

# Characteristics of Pancreaticoduodenal Resection on Periapillary Tumor Cases by Jakarta Tertiary Hospital Team: Three Decade Report

Toar JM Lalisang\*, Yarman Mazni\*, Yefta Moenadjad\*, Sahat Matondang\*\*

\*Department of Surgery, Faculty of Medicine, Universitas Indonesia/  
Dr. Cipto Mangunkusumo General National Hospital, Jakarta

\*\*Department of Radiology, Faculty of Medicine, Universitas Indonesia/  
Dr. Cipto Mangunkusumo General National Hospital, Jakarta

## Corresponding author:

Toar JM Lalisang. Department of Surgery, Dr. Cipto Mangunkusumo General National Hospital. Jl. Diponegoro No. 71 Jakarta Indonesia. Phone/facsimile: +62-21-3148705. E-mail: toar.m@ui.ac.id

## ABSTRACT

**Background:** There were only few publications related to pancreaticoduodenal resection (PDR) /Whipple procedure in Indonesia in the past decade.

**Method:** Retrospectively report of the characteristics and outcomes of PDR performed by Cipto Mangunkusumo Hospital surgical team from 1993 to 2017 were collected.

**Results:** PDR were performed in 213 patients, with a mean age of 50.6 years and 54.4% patients were females. Predominant preoperative clinical findings were jaundice (68.9%) and mild hypoalbuminemia (69.9%). Biliary decompression was performed in 112 (52.6%) subjects. Average surgical waiting time was 3.5 months. While PDR were performed in 84 (39.5%) subjects, pyloric preserving pancreaticoduodenal technique was predominated in 128 (59.8) and predominated, especially during the latter years. Fifteen (9.0%) cases were benign. Thirty-one (14.6%) subjects underwent relaparotomy, 16 (51.6%) of whom died post-operatively. Overall operative mortality decreased from 16.9% to 5.5% in 2016, while resection rate generally increased over time, ranging from 2 - 21/year. Less than 10% of subjects survived for > 5 years, while < 20% survived for < 24 months. Overall morbidity was 65.1% in 177 survivors, with surgical site infection in 52.5%, pancreatic fistula in 24.2%, and post-pancreatectomy haemorrhage (PPH) as a fatal postoperative complication in 19 (8.9%) cases. Patients who died within 30 days postoperatively had significantly more relaparotomies and PPH ( $p < 0.001$ ).

**Conclusion:** Prolonged jaundice and mild hypoalbuminemia are dominant characteristics in our Indonesian PDR subjects. Cipto Mangunkusumo Hospital is a high-volume PDR centre and world class hospital. Mortality rates decreased with the increasing resection rates. Relaparotomy and PPH are predictors of poor outcome.

**Keywords:** hypoalbuminemia, prolonged jaundice, whipple.

## ABSTRAK

**Latar belakang:** Tidak banyak publikasi terkait reseksi pankreaoduodenal/prosedur Whipple di Indonesia pada dekade terakhir.

**Metode:** Penelitian dilakukan secara retrospektif menggunakan data prosedur Whipple yang dilakukan oleh tim bedah Rumah Sakit Dr. Cipto Mangunkusumo dari 1993 hingga 2017.

**Hasil:** Prosedur Whipple dilakukan pada 213 subjek dengan rerata usia 50,6 tahun dan 54,4% di antaranya perempuan. Temuan klinis preoperatif dominan yang didapatkan adalah ikterus dan hypoalbuminemia ringan.

*Dekompresi bilier dilakukan pada 112 (52,6%) subjek. Rerata waktu tunggu operasi adalah 3,5 bulan. Reseksi dilakukan pada 84 (39,5%) subjek, pada 128 (59,8%) subjek dilakukan teknik pyloric preserving pancreaticoduodenal. Sebanyak 15 (9,0%) kasus merupakan kasus jinak. Dari 31 (14,6%) pasien yang menjalani relaparotomi, 16 (51,6%) di antaranya meninggal pascaoperasi. Mortalitas operasi menurun dari 16,9% ke 5,5% pada tahun 2016 sementara frekuensi reseksi semakin meningkat, antara 2-21 per tahun. Kurang dari 10% subjek bertahan hidup > 5 tahun sementara < 20% subjek bertahan < 24 bulan. Morbiditas didapatkan sebesar 65,1% dari 177 subjek dengan infeksi daerah operasi sebanyak 52,5%, fistula pankreas 24,2% dan perdarahan pascapancreatektomi 19 (8,9%) subjek. Relaparotomi dan perdarahan pascapancreatektomi jumlahnya signifikan pada subjek yang meninggal < 30 hari pasca operasi ( $p < 0,001$ )*

