STATE-OF-THE-ART REVIEW

Surgical management of pancreatic cancer

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Abstract

Pancreatic cancer is one of the top 10 cancers in terms of incidence, and continues to be associated with poor 5-year survival. Surgery for localized disease provides the best treatment option with potential for cure. This article discusses pre-operative management, and the evidence for and against biliary drainage prior to surgery, indications for the different types of pancreatic resections and variations in surgery based on evolution of techniques over time, including the extent of lymphadenectomy. The diverse options for reconstruction and their merits are highlighted and the evidence for and against post-operative drainage is presented. Aspects of perioperative management are discussed, with emphasis on complications specific to pancreatic surgery, the role for enhanced recovery and use of somatostatin analogues. The evidence for centralization is outlined, and measures to improve outcomes following these complex resections are detailed.

Pre-operative assessment

Rigorous pre-operative assessment to evaluate fitness for surgery is essential, in view of the considerable perioperative morbidity of 30–50%, and mortality rates that vary from 3.8%, in high-volume centres, to 16.3%, in low-volume centres. Comorbidities, such as type 2 diabetes mellitus and cardiovascular disease, add to the post-operative risks, and patients with poorly controlled medical conditions may need a period of optimization prior to surgery.

Pre-operative management of jaundiced patients

Patients with cancer of the head of pancreas often present with jaundice. In those with resectable disease, the options are to either proceed with resection or perform pre-operative biliary drainage and subsequent surgery. A randomized controlled multicentre trial from the Netherlands randomized 202 patients with a serum bilirubin of 40–250 mmol/l to either immediate resection (mean time to surgery 1.2 weeks) or pre-operative biliary drainage by endoscopic retrograde cholangiopancreatography with insertion of a plastic stent or, if that failed, percutaneous transhepatic cholangiography, followed by surgery (mean time to surgery 5.2 weeks). The authors reported a significantly higher risk of complications in the group undergoing pre-operative biliary drainage (74% vs. 39%; P < 0.001) and that these adverse events were frequently related to biliary drainage. There were no differences in surgery-related complications, length of stay or mortality between the two groups. Criticisms of this study are the high rate of cholangitis in the biliary drainage group (26%) and that some participating centres were low-volume units.

Introduction

Pancreatic cancer is the 10th most common cancer in the UK and the fifth commonest cause of death from cancer. In the Gulf Cooperation Council states, pancreatic cancer was the 10th leading cancer in men. Death rates for pancreatic cancer continue to rise in the United States of America (USA). Surgery offers the only possible hope for curative therapy, but 5-year survival figures are dismal at 20%. Pancreatic resection remains a high-risk surgical procedure with considerable post-operative morbidity. This review outlines the current best practice in surgery for pancreatic cancer and discusses evidence for different surgical techniques and current controversies.

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In jaundiced patients who are fit to proceed with resection, most specialist units would advocate proceeding with surgery, with pre-operative biliary drainage being reserved for patients who present with cholangitis, have very high bilirubin levels with associated coagulopathy or renal impairment, when neoadjuvant therapy is considered appropriate or if there is likely to be a significant delay to resection because of limited theatre capacity or time needed for patient optimization. Metal endobiliary stents can be used preoperatively and are reported to have better patency rates, without adversely affecting surgical outcomes. The optimal duration to wait once a patient is stented is unclear, with four randomized controlled trials (RCTs) utilizing a time framework of 7–18 days, and a Dutch study using 4–6 weeks, based on experimental and clinical studies that suggest this is the time needed for restoration of liver synthetic and clearance functions.

Surgery for pancreatic cancer

The type of resection is dictated by the location and type of tumour. Tumours of the head of pancreas and periampullary region require partial pancreateoduodenectomy, while body and tail lesions are treated by distal pancreatectomy. Diffuse gland involvement, as in main duct intraductal papillary mucinous neoplasia (IPMN), requires total pancreatectomy.

Pancreatoduodenectomy

This operation was first undertaken by Kausch in 1908, and popularized in the 1930s by Whipple. Classic pancreateoduodenectomy, also known as the Kausch–Whipple procedure, involves resecting the head of the pancreas, distal stomach, duodenum, upper jejunum and distal biliary tree, including the gallbladder. A modification of this technique preserves the distal stomach and pylorus and is termed a pylorus-preserving pancreateoduodenectomy (PPPD). On meta-analyses, both operations are comparable for morbidity, mortality and survival; however, a Japanese RCT has shown a significantly higher rate of delayed gastric emptying following PPPD. Tumours involving the first part of the duodenum and distal stomach warrant classic Kausch–Whipple operation, while other tumours can undergo either type of resection.

