Total Pancreatectomy: Indications, Advantages and Disadvantages – A Review

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 Mozilla Ugly

\textbf{ABSTRACT}

\textbf{Background:} Total pancreatectomy is an obligatory surgical procedure in locally advanced or centrally located pancreatic neoplasms to achieve complete tumour clearance. Owing to sound understanding of tumour biology and evolution in intervention technique and improved postoperative care, nowadays the indications of total pancreatectomy have taken a significant change.

\textbf{Aim:} To review the indications of total pancreatectomy and its advantages and disadvantages under current perspectives.

\textbf{Methods:} Major databases, including PubMed, EMBASE, Science Citation Index Expanded, Scopus and the Cochrane Library, were searched for studies of total pancreatectomy and the results reported by various authors were summarized.

\textbf{Results:} The indications of total pancreatectomy in subjects diagnosed with chronic pancreatitis were classified into four subgroups, including “Tumour”, “Trouble”, “Technical difficulties” and “Therapy-refractory pain”. Today, total pancreatectomy has more specific and different indications than before. Currently, IPMN (intraductal papillary mucinous neoplasm) seems to have the most essential indication quantitatively. Morbidity and mortality related to total pancreatectomy are more profoundly decreased than before due to improvements in the operative techniques and post-operative managements. Some of the metabolic disorders are reported as major disadvantages of total pancreatectomy.

\textbf{Conclusion:} Despite the disadvantages of total pancreatectomy, it remains an inevitable procedure for subjects with chronic pancreatitis, improvements in operative techniques and postoperative management ensuring long-term survival, a better quality of life, and diminished mortality and morbidity rates.

\textbf{Keywords:} total pancreatectomy, chronic pancreatitis, indications, advantages, disadvantages.
INTRODUCTION

Chronic pancreatitis is a progressive inflammatory process, which affects the pancreatic gland and leads to damage and decrease in glandular tissue (1). Based on changes in pancreatic histopathology, it is classified into three types: a) chronic obstructive pancreatitis; b) chronic calcifying pancreatitis (the commonest type, which includes alcoholic chronic pancreatitis); and c) chronic inflammatory pancreatitis, including chronic pancreatitis resulting from the chronic inflammation of the biliary tract and stenosis induced by scar formation (2, 3).

With only 1-5% long term survival rate characterising poor prognosis of this tumour entity, pancreatic cancer management is still an interdisciplinary challenge (4). From the perspective of oncology, the fourth main reason for mortality due to cancer in the Western world is represented by pancreatic cancer, with > 100,000 deaths per year in the USA and Europe (5). Early detection is a chief problem, since at the time of diagnosis, 80 to 90% of pancreatic cancers are locally or systemically advanced. Nevertheless, 25% five-year survival rates are possible in subjects who are suitable for resection, which points to surgery being the only chance of cure and survival in the long term. Yet, as an adjuvant treatment, the surgical remedy has to be entrenched in a concept of oncology as postoperative chemotherapy is a vital aspect to further improve survival (6-8). To attain a better result in subjects with pancreatic cancer in the future, several ongoing studies on new therapeutic agents such as supportive agents, antibodies and antimetabolites reflect the present clinical and scientific struggle (9). On the basis of an initial tumour resection, long term survival needs can be achieved despite new chemotherapeutical or targeted substances (6, 10).

Ever since surgeons realized that the complete removal of the pancreas was feasible, this treatment has been a topic of contentious deliberations. The sporadic total pancreatectomy reports from 1940s and 1950s grew to a frank interest about the possible benefits of the technique, with accumulation of surgical experience in the 1970s, but they were about to disappear later due to the negative metabolic consequences of the operation. In treating locally advanced pancreatic cancer, multifocal or recurrent exocrine and endocrine tumours, complete removal of the gland has been recognized as a potential treatment option (11-14). In an emergency, complete removal of the remaining organ may be required during difficult times such as peroperative complications arising from pancreatic anastomotic leakage with or without bleeding or apoplexy of the pancreatic remnant (15, 16). To improve survival of pancreatic cancer subjects, total pancreatectomy was attempted with the justification to avoid anastomosis-related morbidity and mortality and to reduce recurrence rates of tumour (17-19).

Chronic pancreatitis can be treated by opting for surgery if conservative treatment is ineffective. However, reports on current indications for total pancreatectomy and its outcomes in the literature remain sparse as well as data published on postprocedural quality of life remains limited, despite a growing demand for total pancreatectomy and its increasing rate of performance at large pancreas centres recently (20-23).

