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***Retrospective Study***

**Trends and outcomes of pancreaticoduodenectomy for periampullary tumors: Results of a 25 years single center study on 1000 consecutive cases**

Nakeeb AE *et al*. Trends and outcomes of pancreaticoduodenectomy for periampullary tumors

Ayman El Nakeeb, Waleed Askar, Ehab Atef, Ehab El Hanafy, Ahmad M Sultan, Tarek Salah, Ahmed shehta, Mohammed El Sorogy, Emad Hamdy, Mohamed El Hemly, Ahmed A El-Geidi, Tharwat Kandiel, Mohamed El Shobari, Talaat Abd Allah, Amgad Fouad, Mostafa abu zeid, Ahmed Abu El Eneen, Nabil Gad El-Hak, Gamal El Ebidy, Omar Fathy, Ahmed Sultan, Mohamed Abdel Wahab

**Ayman El Nakeeb, Waleed Askar, Ehab Atef, Ehab El Hanafy, Ahmad M Sultan, Tarek Salah, Ahmed shehta, Mohammed El Sorogy, Emad Hamdy, Mohamed El Hemly, Ahmed A El-Geidi, Tharwat Kandiel, Mohamed El Shobari, Talaat Abd Allah, Amgad Fouad, Mostafa abu zeid, Ahmed Abu El Eneen, Nabil Gad El-Hak, Gamal El Ebidy, Omar Fathy, Ahmed Sultan, Mohamed Abdel Wahab,** Gastroenterology surgical center, Mansoura University, Mansoura 35516, Egypt

**Author contributions:** Nakeeb AE designed research; Nakeeb AE, Askar W, Atef E, Hanafy EE, Sultan AM, Salah T, shehta A, Sorogy ME, Hamdy E, Hemly ME, El-Geidi AA, Kandiel T, Shobari ME, Allah TA, Fouad A, zeid me, Eneen aaE, El-Hak ng*,* Ebidy GE, Fathy O, Sultan A and Wahab MA performed research; Nakeeb AE analyzeddata; Nakeeb AE, shehta A and SorogyME wrote the paper.

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**Correspondence to: Ayman El Nakeeb, Professor,** Gastroenterology surgical center, Mansoura University, Mansoura 35516, Egypt. elnakeebayman@man.edu.eg

**Telephone: +**2-50-6752021

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**Abstract**

***AIM***

to evaluate the evolution, trends in surgical approaches and reconstruction techniques, and important lessons learned from performing 1000 consecutive Pancreaticoduodenectomy (PD) for periampullary tumors.

***Methods***

This is a retrospective review of the data of all patients who underwent PD for periampulary tumour during the period from January 1993 to April 2017. The data were categorized into three periods, early period (1993-2002), middle period (2003-2012) and late period (2013-2017).

***Results***

The frequency of PD is increasingly performed after 2000. With time, elderly, cirrhotic, obese patients, patients with uncinate process carcinoma and borderline tumour are increasingly selected for PD. The median operative time and postoperative hospital stay decreased significantly over the periods. The hospital mortality is declined significantly from 6.6% to 3.1%. The postoperative complications is significantly decreased from 40% to 27.9%. There was significant decrease in post-operative pancreatic fistula in the second ten years from 15% to 12.7%. There was a significant improvement of median survival and the overall survival among the periods.

***Conclusion***

Surgical results of PD were significantly improved with mortality rate nearly reach 3%. Pancreatic reconstruction following PD is still debatable. The survival rate was also improved but the rate of recurrence is still high 36.9%.

**Key words:** pancreaticodudenectomy; pancreaticogastrostomy; Pancreaticojejunostomy; Postoperative pancreatic fistula; Periampullary tumour

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**Core tip:** pancreaticoduodenectomy (PD) is a complex abdominal procedure. The hospital mortality rate has decreased to less than 5% however the rate of postoperative morbidities remains high, from 40% to 50%. Pancreatic reconstruction following PD is still debatable. The long survival rate after PD is clearly improved with time but still poor. The frequency of PD is increasingly performed. With time, elderly, cirrhotic, obese patients, patients with uncinate process carcinoma and borderline tumour are increasingly selected for PD. The median operative time and posoperative hospital stay decreased significantly. The hospital mortality is declined significantly from 6.6% to 3.1%. The postoperative complications is significantly decreased.

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**Introduction**

The first successful localizes resection of periampullary tumour was performed by Dr William S Halsted in 1898. For the first time, Allen O Whipple described pancreaticoduodenectomy (PD) in the year 1935 when he modified the procedure that was performed before by Alessendro Codinivillan in Italy and Walter Keusch in Germany[1,2]. In 1963, Whipple's had done 37 PD in his era. From this era till 1980, PD was performed infrequently because the hospital mortality was high above 25%. After 1990 with development of high volume centers with improvement of operative technique, surgical equipment, and perioperative care, PD has become a relatively safe and commonly performed procedure in recent years[3-5].

PD is one of the most complex abdominal operations that is performed for a heterogenous group of periampullary lesionseither benign or malignant. PD involves extensive dissection, resection and different reconstruction procedures[3-8]. The rate of postoperative morbidities remains high, from 40 to 50% however the hospital mortality rate has decreased to less than 5% in many published series[5-8,9-11].