**Simpulan:** *Ikterus berkepanjangan dan hipoalbuminemia merupakan karakteristik dominan subjek dengan reseksi pankreatoduodenal di Indonesia. Rumah Sakit Dr. Cipto Mangunkusumo merupakan pusat reseksi pankreatoduodenal dengan frekuensi tindakan yang tinggi. Terdapat hubungan antara jumlah reseksi dengan mortalitas. Relaparotomi dan perdarahan pascapancreatektomi merupakan prediktor luaran buruk pada subjek.*

**Kata kunci:** *hipoalbuminemia, ikterus berkepanjangan, whipple.*

## INTRODUCTION

Indonesia has the largest national population in the east equator, but no study about pancreatico-duodenal and pyloric preserving pancreaticoduodenal resections has been published in the last 10 years, compared to reports coming from other South East Asia countries.<sup>1-6</sup> In fact, the volume of resection or hospital load to pancreaticoduodenal (PD)/pylorus-preserving pancreaticoduodenectomy (PPPD) in South East Asia region, even from hepatopancreaticobiliary (HPB) leading centres, were low.<sup>1-7</sup>

Pancreaticoduodenal resection is the only treatment of choice shown to contribute to prolonged-survival, even though the risk of major complications is around 57%.<sup>8,9,10</sup> Morbidity and survival rate of operable and resectable malignant peri-ampullary tumors (PT) remain a challenge in the field of surgery, although the operative mortality was less than 4% in HPB surgery centres since the last millenium.<sup>7,8,11-14</sup>

A high success rate of complex high-risk tertiary surgical procedures for malignant PT indicates the quality of surgical care in a world class hospital and an excellent medical center.<sup>12,14,15</sup> Surgical skills and experiences contribute to outcomes, in addition to perioperative assessment and support.<sup>7,10,12,16</sup> This paper reviewed the characteristic and the outcome of the PD/PPPD resection.

## METHOD

Retrospective reports of patients who were preoperatively diagnosed with PT were collected from 1993 until 2017. These patients underwent PD or PPPD resection and total pancreatectomy (TP). Data

were divided into 3 periods of time. The PDR data of the first period, which was from 1993-2003, was published descriptively in 2004.<sup>4</sup> The second period, between 2004 and 2010, was specified due to almost all dissection, resection, and pancreaticojejunostomy anastomosis was performed by the authors themselves. In the last period, 2011 until December 31<sup>st</sup> 2017, there were 3 surgeons who performed the operation.

Subject characteristics, perioperative work-up, procedure of resection, and histopathological findings were the variables of interest and were analysed. Data was presented in mean, standard deviation, or range. Morbidity was defined as it was already written in other journal before.<sup>4</sup> Operative mortality was defined as death occurring up to 30 days after the operation or during hospitalization. Kaplan-Meier analysis was used in the evaluation of overall survival and malignancy survival based on staging.

## RESULTS

Two hundred and thirteen resection procedures were documented. Demographic characteristics, laboratory preoperative and perioperative data, resection type, and complications of the operation are described in 3 periods of time in Table 1. Jaundice was the most common clinical finding in 147 (68%) procedures followed by abdominal pain, while nausea, vomiting, abdominal mass, and melena were minor findings. The average pre-hospital symptom duration was 2.6 months, with a month of preoperative work-up.

Routine abdominal ultrasounds were done in all patients at initial workups. Later, diagnostic workups included standardized abdominal contrast-enhanced

computed scan. During the last 10 years, magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) was performed for diagnostic and resectability confirmation. Mismatches in preoperative imaging interpretation and intraoperative finding were found in around 30% of subjects (64 cases), due to the time lag from radiologic examination to the operative procedure with an average of 3.5 months.