Involved of the portal or superior mesenteric veins does not preclude resection. Patients who undergo venous resection have similar perioperative mortality risk and 5-year survival rates to those who undergo a standard resection. Limiting factors are surgeon experience, the presence of suitable vessel proximally and distally and experience in vascular reconstruction (Figures 1 and 2). Arterial involvement and resection are more controversial, and encasement of the coeliac axis, hepatic artery or superior mesenteric artery are widely considered as indicating locally advanced unresectable disease.

Neoadjuvant treatment may be able to downsize conventionally unresectable disease, and has been shown to have benefit in retrospective studies, and some phase I and phase II clinical trials. Rationale for neoadjuvant therapy are the ability to downsize locally advanced disease and allow subsequent curative resection, deal with micrometastases and avoid surgery in those with poor tumour biology who progress on treatment. Prerequisites for a neoadjuvant approach are a fit patient with durable biliary decompression if jaundiced, adequate nutritional support, satisfactory management of comorbidities, such as type 2 diabetes mellitus, and good symptom control to enable treatment delivery and effective management of any side-effects associated with chemotherapy/chemoradiotherapy. Results from two ongoing randomized trials, NEOPAC and ESPAC 5F (www.isrctn.com/ISRCTN89500674), will add more objective data to the existing evidence.

A principal cause of morbidity and, consequentially, mortality following pancreateoduodenectomy is leak from the pancreaticoenteric anastomosis. There has therefore been much interest focused on the surgical technique used. Pancreatecojejunostomy (Figures 3 and 4) is the most commonly used method and a number of techniques have been described, including end-to-side, end-to-end, duct-to-mucosa and invagination techniques. RCTs have not demonstrated any clear superiority of one technique over another. One of the problems with comparison of these studies has been the lack of a uniform definition of a pancreatic fistula; however, this has been addressed by the International Study Group on Pancreatic Fistula that has now published a standard definition.
**FIGURE 1** Pancreatic head/uncinate process tumour with involvement of the superior mesenteric vein. Vascular slings on portal vein (PV), splenic vein (SV), first jejunal branch (JB) and superior mesenteric vein (SMV) for control. Arrow indicates tumour.

**FIGURE 2** Anatomy post resection of tumour by classic Whipple. Portal vein (PV), splenic vein (SV), superior mesenteric vein (SMV), pancreas and bile duct (arrow indicating this) displayed.
FIGURE 3 Probe in pancreatic duct (arrow indicating this) prior to reconstruction. Pancreas, portal vein (PV) and splenic vein (SV) seen.

FIGURE 4 Completed pancreaticojejunostomy (arrow indicating suture line).
Reconstruction using a pancreaticogastrostomy rather than a pancreaticojejunostomy has been proposed as a means of reducing the complication rate, and non-randomized studies have reported favourable results. However, subsequent randomized studies have not supported these findings, although a recent single-centre RCT did show a significant reduction in pancreatic fistula rate with pancreaticogastrostomy (8.0%) compared with pancreaticojejunostomy (19.8%).

Biliary drainage was originally described by Kausch, and then Whipple using the gallbladder as a conduit. This was, however, associated with a high incidence of biliary sepsis, and end-to-side hepaticojejunostomy has now become the method of choice to restore biliary continuity. Use of either a continuous suture or interrupted sutures to perform the anastomosis is down to surgeon choice with no published evidence of the superiority of either technique. Restoration of the gastrointestinal track is achieved by performing a gastrojejunostomy in the classic Kausch–Whipple procedure, or duodenojejunostomy in patients undergoing a PPPD. The anastomosis can be either antecolic or retrocolic, although a small RCT of 40 patients found reduced delayed gastric emptying with an antecolic anastomosis in patients undergoing PPPD.

**Distal pancreatectomy**

Suspected malignant tumours of the body and tail of the pancreas warrant distal pancreatectomy with splenectomy, to ensure adequate excision of the primary tumour and lymphadenectomy. In patients with benign/indeterminate tumours, such as side-branch IPMN, spleen-preserving distal pancreatectomy can be undertaken. This avoids the complication of overwhelming post-splenectomy sepsis. The splenic vein can be either kept intact or divided (termed Warshaw’s technique, where venous drainage relies on the short gastric vessels), although the latter technique is associated with splenic infarction.

