Pancreatic Cancer: Is the Surgeon Still Relevant?

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Abstract

Despite advances in multimodal therapy, surgery remains central to the management of patients with resectable pancreatic adenocarcinoma. Complete surgical clearance of disease offers the only real, albeit slim, chance of cure. For the greater proportion of patients with resectable macroscopic but occult microscopic disease, who ultimately recur early, short-term outcomes are still better compared to other currently available treatment modalities. Morbidity rates following pancreatic resection are worse than cancer surgery data for other intra-abdominal sites however, and involved margins are an unsurprising predictor of poor oncological outcome. Patient selection is therefore key. Refinements in surgical technique and treatment algorithms, such as the evolving use of neoadjuvant therapy, have improved appropriate selection for surgery, resectability rates and early postoperative outcomes. Review of contemporary Australian observational follow-up data highlights favourable local morbidity and mortality results, but persistently disappointing long-term survival outcomes reflective of the international picture. The surgeon’s current role remains to achieve complete local resection with minimal morbidity. Such an achievement maximises the successful utilisation of multimodal therapies targeting microscopic disease, and preserves the remaining quality of life for those patients with ultimately incurable disease suffering from aggressive tumour biology.

Adenocarcinoma of the pancreas is arguably the most sinister of all solid organ neoplasms. The disease is predicted to become the tenth most common malignancy by the end of 2015, yet it rates as the fifth most common cause of cancer-related death. Despite advances in diagnosis and therapeutics, age-standardised mortality has not changed in over 50 years. Late detection remains a major contributor to this statistic, with over 50% of patients suffering systemic disease at diagnosis. Accordingly, reported five-year cancer specific survival was only 6% between 2007-2011, a modest improvement from 4% between 1982-1986 attributed largely to the
introduction of gemcitabine. Historical US observational data from the early 1990s reported moderately improved outcomes in the 14.2% of patients undergoing surgery for resectable disease (48% one-year survival) compared to the 85.8% of patients treated non-operatively for unresectable disease (23% one-year survival). However, the same series reported a three-year survival rate of only 17% in the patients managed with resection, providing a dismal medium-term outlook despite radical and frequently morbid surgery. Nevertheless, operative resection has since continued to provide the main therapeutic modality in the setting of localised disease. Given that survival statistics have not changed in 20 years, and that non-invasive multimodal therapies have arguably since improved, it is important to re-evaluate the current role of curative surgery in this devastating disease.

**Established surgical principles**

Radical resection of the primary tumour with regional lymphadenectomy to achieve complete microscopic resection is the established goal for all surgery with curative intent. The nature of the operation is dictated entirely by tumour location within the pancreas. While extended regional lymphadenectomy improves staging, there is no evidence that it improves long-term survival.

For resectable tumours in the head and uncinate process that is right-sided, relative to the superior mesenteric vein and artery, a Whipple procedure is performed. This involves en-bloc resection of the head and uncinate process with attached gastric antrum, duodenum, bile duct, gall bladder and regional lymph nodes. Reconstruction requires three anastomoses, of which the pancreatojejunostomy (or -gastrostomy) most commonly provides morbidity in the form of leakage. Technical variations exist but are beyond the scope of this review.

Only 10% of patients with left-sided pancreatic cancer, that is involving body and tail, have resectable disease at presentation. In this situation, a distal or left-sided pancreatectomy with splenectomy is performed without the need for anastomosis. There is no role for splenic preservation in the setting of adenocarcinoma.

Resectability relates to the extent of local and systemic disease, with identification of the latter providing an absolute contraindication to curative resection. Local tumour extension is most commonly relevant to the relationship of right-sided tumours to local vascular structures. Direct involvement of the superior mesenteric vein is considered resectable where an appropriate segment of the vein below and portal vein above allows reconstruction, which can be by direct closure, segmental resection with end-to-end anastomosis, or interposition graft. A recent meta-analysis involving 19 studies, from 1994-2010, of pancreatectomies for pancreatic cancer, including 661 patients with and 2247 patients without portomesenteric venous resections found no difference in overall survival between the cohorts with and without vascular resections. However, major venous resections may lead to greater overall rates of intra-operative and post-operative morbidity rates. On the basis of the currently available evidence, there are data to support operative exploration and resection in the presence of reconstructable mesentericoportal axis involvement. In contrast, arterial resection for locally advanced disease, as defined by encasement of the superior mesenteric artery by more than 180 degrees, offers no benefit over palliative non-resectional treatment. Pre- and intra-operative assessment of resectability is critical because of the adverse impact of involved margins on survival. A retrospective observational follow-up of 121 patients undergoing attempted curative resection in Queensland from 2007-2009 highlights the point. Patients with clear margins in this series exhibited a one-year survival of 85% in contrast to a one-year survival of only 50% for those with positive margins. The issue of margin status is compounded by the significant potential morbidity, and subsequent poor quality of life associated with attempted radical surgery. The reduced life expectancy and high morbidity risk associated with attempted but failed oncological clearance clearly serves no palliative benefit to the patient.

