion

In the Surgical Clinic no III, part of the "Prof. O. Fodor" Regional Institute of Gastroenterology and Hepatology from Cluj-Napoca, the interest in pancreatic surgery dates back to the early 90s, with a gradual increase in casework, from 6 CDP/year in 1993-1997, up to 40-50 DPC/ year currently. With increasing surgical experience, morbidity decreased gradually from 53% in the first year to 33% in 2008 (Fig. 1). Retrospective studies performed during 1993-2008 showed an incidence of 10% for pancreatic fistula, 43% for delayed gastric emptying, 2% for bleeding from the pancreatic stump and 4% for pancreatic stump pancreatitis (16,17).

In order to improve these results, we tried to identify factors associated with increased incidence of these complications. Thus, elevated transaminase levels were associated

**Table 1.** Age influence over morbidity

	Mean	Standard deviation	Median	Minimum	Maximum
Age	59.85	10.41	60	28	84
Age of patients with postoperative complications	62.51	9.13	63.5	42	79
Age of patients without postoperative complications	57.52	10.94	58	28	84

**Table 2.** Postoperative morbidity after DP, period 2009-2012

Morbidity	Global incidence: 46% (n=84)	High experience surgeon: (n=42)	Medium/ Low experience surgeons: (n=42)
Pancreatic fistula	5.5% (10)	3.6% (3)	7.2% (7)
Delayed gastric emptying	13.3% (24)	15% (13)	12% (11)
Bleeding from the pancreatic stump	7 % (13)	2.4% (2)	4% (4)
Pancreatitis of the pancreatic stump	3% (6)	6% (5)	8% (8)
Nonspecific complication after DP	17% (31)	22.9% (19)	12.3% (12)

**Table 3.** Complications / reinterventions relationship

Morbidity	N (%)	Reinterventions (N)		p*	OR**
		Yes	No		
Complications (Total)	84 (46%)	29	55	-	50.091
Pancreatic fistula	10 (5.5%)	8	2	-	26.909
Delayed gastric empty-ing	24 (13.3%)	5	19	0.383	-
Bleeding from the pan-creatic stump	13 (7%)	7	6	0.002	-
Pancreatitis of the pan-creatic stump	6 (3%)	5	1	-	29.8
Intraperitoneal hemorr-hage	10 (5.5%)	8	2	-	26.909
Digestive fistula	6 (3.3%)	6	0	-	0
Biliary fistula	13 (7.2%)	8	5	<0.001	-

Fisher's Exact Test

\*OR=odds ratio, calculated for contingency table with cell frequency less than 5

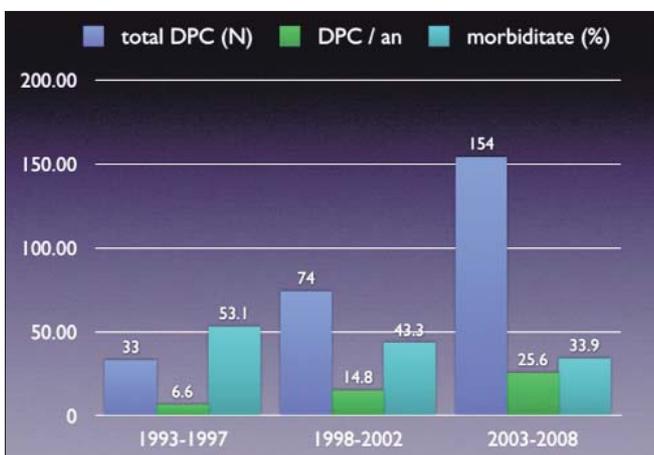
with an increased incidence of pancreatic fistula (p=0.01). Anemia and hypoproteinemia also negatively influenced the rate of occurrence of septic shock and delayed gastric emptying (p=0.06, p=0.01 and p=0.03, p=0.01), probably by involving other morbid conditions such as digestive fistulas or intra-abdominal abscesses. Importantly, one of the conclusions of those studies was that the low experience of the surgical team (less than 10 CDP made) is associated with a significantly higher incidence of pancreatic fistula against experienced teams (more than 50 CDP made). Moreover, surgery time over 240 minutes and blood loss more than 400 ml, often encountered situations where low experienced surgical teams performed the operations, were associated with a higher rate of biliary fistula (p=0.02), postoperative hemorrhage (p=0.05) and delayed gastric emptying (p=0.02) (16,17). Those studies also have identified factors that cannot be improved preoperatively: obesity and low consistency pancreatic parenchyma, which were both significantly associated with pancreatic fistula (p=0.03 respectively p=0.03) (16).

In the same period, in our service, the surgeon with the most experience in pancreatic surgery had analysed his casuistry in terms of results after DP. Thus, between the years 1994-2002, he conducted 66 DP, accompanied by a pancreatic

