



## SURGICAL AND ONCOLOGICAL OUTCOMES OF PANCREATODUODENECTOMY– SINGLE INSTITUTIONAL RETROSPECTIVE ANALYSIS

### Oncology

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### ABSTRACT

**Background:** Whipple's pancreaticoduodenectomy (PD) described in 1945 had mortality of 38%. With advances in surgical management of PD, mortality rate for PD has been reported to be less than 5%. Postoperative pancreatic fistula (POPF) remains a major complication and morbidity after PD with incidence upto 40%.

**Materials and Methods:** This is a retrospective analyses of patients who underwent PD from a tertiary cancer center in southern India from Jan 2013 to Dec 2017. Preoperative, intraoperative, postoperative details and surgico-oncological outcomes are presented.

**Results:** Of 76 patients presumed as operable periampullary cancers, 16 were declared inoperable and data analyzed for remaining 60 patients. 44% underwent classical Whipple's PD and 56% pylorus preserving PD. Duct to mucosa pancreaticojejunostomy was performed in all patients. Mean operative time, blood loss and hospital stay was 293±68.6min, 695±300ml and 13±6days; 8% developed grade A delayed gastric emptying (DGE); POPF Grade B in 5%. Wound infection (25%) and pneumonia (15%) are common postop complications; Five patients (8%) had biliary fistula; 30 day in-hospital-mortality was 1.6%; 60% had periampullary tumours; Median survival was 22 months (Range 7-76 months); 10% developed liver metastasis on follow up.

**Conclusions:** Pancreaticoduodenectomy is a safe operation in experienced hands. Surgical results from our center is comparable to the literature published from centers of excellence.

### KEYWORDS

Pancreaticoduodenectomy, whipple's operation, POPF

#### INTRODUCTION:

Pancreaticoduodenectomy (PD) for cancers arising in pancreas was described by Whipple, et al in 1945 with 31% mortality (1). With increasing surgical experience and better postoperative management, mortality has come down and recent studies from experienced centers have reported less than 5% mortality (2-3). Morbidity associated with PD include postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), biliary leak, wound infection, postoperative pancreatic hemorrhage, need for reoperations and prolonged hospital stay. Incidence of POPF ranges from 3-45% and also accounts for high mortality. The objective of this study is to describe the surgical outcomes of PD by an experienced surgical team and compare with the available results from best centers.

#### MATERIAL AND METHODS:

This study is a retrospective analysis of patients who underwent PD during the period of Jan 2013 to Dec 2017 in a tertiary cancer center in southern India. The patients who satisfy the following inclusion criteria are included in this study: Age more than 18 years, ECOG performance status 2 or less, bilirubin less than 20mg/dl, operable periampullary cancers as per imaging.

The preoperative, intraoperative details and postoperative outcomes of patients who underwent PD are presented in this study. All patients underwent detailed preoperative evaluation in form of blood counts, serum biochemistry, coagulation profile, chest radiograph, upper gastrointestinal endoscopy, Fine needle aspiration cytology (FNAC)/ biopsy of the lesion if feasible, Triple phase contrast enhanced computed tomogram. We rely on proper preoperative imaging to assess the operability of the lesion and if deemed operable posted for surgery. Patients with bilirubin more than 20 mg/dl were considered for preop stenting and surgery performed after 4 weeks.

Intraoperatively, abdomen opened by roof top incision and assessed for metastatic disease. We routinely do uncinate first approach and resectability is assessed after Cattell-brush maneuver and Kocherisation. After mobilization, division of stomach or duodenum and bile duct is performed. Sharp division of the neck of pancreas is performed after taking hemostatic sutures on superior and inferior pancreatic edges. At the end, jejunum is transected after ligating the

first jejunal branch. After ensuring hemostasis, jejunal cut end is brought into supracolic compartment and end to side, duct to mucosa pancreaticojejunal (PJ) anastomosis is performed with 4-0 PDS suture as described by Heidelberg group with slight modifications (4,5). We routinely use pancreatic stent of adequate size. This is followed by hepaticojejunostomy (HJ) 15cm distal to PJ anastomosis in single layer interrupted 4-0 PDS suture. Following this an antecolic gastro or duodenojejunosomy is performed 45 cm distal to HJ site in 2 layers using 3-0 PDS. We do not perform jejunojejunosomy or feeding jejunostomy routinely. After closing mesocolic defect, soft flank drains are kept through both flank areas with their tips crossing the anastomosis posteriorly. Omental or falciform ligament flap is placed on superior mesenteric vessels.

All patients postoperatively were shifted to ICU. Routine postoperative instructions are followed with respect to antibiotics and analgesics. Nasogastric tube is removed on day 3 and patient allowed orally. Daily vitals, drain and urine output charting is maintained. Serum and drain amylase levels were sent on day 3. Drains were removed when output is serous and less than 50ml per day.

POPF is defined as per the new International study group on pancreatic surgery (ISGPS) 2016 definitions (6). As per new definition, POPF is broadly divided into biochemical leak (BL) (formerly grade A) and clinically relevant POPF (Grade B & C). A clinically relevant POPF is defined as a drain output of any measurable volume of fluid on or after day 3 with amylase level greater than 3 times upper Institutional normal serum amylase level, associated with a clinically relevant development/condition related directly to the POPF.

