

## SURGICAL THERAPY OF PANCREATIC CANCER

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### 1. ABSTRACT

Surgical resection remains the only curative modality for pancreatic cancer. Improvements in surgical technique have greatly reduced the morbidity and mortality from pancreatic resection. These results clearly justify the use of pancreatic resection for localized and resectable pancreatic cancer. New surgical techniques such as laparoscopy can aid in the proper selection of candidates for curative resection. Integration of surgery with more effective treatments to prevent systemic relapse are needed to further improve survival.

### 2. INTRODUCTION AND HISTORICAL PERSPECTIVE

Pancreatic adenocarcinoma is one of the leading causes of cancer death in the United States, and was responsible for an estimated 27,000 new cases and 28,000 deaths in 1997 (1), making it the fifth leading cause of cancer death after cancer of the lung, large intestine, breast and prostate. It is second only to colorectal cancer as a cause of death from cancer of the digestive tract. The overall outlook for patients with pancreatic cancer is quite gloomy. A recent survey by the Commission on Pancreatic cancer in the USA, reporting on a total of 16,942 patients, found a resectability rate of 13.3%, an operative mortality of 7.2% and a 5-year survival rate of 4% (2). Despite this apparent gloom, of all the treatment modalities employed in the management of pancreatic cancer, only surgery has curative potential.

The earliest recognition of pancreatic cancer has been attributed to Morgani, but definitive differentiation between pancreatic cancer and chronic pancreatitis cannot be made from his descriptions (3,4). The gross characteristics of the disease were described nicely by

Mondiere in 1836 (5,6). DaCosta, the first American physician to write about pancreatic carcinoma, collected and reported 37 cases--35 from autopsy records, one personal case, and one reported to him (3,5,7). By the end of the nineteenth century numerous cases of cancer of the head of the pancreas were confirmed histopathologically and the signs and symptoms of the disease were well described (3). Bard and Pic, in 1888, correlated signs and symptoms of pancreatic carcinoma with autopsy findings in seven patients with disease, and distinguished between duct and acinar cell cancers (8). Courvoisier, in 1890, described the classic sign of a palpable distended gallbladder in patients with pancreatic cancer (9). Pain as a predominant symptom in cancer of the body of the pancreas was described by Chauffard in 1908 (10).

Attempts to treat pancreatic cancer surgically were made at the end of the nineteenth century. Trendelenburg was one of the first to successfully excise a solid tumor of the body and the tail of the pancreas in 1882. The patient died shortly after discharge (3,11). Kappeler, in 1887, performed the first cholecystojejunostomy for palliation in a patient with cancer of the pancreas who survived 14 ½ years after the operation (3). Biondi, in 1894, removed a tumor from the head of the pancreas with postoperative development of a biliary and pancreatic fistula that healed within 25 days (3). Halsted, in 1898, successfully performed the removal of an ampullary carcinoma. He excised a portion of the pancreas and the duodenum around the ampulla and re-implanted the pancreatic and common bile duct into the repaired suture line of the duodenal excision. The patient developed common duct stenosis 3 months after the operation, died 6 months later, and the autopsy showed recurrence of the cancer in the pancreas and the duodenum (12).

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In 1898, Codivilla performed an en bloc resection of the head of the pancreas and a part of the duodenum for pancreatic carcinoma. He closed the pylorus, invaginated the duodenal stump, ligated, transected the common bile duct, and performed a Roux-en-Y cholecystenterostomy and gastroenterostomy. The patient died 24 days after the procedure and an autopsy showed widespread metastases (3,5,13). In 1912, Kausch performed a successful two-stage pancreaticoduodenectomy with implantation of the pancreatic stump into the distal end of the transected duodenum. The patient survived for 9 months, died from cholangitis and an autopsy, showed no recurrence or metastasis (3,14). In 1914, Hirschel performed a one-stage pancreaticoduodenectomy, for carcinoma of the ampulla. The patient experienced relief from the jaundice but died a year after the operation (3,15). Tenani, in 1922, performed a successful two-stage partial pancreaticoduodenectomy. In the first stage, the common bile duct was divided, its end was connected to the lower end of the duodenum, and a gastrojejunostomy was performed. The second stage was performed 1 month later and included resection of the second portion of the duodenum, with a portion of the head of the pancreas and implantation of the pancreatic head into the lower end of the transected duodenum (3,16,17).

