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Evaluation of the pre-operative and post-operative factors following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma

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Abstract

Early diagnosis, meticulous selection of the patients who are liable for resection and referral of these patients to specialized centres, can improve the short and long-term outcome. For a better selection of the patients that may have the benefits of surgery and postoperative adjuvant therapy, we should assess the risk factors that can affect the outcome. Most of the studies reported these prognostic factors for survival after resection of PDAC, like the age of the patients at the time of surgery, one or more co-morbidity, tumor size and stage, pathological grade of the tumor, the presence of positive lymph nodes (LNs), the surgical margin of resection etc. The aim of this study was to analyze the clinical outcome and the potential prognostic factors that may affect survival after PD for PDAC.

The present study was planned in Department of Gastrointestinal Surgery, Indira Gandhi Institute of Medical Sciences, Patna, Bihar. The 25 cases of the Pancreaticoduodenectomy (PD) were enrolled in the present study. The study was conducted from Jan 2018 to Nov 2018. The diagnosis of pancreatic ductal adenocarcinoma (PDAC) was done by histopathological study of the specimen after surgery. Other pathology after PD or other periampullary adenocarcinoma were excluded from the present study.

The data generated from the present study concludes that High tumor marker CA19-9, tumor size, and grade are significant risk factors for poor survival after resection of PDAC and should be taken into account in the selection of patients for surgery to improve the outcome. Familiarity with normal anatomical findings is essential to distinguish expected post-operative changes from surgical complications or recurrent disease.

Keywords: PDAC-pancreatic duct adenocarcinoma, pd-pancreaticoduodenectomy, smv-superior mesenteric vein, imv-inferior mesenteric vein, postoperative complications, etc

Introduction

A Pancreaticoduodenectomy, pancreatoduodenectomy [1], Whipple procedure, or Kausch-Whipple procedure is a major surgical operation most often performed to remove cancerous tumours of the head of the pancreas. It is also used for the treatment of pancreatic or duodenal trauma or chronic pancreatitis. Due to the shared blood supply of organs in the proximal gastrointestinal system, surgical removal of the head of the pancreas also necessitates removal of the duodenum, proximal jejunum, gallbladder and occasionally, part of the stomach [2].

The most common technique of a pancreaticoduodenectomy consists of en bloc removal of the distal segment (antrum) of the stomach, the first and second portions of the duodenum, the head of the pancreas, the common bile duct and the gallbladder. Lymph nodes in the area are often removed during the operation as well (lymphadenectomy). However, not all lymph nodes are removed in the most common type of pancreaticoduodenectomy because studies showed that patients did not benefit from the more extensive surgery [3].

At very beginning of the procedure, when surgeons gain access to the abdomen, the surfaces of the peritoneum and the liver are inspected for metastasis. This is an important first step as the presence of active metastatic disease is a contraindication.

The vascular supply of the pancreas is from the celiac artery via the superior pancreaticoduodenal artery and the superior mesenteric artery from the inferior pancreaticoduodenal artery. There are additional smaller branches given off by the right gastric artery, derived from the celiac artery. The reason for removal of the duodenum along with head of the pancreas is that they share the same arterial blood supply (the superior pancreaticoduodenal artery and inferior pancreaticoduodenal artery). These arteries run through the head of the pancreas, so that both organs must be removed if the single blood supply is severed. If only the head of the pancreas were removed it would compromise blood flow to the duodenum, resulting in tissue necrosis.

While blood supply to the liver is left intact, the common bile duct is removed. This means that while the liver remains with a good blood supply, the surgeon must make a new connection to drain bile produced in the liver. The surgeon will make a new attachment between pancreatic duct and jejunum or stomach. During the surgery a cholecystectomy is performed to remove the gallbladder.

This portion is not done en bloc, as the gallbladder is removed separately.