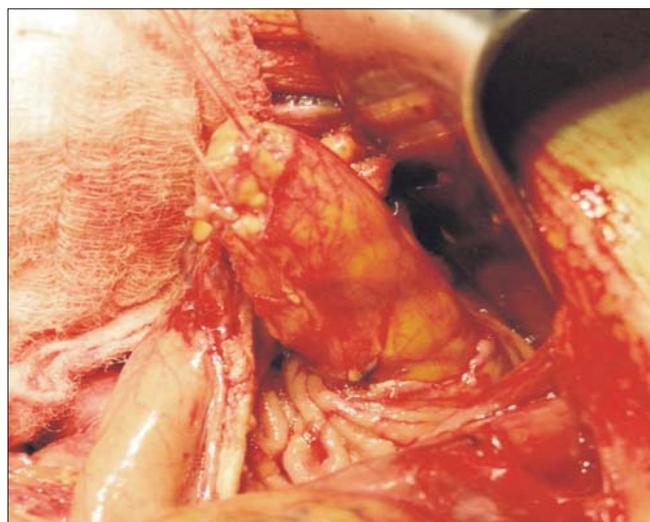
fistula rate of 10%. Note that in 60% of them (n=39), a pancreatico-gastrostomy was performed and in 40% (n=27) he practiced pancreatico-jejunostomy. In the next period (2003-2008), he stopped performing pancreatico-jejunostomy in favour of pancreatico-gastrostomy, anastomosis which he considered to master better from a technical standpoint. The incidence of pancreatic fistula has dropped to 5.5%.

After 2008, the surgeon attempted small changes in his surgical technique, in the idea of improving the results after DP. Thus, to improve the rate of appearance of pancreatic fistula, pancreatico-gastric anastomosis was performed after extensive dissection of the pancreas in order to get a longer pancreatic stump (3-4 cm), so a safer anastomotic partner (Fig. 2). Regarding delayed gastric emptying, he practiced gastro-jejunal anastomosis with entire gastric tranche (Reichel-Polya) for a while. Both changes did not bring significant improvements to the incidence of either complication (16).

With the gradual implementation of standardized perioperative protocol in DP, the morbidity after this intervention did not improve, achieving an incidence of complications of 46% in our service after 2009 compared with 33% in the previous period. This is probably due to the



**Figure 1.** DP - Experience of Surgery Clinic No 3, Cluj-Napoca, since 1993 to 2008



**Figure 2.** Pancreatico-gastric anastomosis; long pancreatic stump

associated pathologies of the patients and the presence of factors that cannot be improved (age, obesity, soft parenchyma of the pancreas). However, we believe that an uneven application of the protocol had an important role in maintaining high morbidity, which can be seen among study subjects because they had hypoproteinemia or anemia, although the recommendations are clear regarding preoperative balance of these values.

In the case of pancreatic fistula, between 2009-2013, an improvement of its incidence has been noticed: 5.5% compared to 10% before 2009. Growing experience of surgical teams tune into this. However, failure to complete the protocol leaves its mark on these results, five fistulas (half of total) occurring in patients with pancreatico-jejunosomy, even if the use of this anastomosis was not recommended due to low experience in our clinic with this technique.

In the case of delayed gastric emptying significant improvements were obtained: 13% in comparison with 43%, most likely originating from the almost exclusive use of the gastro-jejunal precolic assembly.

Low experience of surgical teams was not found to be a factor associated with an increased incidence of complications, due probably to the fact that they reached a higher point on the learning curve, but, very importantly, this was achieved because of surgical team homogenization, achieved by the presence in the surgical team of at least one experienced pancreatic surgeon.

The present study, a prospective one, continues today. Because of that, we can present some preliminary data, not taken into account in all of the above. The most experienced surgeon in the service, during January 2012 - June 2013, fully respected the perioperative DP protocol. In that period, he has performed 40 DP, obtaining a morbidity of 10% (n=4), with no pancreatic fistula (n=0) and 5% rate of occurrence of delayed gastric emptying, while 38 gastro-jejunal anastomosis were performed by precolic approach (0% delayed gastric emptying) and 2 transmesocolic due to local conditions (short mesentery), both followed by delayed gastric emptying. These data emphasize the fact that compliance with recommended guidelines can result in a significant improvement in results.

## Conclusions

It is clear that pancreatic surgery in general and duodenopancreatectomy especially should be reserved to be done in specialized centers. Following the results obtained in our service, results that were gradually improved, with the increasing experience and the implementation of a standardized protocol, we believe that the existence of a diagnostic and perioperative management protocol is mandatory, which, together with a standardized surgical technique, will lead to improved results after DP.

We believe that the final results of our study, still in progress, will come to certify these claims, obtaining a significant improvement in mortality and a corresponding survival.

## Note

The results of this study were partially presented at the National Surgical Conference, Sinaia, Romania, on 30 May-1 June, 2013, in the form of an oral presentation entitled: "Factor de risc pentru aparitia complicatiilor dupa DPC pentru patologie maligna periampulara. Rezultate initiale dupa implementarea unei conduite standardizate."

## Authors contributions

Adrian Bartoş made substantial contributions to study conception and design, acquisition of data, analysis and interpretation of data and drafting the article; he is a member of surgical team doing pancreatic surgery; Dana Bartoş made substantial contributions to acquisition of data, analysis and interpretation of data and drafting the article; she is a member of surgical team doing pancreatic surgery; Nadim Al-Hajjar made contributions by acquisition of data, being a member of surgical team doing pancreatic surgery; Cosmin Puia made contributions by acquisition of data, being a member of surgical team doing pancreatic surgery; Doru Munteanu made contributions by acquisition of data, being a member of surgical team doing pancreatic surgery; Raluca Bodea made contributions by acquisition of data, being a member of surgical team doing pancreatic surgery; Lucian Mocan made contributions by acquisition of data, being a member of surgical team doing pancreatic surgery; Florin Zaharie made contributions by acquisition of data, being a member of surgical team doing pancreatic surgery; Cornel Iancu made contributions by acquisition of data, being a senior member of surgical team doing pancreatic surgery; also had contribution to study conception and revising it critically. All the authors gave the final approval of the version that was submitted.

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