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Total Pancreatectomy for Pancreatic Pathology: Contraindication or Privileged Indication?

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Introduction

Total Pancreatectomy (TP) has been a subject of discussion, ever since surgeons realized that it was feasible. TP has been considered as a potential option in the management of chronic pancreatitis refractory to treatment, locally advanced pancreatic cancer, multifocal or recurrent exocrine and endocrine tumours [1-6]. In addition to this, surgeons have carried out TP to treat or avoid perioperative complications, arising from pancreatic anastomotic insufficiency with or without bleeding, following pancreaticoduodenectomy or distal pancreatectomy [3,4]. These complications may occur increasingly, while dealing with a soft pancreas during primary surgery, which may prompt some surgeons to opt for TP [4,7]. However the concern has been, about the management of these patients in a pancreatic state, with its attendant total endocrine and exocrine insufficiency [1-5]. This includes the complete insulin deficiency and the necessity of insulin therapy, exocrine insufficiency with steatorrhea and the need for durable pancreatic enzyme replacement and the development of steatohepatis with progressive liver failure. In addition the lack of bicarbonate secretion may lead to peptic ulcers resulting in continuous use of proton pump inhibitors [4,8]. So is TP a relative contraindication or are there some privileged indications?

Sauve performed the first reported TP for pancreatic cancer in 1884 [9]. However since then TP has been reported by Rockey in 1943 for pancreatic adenocarcinoma [10]. Ross [11] was an early advocate of TP. TP was propagated by him as a procedure of choice to avoid complications of pancreatic insufficiency. However the enthusiasm of 1940s and 1950s waned off in 1970s due to the negative metabolic consequences of the operation. The use of autologous islet cell transplantation as described by Gruessner et al. from university of Minnesota, led to renewed interest in the use of TP, for relief of pain associated with chronic pancreatitis [12].

Presently TP has been carried out in several large pancreas centers with increasing rate,for different indications. Janot et al. [4] recently analyzed and classified the indication of TP into "*Four T's*". These included *Therapy refractory pain* (related to chronic pancreatitis), *Tumour, Trouble and Technical difficulties*". Analyzing the results of 63 of their patients who underwent TP over a period of 4 years, they reported TP to be carried out in 6.7% of all pancreatic procedures (n=948). Among these, the indications included tumour at advanced stage, n=23 (36.5%), technical problems due to soft pancreatic tissue, n=18 (28.6%), troubles due to perioperative surgical complications, n=15 (23.8%) and therapy resistant pain due to chronic pancreatitis, n=7 (11.1%) [4].

One of the commonest indications for TP that is often reported in the literature is for intractable pain in chronic pancreatitis [1-4] (Figure 1). While in the past some of these patients underwent TP alone, off late they are managed with TP and Islet Autotransplantation (IAT) [1,5]. The main objective of TP and IAT is to relieve intractable pain from chronic pancreatitis while preventing or reducing the severity of surgically induced diabetes [1-4]. While it is known that pain from chronic pancreatitis may eventually burn out, the time when it may occur (if at all) is highly variable [13]. In the management of chronic pancreatitis, the distinction between large (more than 5 mm diameter) and small duct disease, determines the therapeutic approach. While patients with large duct disease may respond to surgical or endoscopic decompression, patients with small duct disease often fail to endoscopic decompression, celiac plexus block or splanchnicectomy, as pain recurs in over 50% of them following these procedures [14]. In a systematic review of the outcome of TP and IAT for chronic pancreatitis, it was found that it markedly reduced the pain with significant reductions in the use of narcotic analgesia [1]. Moreover concurrent IAT reduced the insulin requirement, with rate of insulin independence ranging from 46% of patients at 5 years to 10% at 8 years [1]. While the review did not provide good evidence regarding the optimal timing of TP/IAP in relation to the evolution, there was general belief that TP/IAT should be carried out early in the course of chronic pancreatitis [1]. This is to avoid the complications of chronic opioid use and to achieve higher yield from pancreatic parenchyma that is less compromised by fibrosis or previous surgery [15].