Annual resection rate and operative mortality based on 3 period times were presented in Figure 1. Overall operative mortality was 16.9%, consisting of 22 males and 14 females, which fluctuated, with a range of 1–5 deaths annually. No mortality occurred in 2000, 2004, 2007, and 2011. Operative mortality decreased to nearly half in the last period and compared to the first period dropped to 5.5% in 2016. The highest annual resection procedure was 21 in 2014, and PPPD was more common after 2005. Primary total pancreatectomy (TP) was performed in two subjects with pancreatic head malignancy whom died within 6 months postoperatively, suffering from severe hypoglycaemia due to apancreatic diabetes. Another TP was indicated to treat anastomotic leakage at relaparotomy. The patient died several days postoperatively. Postoperative length of stay

(LOS) ranged from 9-32 days, with an overall mean of 17.6±8.7 days. In the last 3 years, the average LOS decreased to 12.9 days.

Pathologically, 198 (92.9%) malignancies were documented, consisting of stages I, II, III, and IV (20.4%, 47.6%, 30.7%, and 1.8%, respectively). Adenocarcinoma was found in 187 (94.7%) subjects. Carcinoma of ampulla of Vater and pancreatic head cases were mostly in stages I and II, while subjects with carcinoma of duodenum (25 subjects) were mostly in stages II and III. All stage IV subjects were found to have carcinoma of the pancreatic head post-operatively.

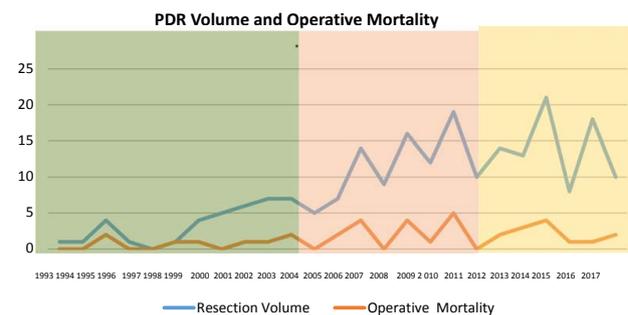


Figure 1. Resection rate and operative mortality in 1993-2017

Gastrointestinal stromal tumour (GIST), neuroendocrine tumour, squamous cell carcinoma, and malignant lymphoma were found in 2 (1.01%)

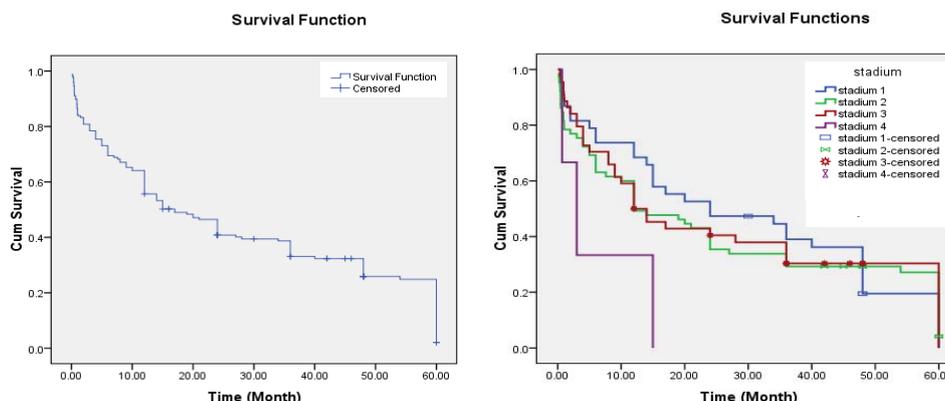
Table 1. Demography, perioperative, surgery technique and output data presented mean in 3 periods of time