### 3. WHIPPLE PANCREATICODUODENECTOMY

Despite these isolated successful attempts during the early part of the twentieth century, no significant interest was shown in pancreatic resections until 1935, when Whipple and his associates developed and popularized the technique for a two-stage operation for carcinoma of the ampulla of Vater, the Whipple procedure (18). The first stage of the operation consisted of a cholecystogastrostomy and gastrojejunostomy, while at the second stage a resection of the second and third parts of the duodenum along with a portion of the head of the pancreas was performed. The first and fourth parts of the duodenum were inverted and closed. The lower end of the common bile duct, the pancreatic duct, and the pancreatic stump were closed. Brunschwig, in 1937, successfully performed a wide resection of the head of the pancreas with the entire duodenum in two stages (19). In 1940, Trimble performed the operation in one stage with similar results (20).

Several modifications of the original procedure described by Whipple were made by other surgeons. Hunt, in 1941, invaginated the cut surface of the pancreas into the jejunum to avoid steatorrhea, hemorrhage, pancreatic fistulae that occurred often after closure of the pancreatic stump (21). For the same reason Zininger, in 1942, anastomosed the pancreatic duct to the jejunum (22). Leakage from the ligated common bile duct and frequent failure of the cholecystoenterostomy to drain the biliary tract led Whipple to recommend choledochojejunostomy as the anastomosis of choice for restoration of continuity between the gastrointestinal and biliary tracts (23). Another modification was the increased extent of the gastric and pancreatic resection. The original procedure spared the pylorus, but subsequent removal of the entire duodenum and 50% to 70% of the stomach had to be performed (5). While only a local resection of the tumor was performed in the first of the

three patients reported by Whipple and associates (18), larger portions of the pancreas were removed in the other two patients. Increasing amounts of gland were subsequently resected leading to sectioning at the level of the neck of the pancreas or beyond, thus allowing resection of larger tumors with adequate margins (5). By 1942, Whipple described his operation as resection en masse of the distal half of the stomach, the entire duodenum, the terminal portion of the common bile duct, and the head of the pancreas, followed by an end-to-end choledochojejunostomy, anastomosis of the pancreatic duct to the wall of the jejunum with tacking of the stump of the pancreas to the jejunal wall and a gastrojejunostomy in this sequence, using a vertical limb of jejunum that starts at the duodenojejunal junction (24). Today the Whipple pancreaticoduodenectomy is the procedure of choice for most surgeons treating patients with adenocarcinoma of the head of the pancreas. The long-term survival and post operative mortality as improve significantly since Whipple described this procedure (table 1).

### 4. TOTAL PANCREATECTOMY

According to Sauv'e (13) total pancreatic resections were performed by Billroth in 1894 and by Franke in 1900. The first reported case of total pancreatectomy for carcinoma was performed in 1943 by Rockey, on a patient who died 15 days after the operation (25). In 1944, Priestley, Comfort, and Radcliffe reported the first total pancreatectomy with uneventful postoperative course on a patient with hyperinsulinism caused by an islet-cell carcinoma (26). Subsequently, other surgeons performed this procedure for pancreatic carcinoma in the 1940s and 1950s (24-32). In fact, Ross (31), in 1954, considered total pancreatectomy the procedure of choice for the treatment of pancreatic carcinoma. Poor long-term survival combined with significant mortality and morbidity discouraged its use by most surgeons treating pancreatic cancer. Resurgence of interest in this operation occurred in the 1970s, mainly, because of the unsatisfactory results of pancreaticoduodenectomy (33-35). Several institutions reported series with reasonable mortality and morbidity rates (33,36-38, 68-77) (table 2). Proponents of total pancreatectomy claim that it provides better eradication of pancreatic cancer and it does not require a pancreatic anastomosis, which is the source of substantial morbidity. Opponents argue that multicentricity is rather uncommon in pancreatic cancer and that brittle diabetes, which is well-known sequela of total pancreatectomy, is extremely difficult to manage and may cause fatalities.

### 5. REGIONAL PANCREATECTOMY

The dismal long-term results after pancreaticoduodenectomy and total pancreatectomy provided the rationale for regional resection of the pancreas described by Fortner in 1973 (39). This operation designed to accomplish removal of the pancreas, the immediately adjacent tissue and the primary lymphatic drainage of the pancreas. The transpancreatic portion of the portal vein is included in the en bloc resection and the splanchnic venous blood flow is re-established by an end-

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**Table 1.** Long-term survival and operative mortality after Whipple pancreatoduodenectomy carcinoma

Institution	# of patients	5-yr survival (%)	Operative mortality (%)	Reference Number
French Assoc. Surgery	555	15	8.0	68
Sloan Kettering	138	21	6.0	70
Toronto	28	7.0	4.6	71
M. H. Hannover	107	13.8	3.5	72
Mayo Clinic	104	10.0	2.4	73
Johns Hopkins	201	21	5.0	74