Relevant nearby anatomy not removed during the procedure includes, the major vascular structures in the area: the portal vein, the superior mesenteric vein and the superior mesenteric artery, the inferior vena cava. These structures are important to consider in this operation, especially if done for resection of a tumour located in the head of the pancreas. If the tumour encases (wraps around 50% or more of the vessel) the celiac artery, superior mesenteric artery or inferior vena cava, it is considered unresectable due to lack of patient benefit from the operation, while having very high risk [4, 5]. Occasionally a portion of the superior mesenteric vein or portal vein is attached or inseparable from the tumour. In this setting vascular surgeons resect the involved portion of the vessel, and the vessel is repaired either via end-to-end anastomosis, repair of the side wall of the vein or a vein graft.

Pancreaticoduodenectomy is most often performed as curative treatment for periampullary cancer, which includes cancer of the bile duct, duodenum or head of the pancreas [6]. The shared blood supply of the pancreas, duodenum and common bile duct, necessitates en bloc resection of these multiple structures. Other indications- include chronic pancreatitis, benign tumours of the pancreas, cancer metastatic to the pancreas, multiple endocrine neoplasia type 1 [7] and gastrointestinal stromal tumours [6].

Pancreaticoduodenectomy is the only potentially curative intervention for malignant tumours of the pancreas [8]. However, the majority of patients with pancreatic cancer present with metastatic or locally advanced unresectable disease [9]; thus only 15-20% of patients are candidates for the Whipple's procedure. Surgery may follow neoadjuvant chemotherapy, which aims to shrink the tumour and increases the likelihood of complete resection [10]. Post-operative death and complications associated with pancreaticoduodenectomy have become less common over the past 20 years, with rates of post-operative mortality falling from 10-30% in the 1980s to less than 5% in the 2000s [11].

Cholangiocarcinoma, or cancer of the bile duct, is an indication for the Whipple procedure when the cancer is present in the distal biliary system, usually the common bile duct that drains into the duodenum. Depending on the location and extension of the cholangiocarcinoma, curative surgical resection may require hepatectomy, or removal of part of the liver, with or without pancreaticoduodenectomy [12].

Treatment of chronic pancreatitis typically includes pain control and management of exocrine insufficiency. Intractable abdominal pain is the main surgical indication for surgical management of chronic pancreatitis [13]. Removal of the head of the pancreas can relieve pancreatic duct obstruction associated with chronic pancreatitis [14].

Damage to the pancreas and duodenum from blunt abdominal trauma is uncommon. In rare cases when this pattern of trauma has been reported, it has been seen as a result of seat belt trauma in motor vehicle accidents [15]. Pancreaticoduodenectomy has been performed when abdominal trauma has resulted in bleeding around the pancreas and duodenum, damage to the common bile duct, pancreatic leakage, or transection of the duodenum [16]. Due to the rarity of this procedure in the setting of trauma, there is not robust evidence regarding post-operative outcomes.

Absolute contraindication for the procedure is metastatic disease in the abdominal cavity or nearby organs. These are found most often on the peritoneum, in the liver, and in the omentum. In order to determine if there are metastases, surgeon will inspect the abdomen at the beginning of the procedure after gaining access. Alternatively, they may perform a separate procedure called a diagnostic laparoscopy which involves insertion of a small camera through a small incision to look inside the abdomen. This may spare the patient from large abdominal incision that would have occurred, if they were to proceed for pancreaticoduodenectomy that might have been cancelled due to metastatic disease. Further contraindications include encasement of major vessels (such as celiac artery, inferior vena cava, or superior mesenteric artery) as mentioned above.

Head-to-head comparison between the classically described pancreaticoduodenectomy and PPPD has not detected any significant differences with regard to operating time, perioperative morbidity, perioperative mortality, and long-term survival at 1, 3 and 5 years. Operative blood loss is slightly lower with PPPD, but the clinical significance of this is not clear.