Delayed gastric emptying defined as per ISGPS 2007 definition (7). Grade A DGE should be considered if nasogastric tube (NGT) is required between the POD 4 and 7, or if reinsertion of NGT was necessary owing to nausea and vomiting after removal by POD 3 and patient is unable to tolerate a solid diet on POD 7, but resumes a solid diet before POD 14. Grade B DGE is present if NGT is required from POD 8-14, if reinsertion of NGT was necessary after POD 7, or if patient cannot tolerate unlimited oral intake by POD 14, but is able to resume a solid oral diet before POD

21. Grade C DGE is present when nasogastric intubation cannot be

discontinued or has to be reinserted after POD 14, or if the patient is unable to maintain unlimited oral intake by POD 21. Grade B and C are considered clinically relevant DGE.

Post pancreatectomy hemorrhage was defined as per ISGPS 2007 definition into three grades based on time of onset, location and severity of hemorrhage(8).

The post-operative morbidity data was collected. All deaths within 30 days of operation are considered as in hospital mortality. Adjuvant treatment was decided after multidisciplinary meeting.

**Statistical analysis:**

Data entry was done in Microsoft excel worksheet. Descriptive statistics viz. mean, Standard deviation (SD), median, minimum and maximum values were computed for all study variables. Median was used when standard deviation is large. Frequency of categorical variables were represented in percentages. The details are presented in table format.

**RESULTS:**

Between Jan 2015 to Dec 2018, 76 patients were eligible for undergoing PD, out of which 16 were declared inoperable on table after laparotomy and exploration. Remaining 60 patients were included in this analysis. The demographic data, baseline characteristics, preoperative details, intraoperative parameters and postoperative outcomes are presented in the table 1 and 2.

The median age is 52 years with more females. Incidence of smoking and alcoholism was 30% and 22%. 21% were diabetics and 17% were hypertensives. In the imaging studies, 86% had evidence of a periampullary mass, 78% had significant intrahepatic biliary dilation, 65% had pancreatic duct dilation and 13% had significant lymphadenopathy. Preoperative pathological diagnosis was possible in 43% of patients.

Most common symptom of presentation was jaundice (65%) followed by abdominal pain (56%). The mean bilirubin level was 4.4 ± 4.1 mg%, Ca-19.9 level was 43.86 U/ml (1.45-41681 U/ml) and mean INR was 1.11±0.16.

Classical whipple's PD and pylorus preserving PD was performed in 44% and 56% respectively. 55% of patients has firm pancreas and 60% had duct size more than 3 mm. Mean operative time and blood loss was 293 ± 68.6 min and 695 ± 300 ml respectively. Mean blood transfusion requirement perioperatively was 1 ± 0.91 units. 30% of patients were extubated on table with mean ICU stay duration was 34.9 ± 15.2 hours. Stent cultures are positive in all patients with preoperative stenting and most common organism isolated was E.coli. 40% of patients have received post-operative octreotide when the anastomosis is deemed high risk by operating surgeon.

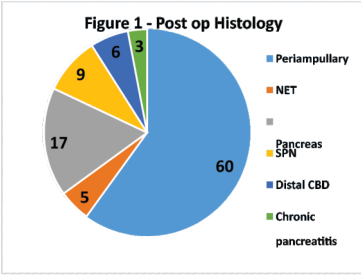
Most common postoperative morbidity in our series was wound infection (25%) followed by pneumonia (15%), DGE (8%), POPF (8%) and biliary leak (8%). Most common organism isolated from wound culture was enterococcus faecalis followed by MRSA. 8% had grade A DGE. 3% had biochemical leak and 5% had clinically relevant grade B fistula. None had grade B or C DGE or grade C POPF or postpancreatectomy hemorrhage. Five patients developed biliary leak; among them two had POPF grade B out of whom only one required percutaneous pig tail catheter insertion, but the other patients were managed conservatively. Mean hospital stay was 13 ± 6 days. 30 days in-hospital mortality was 1.6%. The only patient who died had cardiac comorbidity preoperatively and had decompensation on day 4 but had no evidence of POPF.

Postoperative histologies are shown in figure-1. Most common histology was peri ampullary carcinoma (60%) followed by head pancreas (17%). Average lymph node yield was 10.2 ± 5.9 nodes. Median survival in our patients was 22 months (7 – 76). 20% of patients received adjuvant treatment. 10% developed liver metastasis on follow up.