Many studies were performed to determine the risk factors of post-operative pancreatic fistula and try to present fistula risk scoring system after PD. They used many factors including pancreatic duct diameter, consistency of pancreas, BMI > 25 and final pathology[4-6,11-15]. Pancreatic reconstruction following PD is still debatable even for pancreatic surgeons. Ideally, pancreatic reconstruction after PD should reduce the risk of post-operative pancreatic fistula (POPF) and its severity if developed with preservation pancreatic functions (exocrine and endocrine function)[5-8].

The prognosis of pancreatic head adenocarcinoma is one of the most dismal of all cancers. After PD the 5-year survival is 5% to 20% making the worst survival of other periampullary cancers. Numerous prognostic factors have been found to improve survival rate after PD including lymph node status, free safety margins, tumor size, differentiation, complete excision of mesopancreas and vascular invasion[11-14].

Many points still debatable as regards PD included selection of patients, pancreatic reconstruction, and factors that improve survival rate so the aim of this study to evaluate the evolution, trends in surgical approaches and reconstruction techniques, and important lessons learned from performing 1000 consecutive PD for periampullary tumors in Gastrointestinal Surgery Center – Mansoura University over a period of 25 years.

**MATERIALS AND METHODS**

***Study design***

This is a retrospective review of the data of all patients who underwent PD for periampulary tumour in Gastrointestinal Surgery Center – Mansoura University, Egypt, during the period from January 1993 to April 2017. Patient data are recorded in a prospectively maintained database for all patients undergoing PD since 2000, and before 2000 the data are recorded from the archive files of all patients. An informed consent for the surgical procedures is obtained from each patient. Gastrointestinal Surgery Center – Mansoura University is a high-volume center of pancreatic surgery that was constructed in 1992. The first PD was performed in 1993, and was regularly performed afterwards in our center over a period of 25 years.

***Inclusion criteria***

This study included 1000 patients who underwent PD for different periampulary tumors (benign and malignant lesions) at our Center – Mansoura University, Egypt, during the period from January 1993 to April 2017. Over 25 years period, 1000 consecutive PD were performed by 20 surgeons. The data were categorized into three periods, early period (1993-2002), middle period (2003-2012) and late period (2013-2017). This study was approved by institusional review board IRB

***Exclusion criteria***

Patients with periampullary lesions who were explored during the same period and failed to complete PD procedure due to the presence of locally advanced or distant metastatic disease that was not detected in preoperative radiological workup.

***Preoperative assessment***

Preoperative diagnostic workup includes; clinical assessment, detailed laboratory investigations including tumor markers, and radiological investigations (abdominal ultrasound, abdominal triphasic computed tomography (CT), CT angiography, magnetic resonance cholangio-pancreatography, chest X ray, and bone survey). Preoperative biliary drainage is performed by endoscopic retrograde cholangiopancreatography (ERCP) in selected patients[16].

***Surgical procedures***

Over the study period and with accumulating experience, evolution of the surgical approach and techniques occurred.

***Dissection technique***

In the early period, the anterior approach was utilized in surgical dissection. Afterwards we shifted to utilize the posterior approach (one of artery first approach), aiming to identify vascular invasion at an early stage of the dissection, and to allow more radical excision of the mesopancreas[17].

Standard regional lymphadenectomy is performed, which included resection of nodes within the outlines of the hepatoduodenal ligament, right side of the superior mesenteric vessels, and inferior vena cava.

In the early period diathermy dissection and ligatures was used during the resection stage. Afterwards, a shift to use modern energy device occurred as Ligasure and Harmonic scalpel.

***Approach***

In most of our study period, we utilized an open surgical approach through extended right subcostal, or inverted J incisions.

In late period we started to utilize laparoscopic approach. In the beginning, we used the laparoscopy-assisted approach. This includes complete dissection by the laparoscopy then reconstruction is done through a small upper midline or transverse incision.

In the last year, we performed a totally ten laparoscopic PD. This includes completing the whole approach (dissection and reconstruction) by laparoscopy.

***Meso-pancreatectomy***

A complete removal of all lympho-vascular tissues between the uncinate process and superior mesenteric artery is mandatory in PD. These tissues are the most important site for local recurrence after PD. This concept had evolved in the recent years and became a standard step in the radical resection of periampullary tumors. We adopted this concept in the recent years of our study.

***Division of the pancreatic neck***

Initially, we divided the pancreas neck sharply by surgical scalpel then hemostasis is carried out after division. Recently we started to divide the pancreatic neck by diathermy and Harmonic scalpel.

***Reconstruction***

In the beginning of our series, we performed simple loop pancreatico-jejunostomy (PJ) for the reconstruction of the pancreatic stump. However, a high rate of pancreatic fistula was noticed. A shift of the reconstruction plan occurred to pancreatico-gastrostomy (PG). Short term outcomes were improved and lower rate of pancreatic fistula was noticed, but the long-term outcomes regarding the digestive and nutritional conditions were not appropriate.

With accumulating experience and refinement of the surgical technique, a re-shift to PJ (simple loop or isolated loop), with improved long term outcomes[18,19].

Recently, we adopted a tailored approach for the management of pancreatic stump management. In high risk patients of pancreatic fistula (presence of two or more risk factors) PG is preferred. In low and moderate risk patients (absence of risk factors or presence of one risk factor) PJ is more preferred.