More recently, the indications of total pancreatectomy have considerable changed due to a better understanding of tumour biology and improvements in the intervention method and post-operative care. Hence, the current assessment aims to summarize on the indications of total pancreatectomy and its advantages and disadvantages.

Indications

In 2010, Janot MS et al (19) classified the indications for total pancreatectomy in chronic pancreatitis subjects in “Four T’s”: Tumour; Trouble; Technical difficulties; and Therapy-refractory pain.

Tumour group

The commonest indication for total pancreatectomy is the locally advanced or multifocal pancreatic tumours. Recurrent pancreatic carcinoma, multicentric cancer, intraductal papillary mucinous neoplasia (IPMN) with invasive disease or diffuse involvement of the gland, and extensive neuroendocrine tumours are other examples for indications related to tumour (13, 14, 24-26).

Trouble group

In the “trouble group” subjects, total pancreatectomy was moreover a procedure of emergency
or an *ultima ratio* in ICU cases, i.e., pancreatic anastomosis insufficiency, insufficiency of pancreatic stump complicated by acute bleeding, pancreatic remnant necrosis followed by sepsis, where no success was seen by using conservative therapy. After the initial operation, acute bleeding occurred in five to 14 days in subjects who developed vessel arrosion owing to pancreatic anastomosis insufficiency. A permanent high inflammation parameters with > 100 mg/L values of CRP may be an early signal warning for imminent vessel arrosion (27-29).

**Technical difficulties**

In the technical difficulties group, it was not possible to carry out a safe pancreatic anastomosis, sometimes in a friable and soft pancreatic remnant that was not able to hold sutures. In such cases, a life-threatening haemorrhage and sepsis can occur in 15% of all pancreatic fistula, wherein elective total pancreatectomy must be a preferred option. In this group the goal of total pancreatectomy was to avoid an emergency completion pancreatectomy that is associated with a high mortality rate.

**Therapy-refractory pain**

Therapy-refractory pain is another sign for total pancreatectomy. Predominantly, in chronic pancreatitis subjects, symptoms of not responding to medical treatment can persist or develop again after resection surgery or drainage, indicating either disease progression or failure of primary operative procedures, respectively. As shown by numerous studies, a significant pain relief after resection surgery was experienced by 30–60% of chronic pancreatitis subjects. Sometimes, total pancreatectomy is inevitable in these subjects (14, 30-34).

Owing to the better quality of results, there are different and more specific indications for total pancreatectomy today than in the past. The understanding tumour biology and pathophysiological complications is clearer than ever even in adenocarcinoma cases:

- malignant tumours growing from the pancreatic head into the left pancreas;
- pancreatic head cancer where it is not possible to secure a tumour-free resection margin with extended resection or with dubious changes in the pancreatic main duct at frozen section;

- recurrent malignancy in the pancreatic remnant;
- at cancer surgery with resection of the celiac trunk;
- rescue pancreatectomy after a leaking pancreateojenunostomy with sepsis or bleeding after a Whipple-type first resection;
- multifocal IPMN with potentially malignant foci present in all parts of the gland;
- multiple metastases of renal cell carcinoma and melanoma without any residual tumour outside the pancreatic gland (possibly also other specified but uncommon metastatic tumours with a potential for cure by pancreatectomy);
- multifocal neuroendocrine tumours, including multiple endocrine neoplasia;
- hereditary pancreatic cancer with a high-grade risk of cancer penetration for the bearers.

Still, total pancreatectomy is not used as a common procedure in pancreatic cancer surgery practise despite the long list of indications. Around 10% of all resections has been encompassed in larger series recently (35-37). Moreover, for treating intractable pain related with chronic pancreatitis, total pancreatectomy remains a feasible option, particularly in subjects with no tobacco or alcohol abuse and where it is possible to auto-transplant the Langerhans islets (38-40).

**Intraductal papillary mucinous neoplasm**

Intraductal papillary mucinous neoplasm (IPMN) seems to have the most vital indication today quantitatively. For managing IPMN, resection for main duct disease with clearance of all HGD (high-grade dysplasia) is recommended as per international consensus guidelines (41, 42). As main duct IPMN may be linked with extensive multifocal high-grade dysplasia, the role of total pancreatectomy in such settings is increasingly recognized. Preoperative decision may be made at multidisciplinary therapy conferences or intra-operative decision may be made in subjects with positive margins on frozen section. In the USA, Murphy et al reported an increasing use of pancreatectomy nationwide between 1998 and 2006, and they concluded that such a rise was attributable to an increased diagnosis of diffuse neoplastic diseases, specifically IPMN (43-45).
Advantages/disadvantages
The huge improvement in the operative techniques of total pancreatectomy and postoperative management has led to a dramatic decrease in morbidity and mortality related to total pancreatectomy (TP) (46-48), their highest reported values being 86.7% and >20%, respectively (49-52).