**Table 2** Long-term Survival and operative mortality after total pancreatectomy for carcinoma

Institution	# of patients	5-yr survival (%)	Operative mortality (%)	Reference Number
French Assoc. Surgery	555	3.0	7.0	68
Mass. General Hospital	138	14.0	8.0	60
Columbia University	28	1.5	23.4	69
Rennes	107	8.0	13.0	76
Mayo Clinic	89	3.4	10.1	77

to-end anastomosis of the portal and superior mesenteric veins. The celiac axis and the proximal portion of the superior mesenteric artery with their lymphatic vessels and lymph nodes are also removed en bloc and revascularization of the intestine and the liver is accomplished with the use of synthetic vascular graft (39). In 1984, Fortner published the results of regional pancreatectomy on 61 patients. The resectability rate was about 30%. The operative mortality and morbidity rates were dropped from 32% and 76% respectively in the patients treated in 1979 to 8% and 55% in the patients treated in 1982. Twenty percent of the patients with infiltrating ductal carcinoma were alive with disease at the time of the report and more than 90% of these patients had advanced stage disease (40). Recent studies from Japan show that the addition of regional lymphadenectomy and portal or superior mesenteric vein resection to pancreatectomy improves survival in selected patient groups (41,42). Despite these rather encouraging results regional pancreatectomy, a true surgical tour de force, has not gained wide acceptance among surgeons treating carcinoma of the pancreas.

### 6. LEFT HEMIPANCREATECTOMY

Left hemipancreatectomy is reserved for tumors of the tail of the pancreas which are rarely discovered before they are operable. Even when these tumors are operable, only a handful of long-term survivors has ever been reported (43).

### 7. PYLORUS-PRESERVING PANCREATODUODENECTOMY

Pancreaticoduodenectomy with pylorus preservation was described by Traverso and Longmire 1978 (44). The rationale for the use of this procedure is the

decrease of the functional and nutritional sequelae of pancreaticoduodenectomy that are caused by the partial gastrectomy and the loss of pyloric function. The popularity of this technique for treatment of pancreatic cancer among some surgeons in recent years (45-48) parallels the adoption of less radical procedures for the management of malignant tumors in other anatomic locations. Although some studies demonstrated no decrease in survival with the use of pylorus-preserving pancreaticoduodenectomy (46,48), others showed potential for increased local recurrence and survival compromise in some patients, suggesting caution with the use of this procedure for the treatment of pancreatic cancer (49,50). The place of this operation in the surgical armamentarium for the management of pancreatic cancer needs to be more clearly defined.

### 8. LOCAL EXCISION

The more conservative approach of local excision may be used in the treatment of some periampullary tumors. Today, local excision is recommended for benign villous adenomas of the papilla or duodenum, particularly in high-risk patients who might not tolerate a more radical resection (51). However, up to 50% of these apparently benign adenomas may recur as carcinomas (52).

### 9. LAPAROSCOPY IN PANCREATIC CANCER

This diagnostic modality has been used with increasing frequency during the last decade because of the availability of improved instrumentation and better familiarity of surgeons with the technique. Most patients with peripancreatic malignancy are found at exploration to be unable to undergo resection. Laparoscopy can identify

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small peritoneal omental and liver metastases that cannot be diagnosed with other modalities, thus preventing the performance of unnecessary laparotomies (64-66). Although laparoscopic Whipple procedure has been done, so far it has been met with a more guarded response (67).

### 10. CONCLUSION

A major concern regarding surgery for pancreatic cancer has been the high mortality and morbidity associated with pancreatic resections. Mortality in the earlier years was indeed quite high. In the 1960s most surgeons reported operative mortality rates of 20-40% (53-55), with the single exception of Howard who reported a series of 41 consecutive Whipple resections without an operative mortality (56). The high operative mortality, combined with the dismal long-term survival results (57), have raised serious questions about the value of pancreaticoduodenectomy as a curative approach to pancreatic cancer (58). The significant advances in perioperative care and expertise with pancreatic surgery have contributed dramatic decrease in operative mortality. Several recently published series have shown a significant decrease in operative mortality rate (45,46,59-63,68-77). In addition, most of these series demonstrated an improvement in 5-year survival with rates ranging from 14 to 38% (46, 59-63, 68-77) (Table 1). These results clearly justify the use of pancreatic resection for localized and resectable pancreatic cancer when proper selection criteria are followed and the procedure is performed by surgeons with expertise in major pancreatic surgery. The selection of patients who are proper candidates for curative pancreatic resection has been facilitated by the use laparoscopy (64-66).

Despite the decreasing operative mortality and the improved survival following surgical resection of the pancreas, the overall survival of patients with pancreatic cancer has not changed significantly, because the majority of patients still present with advanced disease not amenable to surgery with curative intent. Undoubtedly, the quest for methods to provide earlier diagnosis and more effective approaches for the management of locally advanced disease will continue and hopefully lead to improved outcome of patients with pancreatic cancer.

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