Year Period	1993-2003	2004- 2010	2011-2017	Total
<b>n resection</b>	<b>37</b>	<b>81</b>	<b>95</b>	<b>213</b>
Gender				
Female	22	34	55	111
Male	15	47	40	102
Age (year)	45.2	52.1	54.2	50.6
Hemoglobin (g/dL)	11.1	11.3	11.4	11.3
Hematocrit (%)	31.2	33.8	33.5	30.4
White blood count (/μL)	10778	11436	9570	11346
Albumin (g/dL)	3.3	3.36	3.30	3.32
Bilirubin (mg/dL)	8.6	7.11	3.56	6.2
Alkaline phosphatase (U/L)	859	532	242	530
Ureum (mg/dL)	31.2	31.7	22	29.4
Creatinine (mg/dL)	0.56	0.7	0.7	0.62
Resection types				
pylorus-preserving pancreaticoduodenectomy (PPPD)	14	63	51	128
Whipple	21	18	44	84
Total pancreatectomy (TP)	2	0	0	2
Intra-operative blood loss (mean in cc)	1111.2	733.8	834	677
Re-laparotomy	7 (18.9%)	14 (17.2%)	10 (10.6%)	31 (14.5%)
Surgical site infection	12 (29.7%)	28 (34.5%)	17 (17.9%)	57 (26.7%)
Pneumonia	1	5 (5.1%)	0 (0)	6
Pancreatic fistula	0	11	16	27
Delayed gastric emptying	2	12 (14.8%)	10 (10.6%)	24
Post pancreatic hemorrhage (PPH)	0	8 (6.8)	11 (5.8)	19
Aspiration	0	2 (1.7)	0 (0)	2
Operative time (minutes)	427.9	428	449.5	439.5
Operative mortality	8 (22.2%)	16 (19.7%)	12 (12.6%)	36 (16.9%)
Length of stay (days)	22.1	18.2	14.2	17.6

**Table 2. Preoperative diagnosis and final pathological result**

Preoperative diagnosis	n (%)	Histopathology	n (%)	Stage I/II/III/IV	n (%)
Pancreatic head tumour	64(30)	Carcinoma of pancreatic head	70(33)	9/28/25/3	65(37)
Papilla/ampulla of Vater tumour	71(33.3)	Carcinoma of papilla/ ampulla of Vater	91(43)	21/42/20/0	83(47)
Distal common bile duct (CBD) tumour	15(7)	Carcinoma of distal common bile duct (CBD)	3(1.4)	3/ 0/ 0/ 0	3 (1.7)
Tumour of the duodenum	16(7.5)	Tumour of duodenum	25(12)	3/12/10/ 0	25(14.3)
Periapillary tumour	22(10.3)	peri-ampillary tumors (PT) non-adenocarcinoma*	11(4,2)		
Others	14(6.6)	Benign tumors	15(9.5)		

\*Signet ring cell; neuroendocrine tumour, GIST; malignant lymphoma



**Figure 2. Kaplan Meier curve of periampillary malignancy overall survival (left) and survival of periampillary malignancy based on stadium (right)**

subjects each; One subject had metastasis of colonic adenocarcinoma on the pancreatic head who was alive without disease until the data were reviewed. Signet ring cell carcinoma was seen in 2 (1.01%) duodenal tumour subjects.

Discrepancies between preoperative diagnosis and final pathologic result were noted in 9-22% of pancreas and Vater malignant cases in detailed showed in Table 2. Most of the benign cases were confirmed after operation.

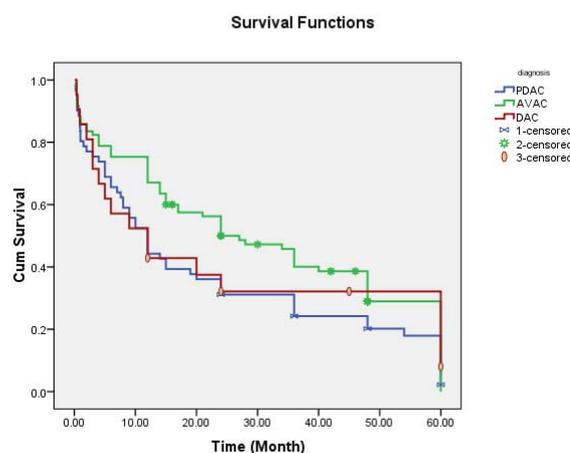
Morbidity was noted in 177 (83.1%) survivors; 31 (14.5%) re-laparotomies were documented, due to inadequate drainage of pancreaticobiliary leakage, leading to abdominal sepsis, bowel transit problems, worsening organ dysfunction, and bleeding post-pancreatectomy haemorrhage (PPH). The worst documented complications leading to operative mortality were abdominal sepsis (10 subjects), multiple organ failure (10 subjects), and post-pancreatectomy haemorrhage (14 subjects). Aspiration pneumonia in two delayed gastric emptying (DGE) subjects was noted to be a lethal complication.