Operability, defined as the ability of a patient to successfully undergo major pancreatic surgery, also provides a major consideration in treatment planning. Although each patient presents a unique risk profile, basic prerequisites include good functional status (ECOG 0-1), adequate renal and liver function and satisfactory haematological parameters. Recent observational follow-up data of 1863 patients with pancreatic cancer from Queensland and New South Wales reported that 97 (51%) of the 1863 inoperable patients with potentially resectable disease were deemed unfit because of their comorbid state. The median age of patients in this series was 71, with advanced age cited as the defining cause of inoperability in a further 31 (18%) of the patients. Diabetes and malnutrition are commonly present, have an adverse impact on post-operative recovery, and should be optimised prior to resection. Right-sided tumours usually present earlier than left-sided tumours in the form of obstructive jaundice, thus explaining the comparatively higher resectability rates reported. However, high-grade biliary obstruction adversely affects multi-organ function thus compromising operability. Equipoise persists regarding the role of pre-operative biliary decompression, and summaries of the reported data include outdated practices. Current thinking is to offer short metal stents to patients presenting with severe symptoms or organ dysfunction in order to achieve operability, and to those where neo-adjuvant therapy is being considered.

**Australian outcome and morbidity data: where are we now?**

Three contemporary Australian follow-up series provide useful insights into the current surgical management of pancreatic cancer and its subsequent outcomes. The earliest of these, by Speer and colleagues, describes the results from a six-year retrospective observational
follow-up study of 763 patients diagnosed with pancreatic adenocarcinoma identified through the Victorian State Cancer Registry from 2002-2003. The most recent of the articles, published this year by Burmeister and colleagues,7 provides the largest Australian follow-up cohort to date with 1863 patients. In this study, all diagnoses of pancreatic cancer between 2007-2009 were identified again through state cancer registries, this time using those of Queensland and New South Wales to represent over 50% of the Australian population. The third article, by Wylie et al and published in 2012, provides retrospective observational follow-up data on 121 cancer patients undergoing attempted curative resection from 2007-2009.8

The two studies analysing all pancreatic cancer patients reported similar median ages of 71 and 72 at diagnosis.7,8 In contrast, the median age of patients in the paper focusing on patients undergoing potentially curative surgery was some 10 years younger at 63.6 The distribution of cancers was almost identical across all the-comer studies, with right-sided cancers contributing 72% of the disease burden.7,8 The Victorian study reported right and left-sided resection rates of 13.7% and 8.2% respectively,8 the combined rate of which is less than the 14.2% reported in the previously cited US data from the 1990s.2 In comparison Burmeister and colleagues reported curative resection attempts in 20% of all patients,7 with 15% of all patients ultimately undergoing complete resection. The same series also provides an insight into patterns of operability, with attempted resection performed in 69% of patients deemed to have potentially resectable disease.7 Where resection was not attempted, comorbid state was the major factor in 51%, with advanced age cited as the main reason in 18%. Interestingly, 20% of patients deemed otherwise eligible for curative resection declined surgery, providing a useful indication of how marginal the risk-benefit balance of pancreatic cancer surgery is presently perceived.

A comprehensive understanding of the current risk-benefit balance in curative pancreatic surgery requires separate assessment of adverse outcome and survival data. Operative risks in pancreatic surgery are recognised to be above average in comparison to surgery on other intraabdominal organs. Morbidity rates following pancreatic resection remain at 40-50%. A systematic review by Harnoss and colleagues of 59 of retrospective articles, which correctly applied the definitions for complications following pancreatic resection, reported median complication rates of 21.9% for post-operative pancreatic leak or fistula (n = 11,244 patients), 5.9% for post-pancreatectomy haemorrhage (n = 3311 patients), and 22.8% for delayed gastric emptying (n = 4553 patients).11 Intra-abdominal abscess and biliary anastomotic leaks are less common complications managed in the majority of circumstances by percutaneous drainage. Despite significant complication rates, Wylie and colleagues reported a post-operative mortality following pancreatic resection of less than 2%.6

Unfortunately, the most striking outcome data from contemporary Australian follow-up studies are the persistently abysmal survival rates. Burmeister and colleagues reported a one-year overall survival of 22%,7 which is even worse than the 25% one-year survival described by Niederhuber in the 1990s.2 Furthermore, the same series saw a 50% 12-month recurrence rate in the 279 patients undergoing completed curative resection.7 During the six-year follow-up period by Speer and colleagues,8 747 of 763 (97.3%) patients died. Closer analysis of the 20 patients surviving to five years darkens the picture even further, as half of these individuals did not even have cancer. Of the 10 that did, three suffered recurrence during the sixth year of follow-up, leaving only seven disease-free survivors after six years.