The success achieved with TP/IAT has lead to this procedure being offered early in the course of natural history of chronic pancreatitis [1,2,5]. It has been reported that sex, weight and body mass index correlated with islet yield, with higher islet equivalents per kilogram bodyweight in the insulin independent group [16]. Post transplant

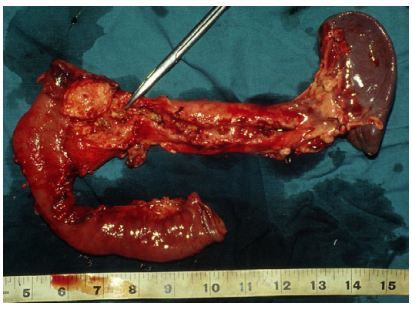

Figure 1: Total pancreatectomy for a patient with chronic pancreatitis with intractable pain and failure to non surgical approach. Duct full of calculi can be noted.

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insulin independence other than number of islets transplanted, depends on the maintenance of normoglycaemia, in the immediate postoperative period to ensure recovery of transplanted islet cell function, which can occur as late as 1 year following transplantation [17]. One of the concerns of IAT however is the rise in the portal pressure after transplant and hence islet purification was considered important, if the tissue digest exceeded 20 cm^3, [15]. However it has been noted that purification decreases the number of islets recovered and at least 40% of islet cell mass is lost during purification [18]. Hence some feel that islet purification is not a must and has to be weighed against wastage of islet cells [19]. In a recent report, the factors of rise in portal pressure post IAT was analyzed and the authors have recommended to achieve a total volume of islet cells of <0,25 cm^3/Kg during islet harvesting and to halt intraportal infusion at least temporarily if portal vein pressure exceeded 25 cm H_2O [6]. In one of the recent large series, the outcome of TP/IAT in 409 patients(including 53 children) revealed the actuarial patient survival was 96% in adults and 98% in children (1 year) and 89% and 98%(5years) [2]. At 3 years, 30% were insulin independent (25% in adults, 55% in children) and 33% had partial function. Previous pancreas surgery lowered islet yield (2,712 vs. 4,077/kg; p=0.003). Importantly, islet yield (<2,500/kg (36%), 2,501 to 5000/kg (39%), >5,000/kg (24%) correlated with degree of function with insulin independent rates at 3 years of 12%,22% and 72% and rates of partial function of 33%, 62% and 24% respectively [2]. After TP/IAT, 85% had pain improvement and by 2 years 59% had ceased to take narcotic analgesia [2].

Another indication of TP that is often debated, is its role in the management of pancreatic neoplasm [3,4,20,21]. Historically, disappointment with oncologic results of pancreaticoduodenectomy for carcinoma of pancreas, enticed surgeons to attempt more extensive operations. The rationale for TP in the treatment of pancreatic adenocarcinoma stem from (1) the desire to avoid complications of pancreatic fistula; (2) the concern that the disease is frequently multicentric and (3) the view that TP represents a more definitive oncologic resection than a partial pancreatic resection with greater lymph node clearance and increase in the percentage of R0 resection. However studies of TP for pancreatic cancer failed to demonstrate improved benefit over less aggressive resections [3,4,20,21]. While some reported similar median survival for patients undergoing TP compared with PD (10 vs. 16 months) [22] others such as researchers from Memorial Sloan–Kettering Cancer Center showed that patients with TP had overall significantly lower survival compared with a contemporary cohort of patients who underwent PD or distal pancreatectomy [23]. Hence it is believed that there is no proven oncologic benefit for routine TP over PD. Given that the pancreatic fistula are now better managed, most tumours are not multicentric and that TP results in higher perioperative morbidity and mortality with no increased long term survival, there is no role for routine consideration of TP in the management of sporadic pancreatic adenocarcinoma [3,4,20,22].

