Surgery for Pancreatic Carcinoma: State of the Art

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Abstract Carcinoma of the pancreas remains a malignancy with a generally dismal outcome owing to the delayed presentation of the disease. To date, surgery affords the best outcomes when a complete resection can be achieved. Improvements in imaging, surgical techniques and adjuvant therapies are perceived advancements in the management of this cancer. This article reviews the latest evidence in terms of the diagnosis and management of pancreatic cancer.

Keywords Pancreatic cancer · Pancreatoduodenectomy · Complications · Anastomosis · Lymphadenectomy · Extended resections

Introduction

Pancreatic cancer (PC) remains a deadly disease with a dismal prognosis in which the mortality rate nearly equals its incidence. In USA, the incidence rate of PC is 8–10/100,000 persons per year with 43,140 new cases estimated to occur in 2010 [1]. The incidence of PC has remained fairly stable over the years [2]. The approximate annual burden of PC in India is 14,230 and the incidence of 2.4/

100,000 persons per year is low compared with western statistics [3]. The 5-year relative survival rate was 4.1% for PC in a population-based study from Mumbai [4].

Despite advances in modern chemoradiotherapy, the best and only chance of cure for patients with PC is an oncological surgical resection aimed at complete removal of all gross and microscopic disease. Early disease and curative-intent surgery are the best predictors of outcome [5].

Codivilla was the first person to perform an en bloc excision of the head of the pancreas and a major portion of the duodenum for a patient suffering from pancreatic carcinoma [6]. Unfortunately, his patient died after 24 days of the surgery as a result of disseminated malignancy (confirmed on autopsy). To this day, the pancreatoduodenectomy (PD) or the Whipple's operation [7] continues to be the operation of choice for carcinomas involving the head, neck and/or uncinate process of the pancreas. In patients with carcinoma of the body and tail, distal or subtotal pancreatectomies constitute optimal surgical therapy.

This article provides a brief overview of the presentation and diagnosis of pancreatic carcinoma while focusing on the current evidence on the technical aspects of surgery for PC.

Presentation

Symptoms and timing of presentation of patients with carcinoma of the pancreas vary depending on the location of the carcinoma. Ampullary carcinomas tend to present the earliest owing to the early obstruction of the biliary tree and resultant painless obstructive jaundice. The classic symptom reported with carcinomas in this location is the 'waxing

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and waning' of obstructive jaundice—a symptom noted in only 30% of individuals [8].

Carcinomas of the pancreatic head also tend to present as painless, progressive, obstructive jaundice. Tumours of the body and tail, in contrast, tend to present the latest, usually as a clinically discernible swelling [9]. By this time, generally, haematogenous and lymphatic spread may have already taken place.

Most common presenting symptoms of carcinomas of the pancreatic head, neck, body and tail are asthenia (>80%), anorexia (>80%), weight loss (>80%) and upper abdominal pain (70–80%) [10]. Features suggestive of gastric outlet obstruction may be encountered in advanced carcinomas of the pancreas.

Upper abdominal pain radiating to the back, though not always, is often a sign of an advanced tumour. New symptoms developing over an established case of chronic pancreatitis should arouse suspicion of PC [10].

Clinical signs in these patients may vary from jaundice in ampullary and pancreatic head cancers with a palpable gallbladder (Courvoisier's law) to a hard, fixed palpable lump in the left hypochondrium in case of tumours of the body and tail.

Patients may have enlarged Virchow's lymph nodes or even a Blumer's shelf in advanced cases. Ascites is a sign of advanced disease.

Investigations

Biochemical Tests

The tumour marker, serum CA 19–9, is routinely measured in pancreatic carcinomas. Its overall sensitivity is approximately 80% with a specificity of 90% [11]. In terms of predicting unresectability, levels greater than 1,000 U/mL have been found to be linked to unresectable disease [11].

An obstructive pattern of liver function tests is encountered in pancreatic head and ampullary lesions obstructing the lower common bile duct.

Anaemia (sometimes associated with waxing and waning jaundice) may be encountered in patients with periampullary carcinomas where repeated sloughing off of the tumour tissue causes episodes of melaena.

Diagnosis

Radiology

Multidetector computed tomography (MDCT) and angiography scans and magnetic resonance imaging (MRI) along with magnetic resonance cholangiopancreatography

(MRCP) have been demonstrated to provide the highest accuracy in terms of non-invasive imaging modalities to diagnose, stage and determine the vascular involvement by pancreatic carcinomas of the head (>3 cm) [12–15], body and tail [16].