Variable	Percentage % (n = 60)
Age	52 years (20-76 years)
Males	42% (25)
Females	58% (35)

Preoperative bile duct stenting	10% (6)
Pre op ASA score	
ASA II	76.7% (46)
ASA III	23.3% (14)
BMI	23.2 ± 5.88 kg/m2
Ca 19.9	43.86 (1.45-41681 U/ml)
Hb%	11.16 ± 2.02 g%
Platelet volume	8.06 ± 0.99 fl
Bilirubin	4.4 ± 4.1 mg%
ALP	272 IU (73-1189)
S. Albumin	3.76 ± 0.6 g%
A/G ratio	1.12 ± 0.46
Prothrombin time	14.86 ± 1.98 sec
INR	1.11 ± 0.16

Variables	Percentage % (n=60)
Classical Whipple's PD	44% (26)
Pylorus preserving PD	56% (34)
Soft pancreas	45% (27)
Firm pancreas	55% (33)
< 3mm size duct	40% (24)
≥ 3 mm size duct	60% (36)
Operative time	293 ± 68.6 min
Blood loss	695 ± 300 ml
Intra op blood transfusion	0.9 ± 0.7 units
Post op blood transfusion	1.47 ± 1.03 units
Wound infection	25% (15)
Pneumonia	15% (9)
DGE	
Grade A	8% (5)
Grade B/C	0
POPF	
Biochemical leak	3% (2)
Grade B	5% (3)
Grade C	0
Post pancreatic hemorrhage	0
Biliary leak	8% (5)
Readmission to ICU	0
Drain removal day	15 days (8-35)
Hospital stay	13 ± 6 days
30 day in hospital mortality	1.6% (1)
Lymph node yield	10.2 ± 5.9 nodes
Median survival	22 months (7-76)



**DISCUSSION:**

Sir Andrew Watt kay named pancreatic resection similar to surgical venturing into "Tiger country"(9). Codivilla first performed PD for carcinoma of pancreas but unfortunately patient died at 18 days from cachexia due to steatorrhea(10). In 1935, Whipple, Parsons and Mullins reported two-stage procedure with good survival of their patients and in 1946 Whipple publishes his 10- year experience and advocated a one stage procedure(11,12). The main surgical indications for PD are periampullary cancers, pancreatic head cystic neoplasms, chronic pancreatitis and pancreatic trauma.

The morbidity and mortality associated with the PD is steadily decreasing and experienced centers in the world have reported less than 5% mortality(13). But morbidity rate of PD, in range of 32-52%, still remains a leading cause of increased hospital stay and treatment costs(5,14). Majority of the morbidity is due to POPF with incidence of 10-28.5%(15). For improving POPF incidence, many types of post PD anastomosis with modifications to standard techniques have been described and tested in literature viz., pancreatico gastrostomy (PG),

pancreatico jejunostomy (PJ), end to end, end to side techniques which can be invaginating or duct to mucosa(14,16,17). A multi institutional analysis, by Ecker et al, of 5323 PDs had revealed significantly higher clinically relevant POPF in PG than PJ(18). The incidence of POPF depends on technique of PJ anastomosis, which is the Achilles heel, and surgical expertise. No specific technique can eliminate the development of clinically relevant postoperative pancreatic fistula but the consistent practice of a particular technique can decrease rates of POPF and hence morbidity(2,19). In our study, we did end to side duct to mucosa PJ anastomosis which have been practicing in our institute for more than 15 years, which reflects the experience attained in executing the procedure. In our study, 55% had firm pancreas and 60% had  $\geq 3$  mm size duct which might have contributed to lower incidence of POPF rates. It has been shown in studies that soft texture is associated with fistula rate of 22.6% and 20.4-fold increase in fistula risk and no patient with firm gland developed a fistula(20). In our series two of the grade B POPF happened in patients who had soft pancreas and another in one patient having firm pancreas with 3mm duct size.

Five patients had DGE and required reinsertion of Ryle's tube due to bilious vomiting on day 4 to 5 and managed conservatively with prokinetics. All were allowed liquids orally after clamping of the tube on day 8-9 and all were able to tolerate solid diet before post op day 14. None of our cases had grade B or C DGE. This may be due to antecolic gastrojejunal anastomosis we routinely do in PD and less incidence of POPF in our study. It has been shown in various studies that retro colic GJ, diabetes mellitus, presence of complications, type of pancreatic reconstruction, and severity of POPF were independent significant risk factors for development of DGE(21,22).

The only mortality we had was a patient with known cardiac comorbidity preoperatively, who had history of myocardial infarction, but he decompensated postoperatively on day 4. He did not have POPF so death is not related to anastomotic failure but merely cardiac insult either intraop or immediate post op period. We did not have any case getting admitted back to ICU and none of the cases were reexplored. Four of the six patients who had preoperative biliary stenting developed wound infection which also supports the high chances of wound infection in stented patients as shown in Velanovich study(23). The median survival measured in our study is 22 months with range of 7 months to 76 months as 60% of our patients had periampullary cancers which carry better survival than pancreatic head cancers. As practice makes man perfect, we have more than 15 years' experience in performing PD and we present our data with mortality and morbidity rates almost similar when compared to experienced centers as shown in table-3.

## CONCLUSION:

Pancreaticoduodenectomy is a complex procedure associated with morbidity and mortality. The most common cause of morbidity is due to POPF. Gaining experience by adhering to a meticulous adaptable anastomotic technique, standard perioperative management strategies, early intervention will significantly decrease the morbidity, mortality, hospital stay and treatment related costs.

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