***Postoperative management***

All patients are transferred to the intensive care unit (ICU) postoperatively. Antibiotics and analgesic are given to all patients. Octeriod analogue is given to some patients postoperatively. Abdominal drains and nasogastric tubes outputs are recorded daily. Patients started oral feeding once bowel sounds are restarted and can tolerate it by a fluid diet then a regular diet.

Abdominal ultrasound is done routinely in all patients postoperatively. Serum amylase and liver function tests were performed in postoperative day (POD) one and five. Ultrasound-guided tubal drainage is carried out in patients who had an abdominal collection.

Follow-up is scheduled at one week, three months and six months postoperatively, and then at one year. Patients are also seen at outpatient clinics if symptoms developed between follow-up visits.

***Definitions***

Complications will be defined as adverse events resulting in deviation from the normal postoperative course within 30 d after operation. Severity of complications will be assessed using the Clavien classification system from 1 to 5. Major complications represent those requiring endoscopic, radiologic, or surgical intervention or greater, and were defined as class 3 or higher[20].

Postoperative pancreatic fistula will be defined by International Study Group of Pancreatic Fistula (ISGPF) as any measurable volume of fluid on or after postoperative day three (POD 3) with amylase content greater than three times the serum amylase activity, and classified into three grades A, B, C[21-23].

Delayed gastric emptying will be defined as output from a nasogastric tube of greater than 500 mL per day that persisted beyond POD 10, the failure to maintain oral intake by POD 14, or reinsertion of a nasogastric tube[21-24].

***Outcomes of the study***

The aim of this study is to evaluate the mile stones, trends in surgical approaches and reconstruction techniques, and important lessons learned from performing 1000 consecutive PD for periampullary tumors in Gastrointestinal Surgery Center – Mansoura University over a period of 25 years.

The main outcome of the study is the rate postoperative morbidity, according to Clavien-Dindo classifications, and mortality after PD. Especial concern is focused on POPF, biliary complications, and delayed gastric emptying (DGE) and the predictive factors of each.

Also, we aim to evaluate the survival outcomes of the PD patients including recurrence, and overall survival (OS) and the different predictive factors of each.

***Statistical analysis***

Statistical analysis of the data in this study will be performed using SPSS software for windows, version 20. For continuous variables, descriptive statistics will be calculated and reported as median. Categorical variables will be described using frequency distributions. 2test will be used to compare categorical variables and one way Anouva for continuous variables. The predictive factors for postoperative complications will be evaluated by binary logestic regression method. Survival outcomes will be calculated by Kaplan-Meier method. The predictive factors for survival will be evaluated by Cox regression method. A *p* values < 0.05 is considered to be significant.

**Results**

One thousand patients underwent PD for resection of periampullary tumors from January 1993 to April 2017. Of 1000 patients underwent PD, 556 patients were pancreatic head mass, 312 patients were ampullary tumour, 61 patients were duodenal tumour 41 were cholangiocarcinoma and 30 patients were uncinate process mass. The median age was 54 years. The data were categorized into three periods, The first ten years (1993-2002), the total number was 300 cases underwent PD (30 cases/year. In the next ten years (2003-2012) the total number was 442 cases underwent PD (44.2 cases/year). In the last 5 years (2013-2017) the total number was 258 cases underwent PD (51.6 cases /year) (Figure 1)

***Preoperative data***

Elderly patients are increasingly selected for PD as median age of 53 in the first ten years and 55 in the last five years. Obese patients is increasingly selected in the last five years. There is no significant changes for selection of patients for PBD in the period of the study. PBD is indicated for patients with high serum bilirubin above 10 mg% with high liver enzymes, renal impairment, or associated cholangitis table 1.

***Intraoperative data***

Patients with periampullary tumours and well-compensated chronic liver disease are increasingly selected for PD (Table 2).

In the early period, we performed simple loop PJ (21.7%) for the reconstruction of the pancreatic stump then shift to PG (78.3%). In the second ten years the 94.3% of cases underwent PG. In the last five years there was a re-shift to PJ (simple loop or isolated loop) (46.1%).

Complete mesopancreatecomy was achieved in all cases in last five years

Operative time was significantly reduced with time (from 6 hours in the first ten years to 5 h in last five years).

The median intraoperative blood loss is decreased from 500 cc in the first ten years to 300 cc in last five years).

***Postoperative data***

The overall morbidity of all 1000 patients was 32.3%. The postoperative complications is decreased markedly in the recent years from 40% to 27.9%. There was a significant decrease in POPF in the second ten years from 15% to 12.7% with a decreasing in the severity. But the incidence of POPF increased again in last five years to 14.7%. Delay gastric emptying was the most common complication (18%). It was secondary to other postoperative complications in 15.2%. While primary DGE presented in 2.8% of cases (Table 3).

The median hospital stay and the day of drain removal were significantly shortest in the late period. It decreased from 9 d to 8 d.

The overall hospital mortality of all 1000 patients was 43 patients (4.3%). The hospital mortality is declined significantly from 6.6% to 3.1%.The causes of death were sepsis secondary to POPF in 17 patients, six cases due to cardiac arrest, six cases due to liver cell failure, five cases due to pulmonary embolism, three cases due to pancreatitis, three cases due to respiratory failure secondary to severe chest infection, two cases due to secondary hemorrhage, and one case due to uncontrolled bleeding PG.