Thus, PPPD can be considered a technical variant of pancreaticoduodenectomy, in which blood supply to the proximal duodenum is preserved. Therefore, it is important to emphasize that broad indications for resection will not differ between the two approaches [17]. The two main points of difference between pancreaticoduodenectomy and PPPD that merits discussion, are the following:

- Postoperative delayed gastric emptying (DGE)
- Achievement of R0 oncologic resection (ie, surgical margins negative for tumor)

Patients who undergo PPPD have a much higher incidence of DGE than those who undergo classic pancreaticoduodenectomy. This is the primary morbidity with PPPD patients, leading to more medical interventions and thus increased cost postoperatively unrelated to hospital stay, cost of jejunal feedings and jejunal tube maintenance (eg, home nursing for tube care, emergency department [ED] visits for dislodgment, and tube replacement for dysfunction). If aspiration occurs, it complicates the matter and there can be a threat to the patient's life as well. From an oncologic perspective, PPPD should not be performed with large, bulky tumors or with any tumor that may involve the first or second portion of the duodenum. In addition, with the gastric antrectomy performed in classic pancreaticoduodenectomy, an average of four or more nodes are harvested, than would be with PPPD. These will be positive for nodal metastases approximately 5% of the time. The question therefore arises as to whether the incidence of non-R0 resection in this small cadre of patients should bias the surgeons against PPPD.

In view of the aforementioned considerations and the lack of statistical difference with regard to patient morbidity, mortality, and survival after classic pancreaticoduodenectomy and the pylorus-preserving modification, the individual patient profile and specific tumor characteristics should weight the surgeon's choice of approach. Tumour resectability must be assessed well before the patient arrives at the operating room. The tumour is considered resectable if it is locally confined (ie, if there is no distant disease). Preoperative imaging studies are the

cornerstone of evaluation.

As noted, CT with thin collimation is the most effective tool for identifying local extension. The tumor can be evaluated in relation to important vascular structures. A fat plane should be seen between the low-density tumor and surrounding structures.

The disease is considered resectable if the following conditions are met:

- The tumor does not encase celiac axis or SMA (cannot involve >180º circumference)
- There exists a patent superior mesenteric vein (SMV), portal vein (PV), and SMV-PV confluence (no thrombosis)
- There is no extraregional nodal disease
- There is no distant metastatic disease

Additional imaging is usually not necessary, but in certain cases, endoscopic ultrasonography (EUS), fine-needle aspiration (FNA) or both may be employed for tissue diagnosis before the initiation of neoadjuvant therapy.

Early diagnosis, meticulous selection of the patients who are liable for resection, and referral of these patients to specialized centers can improve the short and long-term outcome. For a better selection of the patients that may have the benefits of the surgery and postoperative adjuvant therapy, we should assess the risk factors that can affect the outcome. Most of the studies reported these prognostic factors for survival after resection of PDAC, like- the age of the patients at the time of surgery, one or more co-morbidity, tumor size and stage, pathological grade of the tumor, the presence of positive lymph nodes (LNs), the surgical margin of resection. The aim of this study was to analyze the clinical outcome and the potential prognostic factors that may affect survival after PD for PDAC.

Methodology

The present study was planned in Department of Gastrointestinal Surgery, Indira Gandhi Institute of Medical Sciences, Patna, Bihar. The 25 cases of the Pancreaticoduodenectomy (PD) were enrolled in the present study. The study was conducted from Jan 2018 to Nov 2018. The diagnosis of pancreatic ductal adenocarcinoma (PDAC) was done by histopathological study of the specimen after surgery. Other types of pathology after PD or other periampullary adenocarcinoma were excluded from present study.

All the patients were taken informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct this study.

Results & Discussion

It has been argued that pancreaticoduodenectomy can be performed safely in the elderly, and that advanced age alone should not be used as a reason to cancel the operation. Many of these studies, however, are from single institutions and May not accurately represent patient outcomes in the Hospitals throughout the United States where a majority of pancreaticoduodenectomies are actually performed [18, 19]. In addition, in a number of these studies, mortality was actually higher in the older age cohort, but the study was underpowered to demonstrate a statistical difference [20].