Closure of the remnant pancreatic stump can be carried out using either a stapler or handsewn anastomosis, with no difference in morbidity or mortality demonstrated in a multicentre RCT. Post-operative pancreatic fistula (POPF) rates of 5% to 34% have been reported, although there is variation between studies in the definition of POPF. Exocrine insufficiency and type 2 diabetes mellitus can develop during follow-up, with one series observing rates of 14% and 17%, respectively.

**Total pancreatectomy**

Intraductal papillary mucinous neoplasia and extended pancreatic cancers are treated with total pancreatectomy. Over the years, there has been a significant decline in perioperative mortality. Furthermore, quality of life following total pancreatectomy is now comparable to patients with type 2 diabetes mellitus from other aetiologies.

**Conventional versus radical lymphadenectomy**

The International Study Group on Pancreatic Surgery have recently defined the lymph node stations to be removed with pancreatic resections, employing the Japanese Pancreas Society nomenclature. Extended lymphadenectomy was not recommended, as none of four RCTs showed this to be of any benefit over standard lymphadenectomy, and it was associated with side-effects of chronic diarrhoea and weight loss.

The minimum number of lymph nodes to be harvested for adequate staging was set at >15, except in patients who had undergone neoadjuvant treatment. A lymph node ratio of >0.2 was a negative independent predictor of survival.

**Drainage following resection**

The use of drains following pancreatic resection is controversial. A RCT from a single institution in the USA 10 years ago found an increased incidence of infective intra-abdominal complications in the cohort that had a drain placed. The same group recently performed a 5-year retrospective analysis of high-volume pancreatic surgeons, dividing them into those who routinely placed a suction drain (Jackson–Pratt drain), those who were selective about drainage and a third group who did not drain. Their results were similar, suggesting that patients who were not drained did not suffer devastating complications following a bleed or the development of a collection/fistula. Interestingly, patients who had a drain inserted were more likely to have pancreatic fistulas, infected collections and longer length of stay in hospital. These results must be interpreted with
caution, as the volume of pancreatic resections undertaken by the no-drain surgeons was double that of surgeons who had a routine drain placement policy, while the proportion of patients with a soft pancreas gland was significantly higher in the drained group. A recent multicentre American RCT of 137 patients found that there was a higher incidence and greater severity of complications in patients who were not drained than in those who had suction drains placed after pancreatectoduodenectomy. This trial was stopped prematurely because of significantly higher mortality in the no-drain group (3% vs. 12%), and after having recruited less than one-fifth of the planned cohort size (752 patients) determined by the power calculations.

Factors associated with risk of leak are a soft pancreas gland, non-dilated pancreatic and bile ducts, greater blood loss and longer surgery (both of which might indicate a technically challenging operation). Currently, in the Department of Surgery at the Royal Infirmary, Edinburgh, the use of drains is left to individual surgeon preference. If tube drains are used, they are left on dependent drainage, the colour and volume of the drain output is monitored every 24 hours, and a drain fluid amylase level is checked on post-operative day 3. If the drain amylase is less than three times the serum amylase, the effluent is serosanguineous and the volume is less than 50ml, the drain is removed.

In patients with drains in situ, fluid amylase levels have been used to aid the decision on drain removal. The University of Verona conducted a prospective RCT of 137 patients and concluded that a drain fluid amylase level of >5000U/l on the first post-operative day (POD) 1 was predictive of developing a pancreatic fistula following resection (sensitivity 100%; specificity 87%). Subsequent retrospective studies have suggested lower values of 600,46 35047 and 100U/l48 on POD1 as cut-off values to promote early drain removal. The question of when to remove drains was addressed in a more recent RCT from Verona, where 114 patients were compared for drain removal on POD3 versus POD5 and beyond. Removing drains at POD3 in patients at low risk (based on drain fluid amylase of <5000U/l on POD1) was found to be safe. The approach of early drain removal based on fluid amylase levels does not take account of patients who develop delayed post-operative pancreatic fistulae. Scoring systems using multiple points have been developed to improve the ability to reliably predict the low-risk patient.

Minimally invasive techniques

Laparoscopic and robotic techniques have been used for pancreatic resections, although they form a small proportion compared with open surgery. Distal pancreatectomy is increasingly being performed using minimally invasive approaches, though the oncological equivalence with open surgery is unclear. Non-randomized evidence synthesis suggests that laparoscopic distal pancreatectomy has the advantages of reduced morbidity and shorter length of stay in hospital. Experience and reporting of laparoscopic pancreatectoduodenectomy is much more restricted.