Pancreatic malabsorption
The short-term and long-term effects of total pancreatectomy, described by Barbier et al (53), included a median weight loss of 9 kg (range 2-14 kg), some patients experiencing weight gain with an average of 13 kg (range 4-22). Subjects who underwent total pancreatectomy had two stools per day (range 1-5); some of them had liquid stools, others nocturnal stools, and for some others, diarrhoea was a limiting factor in their everyday life. Six (3–18) capsules (25,000 units per capsule) was the median daily intake of pancreatic enzyme supplements; other medications taken by subjects for their intestinal transit included diosmectite and loperamide. Prothrombin time and liver function tests were within normal ranges; particularly, no cholestasis was noticed. The renal function was usually preserved, with a median serum creatinine of 82 mmol/L (range 50–163). Nutritional markers included albumin 100% (81–100), pre-albumin 100% (70–100) and normal values of orosomucoid 100% (63–100).

Pancreatic diabetes
Pancreatogenic diabetes mellitus after resection of pancreas differs from type 1 and type 2 diabetes. Severe hyperglycemia or ketoacidosis is seldom caused by pancreatogenic diabetes, unlike type 1 diabetes. Pancreatogenic diabetes also differs from type 2 diabetes, which is characterized as resistant to insulin and relatively deficient in insulin. Pancreatogenic diabetes is extremely insulin sensitive. It is gaining attention as the prime aspect in influencing the quality of life in subjects who underwent total pancreatectomy, being difficult to envisage the effect on carbohydrate metabolism due to metabolic changes. As a result of an augmented peripheral insulin sensitivity and a reduction in glucagon level in pancreatogenic diabetes, frequent exogenous insulin administration can even cause hypoglycemic attacks. Liatrogenic hypoglycemia may lead to hospitalization, irreversible damage to the CNS (central nervous system), or even death, occasionally (54-55). However, given the growing knowledge of pancreatogenic diabetes mellitus pathophysiology, there are good results related to both short-term and long-term survival, the latter being almost entirely dependent on the indications for pancreatic resection (54).

In a recent study on the post-total pancreatectomy quality of life, published by Epelboym et al (56, 7), an audit among subjects with diabetes revealed that the disease had a negative impact on their quality of life, but they were not able to find any difference in ‘life domains’ between total and partial pancreatectomy. Travel and physical activity were most negatively impacted by diabetes, while self-confidence, motivation and feelings about the future, and friendships and personal relationships remained unaffected.

After the first eagerness over the ability to carry out total pancreatectomy, the drawbacks of this surgical treatment became more noticeable. Numerous centres reported perioperative rates of morbidity and mortality which were equivalent to those of Whipple treatment, but with no long-term survival improvements. In admission, total pancreatectomy usually caused major metabolic problems such as brittle insulin-dependent diabetes mellitus, which used to be difficult to control. Furthermore, malabsorption owing to exocrine pancreatic secretion loss was also often tough to manage. Consequently, loss of weight, diarrhoea and malabsorption frequently contributed to a cachexia-like syndrome that considerably decreased quality of life and likelihood of normal physical activity. Steatorrhea and the short food transit time led to immeasurable carbohydrate absorption, which in turn made it difficult to titrate the insulin dose to food intake. The loss of fat-soluble vitamins has also contributed by steatorrhea, vitamin D deficiency resulting in osteopathy and osteoporosis as well as liver disorders. Initial survivor used to suffer repeated attacks of hypoglycaemia and hypoglycaemic coma. For several years, pancreatic tumour treatment through total pancreatectomy has been largely abandoned in clinical exercise, being no longer a feasible choice owing to problems of exocrine and endocrine insufficiency and those related to a reduced quality of life, but also because it offers no oncological benefit (21).
CONCLUSION

Modern treatment regimens, interdisciplinary management and enhanced post-operative care in total pancreatectomy subjects result in long term survival, better quality of life, diminished rates of mortality and morbidity. However, total pancreatic resection can cause insufficiency of endocrine and exocrine with severe metabolic outcomes such as steatohepatitis, malabsorption, difficult glycaemic control and liver failure. Despite the disadvantages of total pancreatectomy, it is still an inevitable procedure to be performed in chronic pancreatitis subjects.

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