Post-pancreatectomy haemorrhage (PPH) and aspiration pneumonia contributed to early operative mortality (7-10 days), while abdominal sepsis and multiorgan failure (MOF) contributed to late operative mortality (10-42 days), which occurred in 5 cases.

Among the survivors, 130 patients (73.5%) had died when this review was made, Overall, 13 subjects

(7.34%) survived for more than 5 years. We estimated that an additional 16 (surgery in 2014 or after) subjects who have not yet surpassed the 5-year period will bring the total to 29 (16.4) subjects. Two subjects with primary periampillary malignancy and one subject with colon metastasis survived up to 10 years. The overall 5 years survival of all PT cases, based on stage and histopathology were shown on Kaplan Meier curves in Figure 2 and 3.

The 5 years overall survival for all PT cases were 15.1% with a median of 19 (95% CI: 13-24) months. The 5 years survivor of all cases, excluding the operative mortality was 13.8%. Median survival was



**Figure 3. Kaplan-Meier curve of pancreatic ductal adenocarcinoma (PDAC), ampulla vateri adenocarcinoma (AVAC) and duodenal adenocarcinoma (DAC)**

17 (95% CI: 0.8-23) months. The malignancy cases over all 5 years survival was 18%, with a median of 15 (95% CI: 10-19.8) months. The 5 years survival of PDAC, AVAC and DAC were 11.7%, 31.8% and 14.3% respectively. Based on staging, the 5 years survival of stage I, II, and III were 10%, 18% and 9.09% respectively. The median survival period for periampullary malignancy stage I was 24 (95% CI: 00-49) months, stage II 12 (95% CI: 4.1-19) months and stage III was 12 (95% CI: 5.6-18.3) months. Three stage IV cases died less than 6 months after surgery.

## DISCUSSION

This study reported the characteristics and outcomes of PD resections in the management of periampullary tumour performed by a single surgical team from the main referral hospital in Indonesia, over a 24-year period. The timeline was divided into 3 periods based on specific conditions. Operative mortality in 2016 reached its nadir of 5.5%, which was similar to other medical centres worldwide.<sup>7-9,12</sup> This progress was related to the gradual increase of resection volume over the years, reaching an averages of 13.6 procedures annually which accounts it as a high volume PDR centre.<sup>1,5,8,16</sup> A recent study set 40 PD resection procedures threshold as a predictive factor for better outcome.<sup>17</sup> In the early years until mid-2000, operative mortality was 2-3 times higher than the leading centre. This finding was related to insufficient preoperative work-up, infection control, a routine standard operational procedures, and the learning curve.<sup>16,13,17,18</sup> Higher resection volume multiplies the surgeon's experience, generating better results even in low volume hospitals

High operative mortality in this report was associated with re-laparotomy procedures, which were performed when indicated due to PPH, sepsis, and multiple organ failure. More than 44.9% of subjects with re-laparotomy died postoperatively, which was high compared to other published reports.<sup>19,20</sup> The incidence increased mostly due to gastroduodenal artery injury secondary to pancreatic leak. Bleeding and sepsis following anastomosis leakage of the pancreaticojejunostomy indicates inadequate drainage.<sup>21,22</sup> Aspiration occurred in two subjects with DGE, due to the early removal of the decompression tube, while active production was ongoing. Aspiration was a sentinel event and contributed to operative mortality.<sup>23,24</sup>

Delayed presentation contributed to a narrow spectrum of safety margin for a successful recovery

after resection, with patients mostly presenting with chronic jaundice and malnutrition<sup>12,25</sup> In addition, 68% of perioperative infection was documented in those with serum albumin < 3.0 mg/dL. Reduced total bilirubin showed better outcomes, similar to past reports.<sup>26,27,28</sup> Furthermore, hospital delay is another characteristic which may endanger patients in this region. During the time lag, their condition may convert from a resectable to an un-resectable, or even inoperable case. Preoperative work-ups and referral waiting lists were the most common causes of delay.