Seventy patients had abdominal collection and required ultrasound guided tubal drainage. Seventy four patients (7.4%) required reexplorations due to internal hemorrhage (26 patients, 7/26 due to erosion of gastroduodenal artery), bleeding GJ (17 patients), bleeding PG (15 patients), peritonitis (12 patients) or debridement and drainage (4 patients). Completion splenopancreatectomy was needed in two cases due to POPF that erode the gastroduodenal artery and complicated by secondary internal hemorrhage

The overall recurrence rate in 870 patients had malignant pathology after PD was 36.9.2%. It was decreased from 50.4%. to 28.7%

After univariate analysis of risk factors for development of POPF found that six variables were found to be significantly associated with POPF (BMI more than 25, liver cirrhosis, soft pancreas, main pancreatic duct < 3 mm, pancreatic duct close to posterior edge < 3 mm, period of the study). These six risk factors of POPF identified in univariate analysis were further analyzed in multivariate analysis. Soft pancreas, main pancreatic duct < 3 mm pancreatic duct close to posterior edge < 3 mm, BMI > 25 kg/m2 and period of the study were found to be independent risk factors Table 4.

***Postoperative pathology***

There was significant difference among groups as regard site of periampullary tumour, type of pathology, number of dissected lymph nodes, number of infiltrated lymph nodes, lymph node ratio, safety margin, perivascular infiltration and perineural invasion (table 5).

***survival rate***

The overall survival 1-,3-,5- year survival for all cases was 90%, 33%, 19% respectively with a median survival of 26 mo. There was a significant difference among the groups as regards the median survival and the overall survival 1-,3-,5- year survival table 3, 6, Figure 2.

The survival analysis in this study revealing that female gender, patients not developed major complications, ampullary tumour, type of pathology, negative safety margin, negative lymph nodes, chemoradiotherapy and period of the study were all favorable prognostic variables in univariate and multivariate analysis. The improvement of survival with recent years may due to complete excision of mesopancreas, greater use of postoperative chemoradiotherapy, improvement of surgical techniques, and strict follow up of most of cases table 6.

**Discussion**

PD is a complex procedure including extensive dissection, resection and multiple reconstruction. Allen O Whipple described PD in the year 1935. From Whipple's era till 1980, PD was performed infrequently because the hospital mortality was high above 25%[2].

Patients selection still an important factor in decreasing postoperative morbidity and mortality. In our series, the frequency of PD is increasingly performed after 2000. Elderly patients are increasingly selected for PD as the median age was 53 years in the first ten years and became 55 years in the last 5 years. In the last five years we accepted patients above 75 years. The significant improvement in the surgical outcome of PD has encouraged surgeons to approach periampulary tumors as aggressively in elderly patients[7,12]. Patients with periampullary tumours and well-compensated chronic liver disease are increasingly selected for PD with accepted surgical outcomes. PD is only recommended in patients with Child A cirrhosis without portal hypertension[13]. PD is associated with an increased risk of postoperative morbidity in obese patient. With time obese patients is not a limitation for PD and increasingly selected[25-27].

Patients with uncinate process carcinoma are increasingly selected for PD. However, the locoregional recurrence rate was common and the overall survival rate was found to be lower than other periampullary tumour[28]. The role of postoperative chemoradiotherapy may improve the results. Borderline resectable pancreatic cancer should be included in indication of PD with advancement of chemoradiotherapy and techniques of vascular resection[29].

The impact of PBD on postoperative outcomes remains controversial. PBD before PD was associated with major postoperative morbidities and stent-related morbidity including infection, pancreatitis or adhesions. There is no significant changes for selection of patients for PBD in the period of the study. PBD is indicated for patients with high serum bilirubin above 10 mg% with high liver enzymes, renal impairment, or associated cholangitis[16,30,31].

In our center, laparoscopic pancreaticoduodenectomy (LPD) has been introduced as a feasible alternative to open PD since 2013 by dissection in some cases then complete LPD was performed at the end of 2013 but unfortunately the patients died in postoperative day 7. We restarted again at January 2016 performing ten complete LPD and in all cases the pancreatic reconstruction was PG. The median operative time was 8 hours so the procedure was performed by two teams (one team for complete dissection and the other one to perform all reconstruction). Only one hospital mortality was occurred due to severe pancreatitis and all cases passed smoothly without any complications. The median hospital stay was 5 d. The most important point to perform LPD a routine safe operation is to perform the procedure under skilled hands in selected patients with suitable surgical techniques[32,33].

The ideal and safe pancreatic reconstruction following PD is still debatable. We performed a comparative randomized study between PG and isolated loop PJ which revealing no significant difference between both methods as regards POPF but the pancreatic function was preserved with isolated loop PJ[18,19]. Recently with accumulating experience and refinement of the surgical technique, we adopted a tailored approach for the management of pancreatic stump management. Another a prospective randomized study comparing duct to mucosa and invagination pancreaticojejunostomy was carried out in our center concluded that invagination PJ is preferred in small pancreatic duct and provides less incidence of postoperative steatorrhae and associated with less severity of POPF if developed than duct to mucosa[19].