Is ‘curative’ surgery still relevant?

Given the relative mismatch between high operative risk and limited cure rates, the role of surgery with curative intent has been challenged. In 2004, adequate equipoise existed for the completion of a randomised trial comparing surgery to radical chemo-radiotherapy in 42 Japanese patients with resectable pancreatic cancer.12 Twenty patients were assigned to resection alone, and 22 received a 5-flouracil based chemo-radiotherapy protocol. Surgical resection was found to provide better one-year survival (62% vs 32%, p=0.05), mean survival time (>17 vs 11 months, p<0.03) and an improved hazard ratio (0.46, p=0.04) thus demonstrating a clear advantage in the surgery arm. While chemo-radiotherapeutic regimens have improved since the study, the absence of further RCT on the subject provides a surrogate marker of the ongoing favourability towards surgery for localised, resectable disease.

Impact of multimodal therapy on outcome and patient selection

Post-operative chemotherapy with Gemcitabine or 5-flourouracil has been shown to improve outcome. However, more than 30% of patients are not fit for post-operative therapy after pancreatic surgery. Furthermore, a significant proportion of patients suffer particularly dismal outcomes despite the resection of apparently localised disease. The identification of such patients would help avoid unnecessary surgery, and its associated morbidity.

Hence, there is a clear mandate for neoadjuvant therapy whereby a period of pre-operative observation provides insight into individual tumour biology. Furthermore, a pre-operative approach can increase the deliverability of cytotoxic medication and improve resectability in both resectable and borderline resectable tumours.13,14 In Australia, we have recently demonstrated that pre-operative chemotherapy with gemcitabine and nabpaclitaxel can be delivered to patients with pancreatic adenocarcinoma.15 Ferrone and colleagues also demonstrated that FOLFIRINOX can be safely administered in the pre-operative setting.16 Combination neoadjuvant chemo-radiotherapy holds further promise still. Regimens
using gemcitabine, 5-fluorouracil or platinum backbones have been investigated in the phase II setting, with favourable results. Further studies will be undertaken to determine the optimal timing and type of chemotherapy or chemo-radiotherapy in order to improve outcomes in pancreatic adenocarcinoma.

Refinement of the surgical approach

Subsequent to advances in multimodal therapy, the ongoing focus in surgery is to achieve complete oncosurgical resection with enhanced early recovery and the minimisation of morbidity. Complete resection of macroscopic disease optimises the theoretical efficacy of chemotherapy to eradicate microscopic disease, and an accelerated, uncomplicated recovery enables its timely institution.

A recent systematic review identified 869 patients in 11 studies of minimally invasive Whipple procedures (pancreatodudenectomy, MIPD), which may be performed laparoscopically or robot-assisted. There were some advantages in intraoperative blood loss, wound complications, and length of stay, compared with the open approach. However, considering the selection bias, the complexity of MIPD and lack of long-term oncologic outcomes, the current application of MIPD should be in high-volume pancreatic surgery centres on patients with small cancers distant from major vessels.

Laparoscopic distal pancreatectomy is increasingly performed as an alternative approach for open distal pancreatectomy in selected patients. Comparing laparoscopic distal pancreatectomy with open distal pancreatectomy, laparoscopic distal pancreatectomy has lower blood loss, reduced length of hospital stay, lower risk of post-operative complications and wound infection, without a substantial increase in the operative time. The improved complication profile of laparoscopic distal pancreatectomy, taken together with the lack of compromise of margin status, suggests that this technique is a reasonable approach in selected cancer patients.

Conclusion

Despite advances in multimodal therapies, surgery remains central to the management of patients presenting with resectable disease. Resection offers the only real, albeit slim chance of cure. For the greater proportion of patients with resectable macroscopic but occult microscopic disease, who ultimately recur early, short-term outcomes are still improved compared to other currently available treatment modalities. The surgeon’s goal is to achieve complete local resection with minimal morbidity. Such an achievement maximises the successful utilisation of adjuvant therapies targeting microscopic disease, and preserves the remaining quality of life for patients suffering from aggressive tumour biology.

References