Other imaging modalities, such as positron emission tomography-computed tomography, have been shown to provide a complimentary role to MDCT and MRCP in the detection of extra-abdominal metastases [17]. Thus, they may play a crucial role in the preoperative work-up of locally advanced cancers, since the treatment options would sharply vary based on the positron emission tomography scan findings.

Endoscopy (ERCP and EUS)

Nowadays, endoscopic retrograde cholangiopancreatography (ERCP) is hardly used as a diagnostic tool. It is now primarily used to aid histological/cytological confirmation of the presence of a periampullary cancer and head cancers, and its use is mainly therapeutic to enable preoperative biliary drainage.

In patients with ampullary or pancreatic head carcinomas with biliary obstruction, preoperative biliary stenting has been a practice [18–20]. A recent meta-analysis [21] found that although the rate of wound infections were higher in patients who had undergone preoperative biliary drainage, there was no convincing evidence to indicate that biliary drainage prevented or promoted postoperative complications following PD. Preoperative biliary drainage is indicated in patients presenting acutely with cholangitis, obstructive jaundice with secondary renal impairment, or in whom delays in the performance of the PD due to comorbidities or referral to specialist centres for surgery are anticipated.

If extended delays (>6 weeks) are anticipated between the stenting and PD, short-length self-expandable metal biliary stents [22, 23] should be considered.

Additionally, to better delineate the T stage of the tumour or the vascular involvement or to obtain tissue biopsies of the tumours of the head <3 cm or that of the body and tail, endoscopic ultrasonography (EUS) is the best modality available [24].

Diagnostic Laparoscopy and Laparoscopic Ultrasonography

The routine use of laparoscopy in the preoperative staging of periampullary cancer and PC is not recommended owing to the risk of complications associated with the procedure and the availability of state-of-the-art imaging in terms of

MDCT and, MRI and MRCP [25]. However, in terms of the benefit in patients with locally advanced disease on imaging, the conclusion is unclear. A recent meta-analysis has concluded that it may be beneficial in downstaging patients deemed to be unresectable on imaging, rendering them as candidates for potentially curative resections [26].

Surgical Management

Based on the staging of the pancreatic carcinoma by a combination of modalities, these tumours may be divided into the following groups in order of worsening prognosis [10, 27, 28]:

- Resectable PC
- Borderline resectable PC
- Resectable locally advanced PC,
- Non-resectable locally advanced PC,
- Resectable but metastatic PC,
- Non-resectable metastatic PC

Surgery offers the best outcome for tumours that are resectable, even those that are locally advanced so long as a complete resection (R0) can be achieved. Surgical resection for carcinoma of the head and/or neck of pancreas involves a PD, whereas a distal or subtotal pancreatectomy is performed for carcinomas of the body and tail and for some tumours at the junction of the neck and body.

Pancreatoduodenectomy

Since the first PD performed by Codivilla [6], technical modifications have been undertaken in the procedure with an aim to improving outcomes for the patient. Only the most significant of these modifications will be discussed in this section. Despite the high morbidity and the risk of mortality associated with PD, centralization of major pancreatic resectional surgery to high-volume centres [29–38] as well as a standardized technique [39, 40] have been linked to improved outcomes.

No difference in oncological outcomes has been noted between pylorus-preserving PD and the Classic Whipple [41]. As a result, in patients undergoing PD for periampullary and pancreatic head cancers, the performance of pylorus preservation or classic Whipple remains the prerogative of the surgeon. In contrast, the performance of the classic Whipple should be reserved exclusively for duodenal cancers (part of periampullary tumours) or large pancreatic head tumours invading the gastric antrum and/or the first part of duodenum.

As part of every oncological PD, a standard lymphadenectomy, i.e., removal of lymph nodes of the right side of

the hepatoduodenal ligament (12b1, 12b1, 12c), posterior pancreaticoduodenal nodes (13a, 13b), nodes to the right side of the superior mesenteric artery (SMA) from the origin of the SMA at the aorta to the inferior pancreaticoduodenal artery (14a, 14b) and anterior pancreaticoduodenal nodes (17a, 17b), has been shown to be associated with improved outcomes with no additional benefit conferred by the performance of an extended lymphadenectomy [42, 43]. Additionally, the extended procedure was associated with an increased rate of intractable diarrhoea in the early postoperative phase.

Current literature [44–48] does not favour the performance of a pancreaticojejunostomy over a pancreaticogastrostomy, as the outcomes of surgery appear to be the same irrespective of the technique employed.

Antecolic gastro-/duodenojejunostomy has been shown to be associated with a significantly reduced rate of delayed gastric emptying [49–51], possibly due to the avoidance of torsion or angulation that may occur with a retrocolic anastomosis.