In our series, 32.3% of patients undergoing PD had a complications. The majority of complications were minor and not life threatening. The postoperative complications is decreased markedly in the recent years from 40% to 27.9%. There is significant decrease in POPF in the second ten years from 15% to 12.7% with decreasing the severity due to shift of pancreatic reconstruction from PJ to PG. But the incidence of POPF increased again in last five years to 14.7% due to reshift again to PJ to achieve better long term follow up as regards function and morphology of pancreas[18,19]. In this study, the development of major complications had a negative impact on overall survival

The median hospital stay is significantly shortest in the last ten years. In many high volume centers there has been significant decrease in postoperative stay after PD as a result of increase the frequency of PD, decreasing incidence of complication especially DGE, decreasing use of pylorus preserving PD which complicated by high incidence of DGE, improvement of postoperative care and management of postoperative complications[6,7,34-36].

In this study, the overall hospital mortality was 4.3%. 17/43 (39.5%) of patients died due to sepsis secondary to POPF. The decrease in hospital mortality following PD over the time is the most prominent achievement in PD. In this study the hospital mortality decreased significantly from 6.6% to 3.1% which is comparable to mortality rate in high volume centers[6-8].

Long term survival after PD for periampullary tumour adenocarcinoma still poor. However, the survival after PD is clearly improved with time due to improvement of surgical techniques, complete excision of mesopancreas, greater use of neoadjuvant and/or adjuvant chemoradiotherapy, and strict follow up of most of cases. There are many high volume centers in whom patients with pancreatic head carcinoma treated by PD have a 5 year survival around 20%[6,7,35,36].

The frequency of PD is increasingly performed and become a relatively safe. With time, elderly, cirrhotic, obese patients, patients with uncinate process carcinoma and borderline tumour are increasingly selected for PD. Surgical results of PD including operative time, hospital stay, postoperative complications were significantly improved with mortality rate nearly reach 3%. Pancreatic reconstruction following PD is still debatable. PG provide better short term outcomes including POPF, but the long-term outcomes regarding the pancreatic function and nutrition were not appropriate. However, PJ provides better long term outcomes. The survival rate was also improved due to complete mesoopancreatectomy, and utilization of adjuvant chemoradiotherapy, but the rate of recurrence is still high 36.9%. Laparoscopic pancreaticoduodenectomy (LPD) has been introduced as a feasible alternative to open PD.

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**Table 1 Demographic and preoperative data *n* (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variables** | **Total (1000)** | **First 10 yr**  **1993-2002** | **Second 10 yr**  **2003-2012** | **Last 5 yr**  **2013-2017** | ***P* value** |
| Age (yr) (median) | 54 (12-88) | 53 | 55 | 55 | 0.22 |
| Sex  Male  Female | 614 (61.4)  386(38.6) | 190 (63.3)  110 (36.7) | 260 (58.8)  182 (41.2) | 164 (63.6)  94 (36.4) | 0.33 |
| DM | 145 (14.5) | 39 (13) | 60 (13.6) | 46 (17.8) | 0.21 |
| BMI  < 25  > 25 | 723 (72.3)  277 (27.7) | 250 (38.3)  50 (16.7) | 326 (73.8)  116 (26.2) | 147 (57)  111 (43) | 0.0001 |
| Abdominal pain | 753 (75.3) | 230 (76.7) | 329 (0.74.4) | 194 (74.2) | 0.12 |
| Jaundice | 909 (90.9) | 265 (88.3) | 406 (91.9) | 238 (92.2 | 0.18 |
| Pre-operative biliary drainage | 511 (51.1) | 163 (54.5% | 226 (51.1) | 122 (47.3) | 0.23 |
| Preoperative serum albumin (gm) | 4 (3.2-5.2) | 4.1 | 4 | 3.9 | 0.23 |
| Preoperative serum bilirubin (mg) | 4 (0.5-38) | 3.1 | 4.7 | 4.3 | 0.0001 |
| Preoperative CEA | 6.4 (0.5-394) | 8 | 8 | 6 | 0.09 |
| Preoperative CA19-9 | 27 (0.5-1200) | 32 | 33 | 34 | 0.12 |