The robotic approach has been used in both distal pancreatectomy and partial pancreatectoduodenectomy. A meta-analysis of seven non-randomized studies, comparing robotic with open surgery, documented lower morbidity and reduced redo surgery in the robotic arm, but the operating time was longer. The superior technical capabilities of robotic surgery, in the form of both improved optics and mechanical advantages, allow it to reproduce complex open surgery more easily than the laparoscopic approach.

As experience with minimally invasive techniques in pancreatic surgery grows, a more robust assessment of the pros and cons of this approach will be possible. In view of the limited number of patients and centres involved, collation of results using registries has been suggested.

Post-operative management

An enhanced recovery after surgery (ERAS) programme, with emphasis on optimization of post-operative analgesia, early feeding and mobilization, can be successfully applied to patients following pancreatic resection. ERAS in pancreatic surgery has demonstrated reduced length of stay in hospital and decreased hospital costs.

Complications of early or delayed post-pancreatectomy haemorrhage, pancreatic and biliary fistulas, delayed gastric emptying and intra-abdominal collections/sepsis are common. Leak from the gastroenterostomy is relatively rare. Standardized definitions for complications have been laid down by the International Study Group for Pancreatic Surgery.
The majority of complications can be managed by non-operative means, using interventional radiology for drain placement of collections or angioembolization for bleeding.66

The use of the somatostatin analogue octreotide has not been shown to significantly reduce the risk of POPF on meta-analyses.67 However, a recent double-blind RCT of 300 patients reported a reduction in clinically significant pancreatic fistulas in patients receiving pasireotide (Signifor®, Novartis International AG, Basel, Switzerland).68 Pasireotide (half-life 11 hours; dose 900µg subcutaneously twice a day) was started on the morning of surgery and continued for 7 days post surgery.

Improving outcomes

There is now overwhelming evidence that pancreatic surgery in high-volume centres improves outcomes. Landmark analysis of surgical outcomes in low- and high-volume centres in the USA, carried out by Birkmeyer et al.,6 established this, with adjusted mortality rates for pancreatic resections in high-volume centres of 3.8% compared with 16.3% in low-volume centres. These findings are reinforced by follow-up studies that demonstrate better long-term survival in high-volume centres.69,70 Since the implementation of centralization policies, outcomes have improved in both the USA and Europe. A 19% decrease in hospital mortality, in the USA, has been observed since pancreatic resections have been concentrated in centres that operate at a higher volume.71 A Dutch analysis following nationwide centralization not only showed increased median survival in high-volume centres (18 months vs. 16 months) but was also associated with a higher resection rate.72

The reason for improved outcomes in high-volume centres is likely to be multifactorial. Certainly pancreatic surgery is technically demanding and increased surgical experience is a factor.73 However, the cumulative experience of the medical and nursing teams is also important. The complication rate following pancreatic resection is high, and prompt management of pancreatic fistulae with interventional radiology has been shown to improve outcomes.74

Interventional radiology is also the mainstay of treatment for life-threatening late post-operative haemorrhage. High-volume centres, although not exclusively, tend to have better provision of round-the-clock access to interventional radiology.

Conclusions

Surgery for pancreatic cancer is a complex undertaking, and the prerequisites are localized disease and a fit patient. Surgeon competence, facilitated in high-volume units with the skills and infrastructure to manage these patients, can help improve both resection rates and outcomes. A pragmatic approach towards biliary drainage is advocated. Traditional criteria of what was considered resectable disease have changed, with venous resection and reconstruction feasible, and downstaging using neoadjuvant therapy being explored. Standardized definitions for complications post surgery now allow for more effective comparison of results across studies.

There remain areas of controversy and lack of clarity where further research may shed light on what best practice should be. A multicentre international RCT of drainage versus no drainage following pancreatic resection in high-volume centres, with stratification for risk factors of soft versus firm pancreas gland, dilated versus non-dilated pancreatic duct, dilated versus non-dilated bile duct, complex versus standard resection and suction versus dependent drainage would shed further light on this debate. Interesting and favourable results for the use of pasireotide in pancreatic surgery to reduce POPF need to be reproduced and validated in different centres. There is some evidence in favour of embracing laparoscopic and robotic surgery, but surgeons must be cognizant of the fact that there is a learning curve, and continued and critical evaluation of results is required to ensure that patients receive the best possible treatment.

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