However there are some specific clinical situations (privileged indications) that may be exceptions and would warrant TP. These include familial pancreatic adenocarcinoma [23-25], locally advanced or multifocal pancreatic tumours, recurrent pancreatic carcinomas, multicenter cancer, Intraductal Papillary Mucinous Neoplasms (IPMN) with invasive disease or diffuse involvement of the gland and extensive neuroendocrine tumours [3,4,10,20]. In patients affected by familial pancreatic adenocarcinoma, first-degree relatives with three or more affected family members have upto 57-fold increase in the risk of developing pancreatic cancer [25,26]. The susceptibility to pancreatic cancer is inherited in an autosomal dominant fashion and germline mutation in BRCA2 has been identified in upto 20% of the affected families [26]. These patients tend to develop malignancy earlier with a more aggressive clinical course in succeeding generations and are likely to be multicentric [26]. Hence, surveillance and TP is reported to have the potential to avert the development of invasive pancreatic adenocarcinoma and is considered as a prophylactic procedure in some these patients [24-26]. IPMN of main duct type, when diffuse has a 30 to 72% risk of invasive or noninvasive carcinoma at the time of presentation and is consideredas another potential indication for TP [27]. Another indication that would warrant TP in order to achieve curative resection is the size and localization of pancreatic cancer. These would include locally advanced and multifocal disease. However some have reported overall poor survival in patients with adenocarcinoma undergoing TP compared to those undergoing pancreaticoduodenectomy or distal pancreatectomy (7.9 vs. 17.2 months; p<0.002) [23].

The most common operation for pancreatic neoplasia is pancreaticoduodenctomy. However the Achilles heel of this operation is the pancreatic anastomosis with an incidence of pancreatic leak ranging from 2-29% [7]. While most of these cases can be managed successfully by non-surgical approach, some 15% of them would require an emergency surgical intervention and are categorized into "*trouble group*" requiring TP [4,7]. These patients would develop pancreatic anastomosis insufficiency complicated by acute bleeding, necrosis of pancreatic remnant followed by severe sepsis [7]. They are critically ill and would usually be in American Association of Anaesthesiologists group 111 or 1V [4]. This group is characterized by high morbidity (73%) and mortality (47%). To compound matters, their reoperation is demanding, in view of their poor general condition, adhesions, altered anatomy, oedematous friable tissues, significant intraoperative bleeding and need for transfusion [4,7]. Such patients who are considered near surgical disaster, are not ideal for any reconstructive surgery and may need and emergency *salvage TP* [4,7]. Mortality still remains high post surgery, not only due to surgical, but medical complications including cardiac, respiratory and renal [4].

In the "*technically difficult*" group, the major concern was carrying out anastomosis on a soft pancreas with narrow duct following pancreatic resection [4]. As the reported risk of leak in these patients is significant and the consequence of some of these with secondary haemorrhage is fatal, some surgeons would consider the option of TP in these cases [3,4,7]. However the major issue is in deciding what constitutes a soft pancreas that would warrant a TP [4]. Defining the objective criteria to decide on soft consistency of pancreas and its appropriate evaluation needs further study. This may decide on the pros and cons of carrying out a prophylactic TP in such patients [4].

So is TP a contraindication or a privileged indication? Based on the reports in the literature, TP remains a viable option in the treatment of (1) intractable pain associated with chronic pancreatitis, (2) patients with familial pancreatic cancer with premalignant lesions, (3) locally advanced neoplasm involving most of pancreas,(4) multicentric or extensive neuroendocrine tumours, (5) patients with IPMN with diffuse ductal involvement or invasive disease (6) and in dealing with life threatening complications following pancreatic anastomosis insufficiency or in case of concern in carrying out a potentially risky pancreatic enteric anastomosis during the index surgery in presence of soft pancreas. While these privileged indications are often reported from pancreas centers [1-6,21-23], the relative contraindication due to the concern of metabolic consequences of apancreatic state have also been addressed to a large extent by several improvements in the postoperative management, including treatment of diabetes mellitus

and substitution of pancreatic enzymes and fat soluble vitamins [1-6]. These have significantly reduced postoperative morbidity and improved quality of life after TP. Recent studies described that there was no significant difference in quality of life in patients with elective TP and partial pancreatectomy [28]. In addition pancreatic surgery is being carried out safely with acceptable morbidity and mortality, especially at a high volume pancreas centers [29,30]. The use of IAT in selected patients with chronic pancreatitis and pancreatic allografts in young patients with premalignant disease have been used in the armamentarium of treatment options for pancreatimized patients [12]. In patients who are not candidates for transplantation, advances in insulin formulations and the use of glucagon rescue therapy allow much tighter control of blood glucose than previously possible [31]. This has markedly reduced the risk of life threatening hypoglycaemia and decreased the risk of long-term complications resulting in improved quality of life in these patients.

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