**Table 2 Operative data *n* (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variables** | **Total (1000)** | **First 10 yr**  **1993-2002** | **Second 10 yr**  **2003-2012** | **Last 5 yr**  **2013-2017** | ***P* value** |
| Cirrhosis | 129 (12.9) | 28 (9.3) | 62 (14) | 39 (15.1) | 0.009 |
| Mass size (cm) median  < 2  > 2 | 3 (0.5-15)  418 (41.8)  582 (58.2) | 3  123 (41)  177 (59) | 3  174 (39.4)  268 (60.6) | 3  123 (46.9)  137 (53.1 | 0.14 |
| Pancreatic texture  Soft  Firm | 596 (59.6)  404 (40.4) | 190 (63.3)  110 (36.7) | 263 (59.5)  179 (40.5) | 143 (55.4)  115 (44.6) | 0.23 |
| Median pancreatic duct diameter (mm)  < 3  > 3 | 5 (1-15)  313 (31.3)  687 (68.7) | 97(32.3)  20367.7) | 137 (30.9)  305 (60.1) | 79 (30.6)  179 (69.4) | 0.47 |
| Pancreatic duct to posterior border (mm)  < 3  > 3 | 421 (42.1)  579 (57.9) | 128 (42.7)  172 (57.3) | 185 (41.9)  257 (58.1) | 108 (41.9)  150 (58.1) | 0.45 |
| Pancreatic stump mobilization (cm) | 2 (1-4)) | 2 | 2 | 2 | 0.45 |
| CBD diameter (mm) | 15 (5-30) | 15 | 15 | 15 | 0.06 |
| Type of reconstruction  PG  Simple PJ  Isolated loop PJ | 791 (79.1)  163 (16.3)  46 (4.6) | 235 (78.3)  65 (21.7)  0 | 417 (94.3)  25 (5.7)  0 | 139 (53.9)  73 (28.3)  46 (17.8) | 0.0001 |
| Duct to mucosa  Invaginated type with duct to mucosa  Invaginated type without duct to mucosa  No anastomosis | 134 (13.4)  644 (64.4)  221 (22.1)  1 (0.1) | 9 (3)  234 (78)  57 (19)  0 | 65 (14.7)  250 (65.6)  126 (28.5)  1 (0.2) | 60 (23.3)  160 (62)  38 (14.7)  0 | 0.0001 |
| Standard approach  Posterior approach | 908 (90.8)  92 (9.2) | 277 (92.3)  23 (7.7) | 388 (87.8)  54 (12.2) | 243 (94.7)  15 (5.8) | 0.004 |
| Complete mesopancreatectomy | 574 (57.4) | 83 (27.7) | 233 (52.7) | 258 (100) | 0.0001 |
| Laparoscopic assisted PD  Complete laparoscopic PD | 11 (1.1)  10 (1) | 0  0 | 0  0 | 11 (4.3)  10 (3.9) | 0.0001 |
| Vascular resection  primary anastomosis  Gortex | 12 (1.2)  0  0 | 0  0  0 | 4 (0.9)  3 (0.7)  1 (0.2) | 8 (3.1)  8 (3.1)  0 | 0.003 |
| Operative time (h) | 5 (3.5-10) | 6 | 5 | 5 | 0.001 |
| Blood loss (cc) | 500 (50-4000) | 500 | 400 | 300 | 0.001 |

PG: pancreatico-gastrostomy; PJ: pancreatico-jejunostomy.

**Table 3 Postoperative data *n* (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variables** | **Total (1000)** | **First 10 yr**  **1993-2002** | **Second 10 yr**  **2003-2012** | **Last 5 yr**  **2013-2017** | ***P* value** |
| Hospital stay (d) | 8 (5-71) | 9 | 8 | 8 | 0.0001 |
| Time to oral intake (d) | 5 (4-56) | 6 | 5 | 5 | 0.33 |
| Total amount of drainage (ml) | 700 (40-35000) | 1200 | 600 | 600 | 0.0001 |
| Drain removal (d) | 8 (4-71) | 8 | 8 | 8 | 0.03 |
| Total postoperative complications | 323 (32.3) | 120 (40) | 131 (29.6) | 72 (27.9) | 0.02 |
| Dindo grade  I  II  III  IV and V | 114 (11.4)  97 (9.7)  69 (6.9)  43 (4.3) | 24  40  36  20 | 47  45  24  15 | 43  12  9  8 | 0.11 |
| Severe complications (≥ III)  Minor  Major | 211 (21.1)  109 (10.9) | 84  56 | 92  69 | 55  17 | 0.23 |
| Pancreatic fistula  Grade A  Grade B  Grade C | 139 (13.9)  67 (6.7)  48 (4.8)  24 (2.4) | 45 (15)  14  20  11 | 56 (12.7)  33  17  6 | 38 (14.7)  20  11  7 | 0.01  0.04 |
| DGE  Types of DGE  Secondary DGE  Primary DGE | 180 (18)  152 (15.2)  28 (2.8) | 76 (25.3)  70 (23.3)  5 (1.7) | 67 (15.2)  54 (12.2)  13 (2.9) | 37 (14.3)  27 (10.5 )  10 (3.9) | 0.06  0.03 |
| Pulmonary complications | 46 (4.6) | 20 (6.7) | 21 (4.8) | 5 (1.6) | 0.01 |
| Bile leak | 73 (7.3) | 39 (13) | 19 (4.3) | 15 (5.8) | 0.001 |
| Postoperative bleeding | 25 (2.5) | 13 (4.3) | 7 (1.6) | 5 (1.9) | 0.49 |
| Pancreatitis | 20 (2) | 12 (4.3) | 7 (1.6) | 1 (0.4) | 0.004 |
| Bleeding PG | 15 (1.5) | 8 (2.7) | 5 (1.2) | 2 (0.8) | 0.14 |
| Wound infection | 50 (5) | 13 (4.6) | 25 (5.7) | 12 (4.7) | 0.77 |
| Re-operation | 74 (7.4) | 25 (8.3) | 33 (7.5) | 16 (6.2) | 0.21 |
| Recurrence | 321 (36.9) | 130 (50.4) | 125 (32.6) | 66 (28.7) | 0.0001 |
| Hospital mortality | 43 (4.3) | 20 (6.6% | 15 (3.4) | 8 (3.1) | 0.02 |
| Postoperative chemoradiotherapy | 275 (27.5) | 0 | 132 (29.9) | 143 (55.4) | 0.0001 |
| Overall median survival (mo)  1-yr  3-yr  5-yr | 26 (1-300)  90%  33%  19% | 21  87%  19 %  11 % | 30  93%  37%  21% | 37  87%  64% | 0.0001 |

DGE: delayed gastric emptying; PG: pancreatico-gastrostomy.