It is interesting that many of the clinical factors that are often associated with operative risk were not found to influence mortality independently. For example, diabetes, body mass index, coexistent chronic obstructive pulmonary disease, dyspnoea, hypertension, cardiac history, stroke and all laboratory values except for sodium level had little effect on mortality.

Table 1: Pre-Operative Patients Characteristics

Variables	No. of Cases
Age	25 – 68 years
Male	16
Females	9
Body mass index (kg/m2)	
≤25	11
>25	14
Co-morbidities (yes)	14
Diabetes Mellitus	8
Hypertension	7
Main symptoms	
Abdominal pain	9
Jaundice	15
Loss of weight	11
Anorexia, nausea, vomiting	12
Preoperative total bilirubin (mg/dl)	4.3 ± 2.9
ALT (U/L)	42.5 ± 11.1
Albumin (g/dl)	3.2 ± 0.71
Carbohydrate antigen 19-9(U/mL)	1859.5 ± 253.9
Normal	8
High	17
Preoperative biliary stent	14
Type of operation	
Whipple	15
PPPD	10
Pancreatic texture	
Firm	16
soft	9
Type of pancreatic reconstruction	
Pancreaticogastrostomy	12
Pancreaticojejunostomy	18
-invagination	11
-duct to mucosa	13
Vascular reconstruction	4
Operative time (min)	395 ± 56
Operative blood loss	458 ± 90
Blood transfusion (unit)	1 - 4
Maximum tumor diameter	2.8 ± 0.9
Tumor stage	
T1	2
T2	8
T3	13
T4	2
Tumor differentiation	
Well	4
Moderate	13
Poor	7
Positive lymph nodes	1 - 3

Table 2: Post-operative complications

Variables	No. of Cases
Postoperative pancreatic fistula	3
Postpancreatectomy haemorrhage	2
Delayed gastric emptying	3
Biliary fistula	1
Gastric fistula	1
Wound infection	3
Pulmonary complications	2
Clavien grades of complication	
0	7
I	5
II	6
IIIa	2
IIIb	1
IVa	1
IVb	1
V	2
Reoperation	2
ICU stay (days)	3 – 11
Hospital stay (days)	12 – 25
Hospital mortality	1
Recurrence of tumor	8

Experience from high volume tertiary care centers around the world has shown a significant decrease in mortality following pancreaticoduodenectomy (PD) over the last couple of decades. Despite a significant decrease in postoperative mortality, PD is still associated with a fairly high postoperative morbidity as reported by various centers in the range of 30–60% [21, 22]. Some of these common postoperative complications including postpancreatectomy haemorrhage (PPH) and pancreaticoenteric anastomotic leak (PEA) leak with intra-abdominal collection and associated septic complications- may require surgical intervention, despite the widespread availability of endovascular and radiological interventions. This morbidity prolongs hospital stay and results in mortality in a significant proportion of patients. Reoperative surgery after PD is a difficult undertaking and the reoperation itself may be the cause of further morbidity and mortality [23]. Due to increasing long-term survival of patients undergoing PD for periampullary carcinoma, some may on long-term follow up, develop complications that may need intervention. These complications may be related to the complications of primary surgical procedure, recurrence of the primary disease per se, and/or complications of adjuvant radiotherapy.

Due to improved long-term survival of patients with nonpancreatic periampullary carcinoma, as compared to pancreatic cancer, quite a few patients present on long-term follow up with complications related to the index surgery or disease recurrence, which may be amenable to surgical intervention. With the increasing use of adjuvant radiotherapy to gain better local control and thereby improve disease-free survival, patients may require intervention for complications of the same. Excluding patients with malignant pancreatic neuroendocrine tumours, this issue has been very sparsely addressed in the literature with most of them being occasional case reports or short case series [24, 25].

Conclusion

The data generated from the present study concludes that High tumor marker CA19-9, tumor size, and grade are significant risk factors for poor survival after resection of PDAC and should be taken into account in the selection of patients for surgery to improve the outcome. Familiarity with normal anatomic findings is essential to distinguish expected post-operative changes from surgical complications or recurrent disease.

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