The TP procedure is no longer used by our surgical team due to difficulty in management of post-operative pancreatic diabetes. Moreover, other studies also concluded that the procedure has many disadvantages.<sup>10,29</sup> The reconstruction technique was done with the single jejunal loop protocol, which is side-to-end pancreaticojejunostomy in combination with duct-to-enteral in complement of Dunking technique; Hence, the combination was named the entero-Dunking technique. As such, there was no tension on the anastomosis, and the jejunal diameter could easily be adjusted to the pancreatic stump, providing good drainage to the distal segment by autoperistalsis.<sup>30</sup> In dealing with pancreaticojejunostomy anastomosis failure, the pancreatic stump including the duct were tied up, then the jejunostomy was closed.<sup>19</sup>

Malignant periampullary tumor, postoperative histopathological finding, and staging were also in line with those in past reports, with predominantly stage I and II.<sup>7,12,18,21,31</sup> An exception was a subject in stage IV who underwent resection, as the criteria of resectability was met and the metastasis was confirmed retrospectively. Primary GIST and signet ring cell of the duodenum were notably rare pathologies.<sup>9</sup> All morbidities found were quite high compared to prior reports, but the destructive problems could be managed well.<sup>12,23</sup>

All types of actual pancreatic fistulation in our cases (24.2%) consisted of pancreatic leaks manifesting as abdominal sepsis and GI bleeding. Forty percent of the type A or B pancreatic leaks healed spontaneously due to good drainage, and was, notably, three times higher compared to the previously published reports (7% in a leading centre).<sup>7,11,12,21,30,31</sup> DGE (10.9%) was higher than in the past reports and was found in both classical Whipple and PPPD.<sup>14,32,33,34</sup> All remaining patients were successfully managed with intermittent gastric decompression, early oral solid enteral feeding in a small-frequent scheme, in addition to oral erythromycin suspension as well as early mobilization.

Length of postoperative stay in the study reduced from 17.6 to 12.9 days in the last 5 years, in parallel with the application of fast tract recovery systems and better perioperative preparation.<sup>11,12,35</sup> Survival was difficult to be accurately evaluated, as loss of follow up after 1 year was quite high (30%). However, Kaplan–Meier analysis showed that survival rate based on the stage of tumour was less than those reported.<sup>16,36</sup> The analysis and direct actual counting showed a 5% discrepancy in the 5-year survival rates. Objectively, survival in stage II resected subjects was better compared to non–operated patients, who survived less than 18 months.<sup>37</sup> In those who survived less than 1 year (particularly in 6 months), considering the period of sickness, we found that the subjects survived in 3 months with a condition that was not necessarily disease–free.

Finally, our data shows that Cipto Mangunkusumo Hospital has applied the mobile team approach, supported by multidisciplinary involvement, in a well–organized fashion. Achievements in resection volume and mortality rate showed improvements equal to world class medical centres, although the outcomes remain varied. Any fluctuations of outcome, especially the operative mortality, was related to the characteristics in the region, i.e., advanced cases, obstacles in scheduling a resection, variation of stage, and chronicity of the disease itself, all of which tend to narrow the spectrum of tolerance to complications. We learned that cases should be carefully selected with zero compromise for error in the preoperative setting, in order to ensure success. Thus, adequate and safe surgery should be the guiding principle for moving forward. The limitation of this study was that we were unable to acquire complete follow-up data for almost 30% of patients due to loss of contact (20% subjects were referred from other regions in the country).

In conclusion, prolonged jaundice and hypoalbuminemia are dominant characteristics, the resection management of resectable PT has better progress and is in line with other excellent centres. Cipto Mangunkusumo Hospital is now a world class hospital and an excellent medical centre. Relaparotomy and PPH were predictors of poor outcomes.

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