**Table 4 Univariate and multivariate analysis of risk factors of development of post-operative pancreatic fistula**

|  | Univariate  *P* value | Multivariate *P* value | Exp(B) | 95%CI for EXP(B) | |
| --- | --- | --- | --- | --- | --- |
| Lower | Upper |
| Age grouping > 60 yr | 0.2 |  |  |  |  |
| Sex | 0.99 |  |  |  |  |
| DM | 0.58 |  |  |  |  |
| BMI > 25 | 0.0001 | 0.0001 | 6.468 | 4.193 | 9.977 |
| Preoperative serum billirubin > 10 mg% | 0.62 |  |  |  |  |
| Preoperative ERCP | 0.52 |  |  |  |  |
| Liver cirrhosis | 0.05 | 0.328 | 0.699 | 0.341 | 1.434 |
| Size of the tumour > 2 cm | 0.91 |  |  |  |  |
| Soft pancreas | 0.0001 | 0.0001 | 0.218 | 0.140 | 0.341 |
| Pancreatic duct diameter > 3 mm | 0.0001 | 0.0001 | 0.182 | 0.118 | 0.279 |
| Pancreatic duct closely related to posterior border of pancreas > 3 mm | 0.0001 | 0.0001 | 0.372 | 0.243 | 0.570 |
| Blood loss >1000 ml | 0.67 |  |  |  |  |
| Blood transfusion | 0.94 |  |  |  |  |
| Type of pancreatic reconstruction | 0.62 |  |  |  |  |
| Duration of operation | 0.75 |  |  |  |  |
| Site of the tumour | 0.34 |  |  |  |  |
| Period of the study | 0.001 | 0.001 | 0.615 | 0.461 | 0.82 |

ERCP: endoscopic retrograde cholangiopancreatography.

**Table 5 Postoperative pathology *n* (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variables** | **Total (1000)** | **First 10 yr**  **1993-2002** | **Second 10 yr**  **2003-2012** | **Last 5 yr**  **2013-2017** |  |
| Site of the tumour  Ampullary tumour  Pancreatic head mass  CBD duct tumour  Duodenal tumour  Uncinate process mass | 312 (31.2)  556 (55.6)  41 (4.1)  61 (6.1)  30 (3) | 92 (30.7)  171 (57)  16 (5.3)  20 (6.7)  1 (0.3) | 145 (32.8)  257 (58.1)  13 (2.9)  27 (6.1)  0 | 75 (29)  128 (49.6)  12 (4.7)  14 (5.4)  29 (11.3) | 0.0001 |
| Pathological diagnosis  Adenocarcinoma  Undifferentiated carcinoma  Papillary cystadenocarcinoma  Lymphoma  Neuroendocrine tumor  Solid pseudopapillary tumor SPT  Chronic pancreatitis  Benign cyst  Adenoma with dysplasia  Gastrointestinal stromal tumour (GIST)  Glomus  Adenosqumous  Pleomorphic adenoma  Adenomyoma | 836 (83.6)  20 (2)  6 (0.6)  4 (0.4)  28 (2.8)  20 (2)  24 (2.4)  12 (1.2)  41 (4.1)  2 (0.2)  1 (0.1)  2 (0.2)  1 (0.1)  3 (0.3) | 250 (83.3)  1 (1.7)  4 (1.3)  2 (0.6)  12 (4)  5 (1.7)  6 (2)  3 (1)  15 (5)  0  1 (0.3)  1 (0.3)  0  0 | 357 (80.7)  19 (4.3)  2 (0.5)  2 (0.5)  10 (2.3)  8 (1.8)  14 (3.2)  8 (1.8)  19 (4.3)  1 (0.2)  0  1 (0.2)  1(0.2)  0 | 229 (88.8)  0  0  0  6 (2.3)  7 (2.7)  4 (1.6)  1 (0.4)  7 (2.7)  1 (0.4)  0  0  0  3 (1.2) | 0.0001 |
| Malignant  Borderline  benign | 870 (87)  48 (4.8)  82 (8.2) | 258 (86)  17(5.7)  25 (8.3) | 382 (86.4)  18 (4.1)  42 (9.5) | 230 (89.1)  13 (5.1)  15 (5.8) | 0.38 |
| Number of dissected lymph node | 6 (0-40) | 5 (0-18) | 6 (0-40) | 6 (0-40) | 0.59 |
| Number of lymph node infiltration | 0 (0-14) | 0 (0-3) | 0 (0-14) | 0 (0-14) | 0.07 |
| Perineural infiltration | 187 (18.7) | 62 (20.7) | 75 (17) | 50 (19.9) | 0.09 |
| Perivascular infiltration | 134 (134) | 40 (13.3) | 66 (14.9) | 28 (10.9) | 0.13 |
| Pancreatic safety margin  R1  R2 | 91 (9.1)  15 (1.5) | 40 (13.3)  7 (2.3) | 41 (9.3)  6 (1.4) | 10 (3.8)  2 (0.7) | 0.01 |

**Table 6 Univariate and Multivariate analysis of factors affecting the survival**

|  | **Median survival** | **1 yr survival** | **3 yr survival** | **5 yr survival** | **Univariate *P* value** | **Multivariate *P* value** | **Exp(B)** | **95%CI for EXP(B)** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Lower** | **Upper** |
| > 60 yr  < 60 yr | 26  24 | 91  87 | 35  31 | 20  18 | 0.07 |  |  |  |  |
| Male  Female | 24  30 | 89  91 | 30  39 | 16  25 | 0.001 | 0.003 | 0.77 | 0.651 | 0.914 |
| BMI < 25  BMI > 25 | 27  25 | 92  84 | 32  37 | 19  20 | 0.99 |  |  |  |  |
| Preoperative serum billirubin < 10 mg%  Preoperative serum billirubin > 10 mg% | 26  25 | 90  90 | 34  33 | 21  18 | 0.6 |  |  |  |  |
| Preoperative CA19-9 < 37  Preoperative CA 19-9 > 37 | 26  25 | 90  89 | 35  31 | 24  14 | 0.17 |  |  |  |  |
| Preoperative CEA < 5  Preoperative CEA > 5 | 26  25 | 90  91 | 34  33 | 21  18 | 0.69 |  |  |  |  |
| History of preoperative ERCP  No history of ERCP | 25  26 | 88  92 | 33  33 | 15  25 | 0.19 |  |  |  |  |
| Normal liver  Liver cirrhosis | 32  25 | 90  90 | 37  33 | 24  19 | 0.11 |  |  |  |  |
| Size of the tumour < 2 cm  Size of the tumour > 2 cm | 28  25 | 91  89 | 37  31 | 20  19 | 0.16 |  |  |  |  |
| Type of pancreatic reconstruction  PG  Simple loop PJ  Isolated loop PJ | 25  32  32 | 90  90  80 | 31  44  48 | 17  28  48 | 0.11 |  |  |  |  |
| Without POPF  With POPF | 26  25 | 90  89 | 34  28 | 19  23 | 0.79 |  |  |  |  |
| Without major postoperative complications  With major postoperative complications | 27  24 | 93  82 | 35  31 | 20  18 | 0.03 | 0.005 | 0.784 | 0.661 | 0.929 |
| Site of the tumour  Ampullary tumour  Pancreatic head mass  CBD duct tumour  Duodenal tumour  Uncinate process mass | 33  23  32  31  12 | 90  81  90  90  79 | 42  28  30  42  18 | 22  11  20  21  0 | 0.02 | 0.3 | 1.049 | 0.958 | 1.148 |
| Type of pathology  Adenocarcinoma  Neuroendocrine tumor  Solid pseudopapillary tumor SPT  Chronic pancreatitis  Benign cyst  Adenoma with dysplasia | 26  65  150  160  130  85 | 90  85  100  96  100  91 | 27  71  94  96  90  67 | 8  60  94  84  70  48 | 0.0001 | 0.005 | 0.97 | 0.951 | 0.991 |
| Lymph node negative  Lymph node infiltrated | 29  25 | 92  87 | 38  27 | 27  8 | 0.0001 | 0.0001 | 0.559 | 0.413 | 0.757 |
| Lymph node ratio  0  < 0.2  0.2-0.4  > 0.4 | 28  25  25  24 | 91  89  86  88 | 38  31  28  21 | 27  18  11  4 | 0.0001 | 0.15 | 0.908 | 0.797 | 1.034 |
| Without perineural infiltration  With perineural infiltration | 25  24 | 89  91 | 35  28 | 21  12 | 0.06 |  |  |  |  |
| Without perivascular infiltration  With perivascular infiltration | 29  25 | 91  86 | 44  35 | 24  14 | 0.29 |  |  |  |  |
| Pancreatic safety margin  R0  R1  R2 | 26  22  12 | 90  92  70 | 35  27  19 | 20  19  0 | 0.0001 | 0.0001 | 1.695 | 1.345 | 2.136 |
| With postoperative chemoradiotherapy  Without postoperative chemoradiotherapy | 39  24 | 92  89 | 53  28 | 34  15 | 0.0001 | 0.0001 | 0.567 | 0.435 | 0.741 |
| Period of the study  1993-2002  2003-2012  2013-2017 | 21  30  37 | 87  93  87 | 19  37  63 | 11  21 | 0.001 | 0.0001 | 0.64 | 0.555 | 0.738 |

PG: pancreatico-gastrostomy; PJ: pancreatico-jejunostomy; POPF: Post-operative pancreatic fistula.



**Figure 1 In the first ten years (1993-2002) the total number was 300 cases underwent PD (30 cases/yr. In the next ten years (2003-2012) the total number was 442 cases underwent PD (44.2 cases/yr).** In the last 4 yr (2013-2017) the total number was 258 cases underwent PD (51.6 cases/yr).



**Figure 2 The overall survuival curves of patients according to the 3 periods.** The overall survival rate significantly improved and 5-yr survival rate for early period is 11%, 21% for the middle period and 64% for the late period (*P* = 0.0001).