A review of the literature demonstrated that in order to improve outcomes of the anastomoses following PD, good vascularity, absence of tension, absence of main pancreatic ductal and distal obstruction, use of fine (4–0, 5–0, 6–0) sutures, main pancreatic duct to mucosa approximation and high volume (including high surgeon-volume) were important factors [52].

Distal/Subtotal Pancreatectomy

Brennan et al. [53] suggested an equally aggressive approach to PC when managing tumours of the body and tail of the pancreas. Current evidence supports the performance of a splenectomy along with a distal/subtotal pancreatectomy to attain a complete resection for carcinomas [54].

While the choice of closure of the pancreatic remnant has been a matter of debate, current evidence [55] concedes that although there is a trend towards the use of staplers [56], the available information cannot convincingly make a definite choice between sutures or staplers [57].

Extended Resections

The term ‘extended resections’ encompasses numerous subclasses including, extended lymphadenectomy (discussed above), vascular resections, multivisceral resections and metastasectomies.

In the case of carcinomas of the body and tail, it has been observed that at the time of surgery approximately 35% of the patients [58] with tumours of the body and tail

have evidence of involvement of surrounding structures either by tumour infiltration or inflammatory adhesions. In such circumstances, it is advisable to even resort to en bloc resections to obtain negative surgical margins. Shoup et al. [59] found that patients undergoing extended resections for the carcinomas of the pancreatic body and tail have long-term survival rates similar to those for patients undergoing standard resection for less aggressive tumours, and markedly improved long-term survival compared with those who are not considered resectable because of locally advanced disease.

Multivisceral Resections

Multivisceral resections are technically feasible and, based on the limited data available, these resections are associated with improved survival (5-year survival rates of 16–22%) [59, 60] as compared with no resection, and comparable survival to standard resections for lesions that do not involve adjacent organs when performed in high-volume centres with the necessary expertise [61]. Given the high morbidity and even mortality associated with these procedures, they should be performed only when the possibility of achieving R0 seems distinctly feasible.

Borderline-Resectable Tumours

More recently, an entity termed borderline-resectable tumour (BRT) has been proposed and its definition continues to evolve [28, 62–64]. The National Comprehensive Cancer Network describes borderline-resectable pancreatic head (and body) cancer as tumour abutment of the SMA, severe unilateral superior mesenteric vein (SMV) or portal vein (PV) impingement, gastroduodenal artery encasement up to its origin from the hepatic artery, or colon and mesocolon invasion [62]. The ideal treatment of patients with BRTs needs to be established. The choice of management of these patients varies between neoadjuvant chemoradiotherapy [28] versus surgery at the first instance [27, 65]. Till further data is available, to dictate the benefit of each treatment strategy over the other, the management of the BRT remains controversial.

Vascular Resections

A meta-analysis on venous resections at the time of PD [66] failed to demonstrate any benefit in overall survival. Following this manuscript, there were publications [67, 68] indicating that if an R0 could be achieved, this could translate into improved outcomes (5-year survival rates of 23%) [67].

However, it must be pointed out that certain factors play a role in these outcomes [61], viz. (1) Depth of venous invasion [69]—Involvement of tunica media and intima was associated with poor outcomes even in a complete resection; and (2) Length of invasion [67]—Length of involvement more than 3 cm was associated with poor outcomes.

There is no data to support the performance of arterial resections at the time of surgery for PC [61].

Technical Refinements to Improve Resections in Extended Resections

The Uncinate-First Approach

The uncinata-first approach was specifically described in 2007 [70] and is similar to the approach described by Hackert et al. [71]. This approach seems to be more suitable for infiltration of the SMV or portal vein. The SMA-first approach seems to be suitable for infiltration of the arterial axis.

The SMA-First Approach

The operative technique of the SMA-first approach comprises of early dissection of the SMA (after ‘kocherization’ of the duodenum) along with the posterior pancreatic capsule. The potential advantage of this approach [72–74] is that technical difficulties that may be encountered either due to tumour infiltration of the SMV, main PV or tumour proximity to the right side of the SMA can be handled right at the initial stages of the resection. This may also help in reducing the chances of margin-positive pancreatic head resections. Other reported advantages are improved lymph node yield by dissection of more lymph nodes along the right border of the SMV/main PV and SMA [72–74]. Both these approaches aid in vascular resections, large uncinata process tumours and also in multivisceral resections (Fig. 1)

Pancreatic Resection in Metastatic Disease

Although technically feasible [75], there is no clear evidence to demonstrate an overall survival benefit of the performance of metastasectomy in patients with resectable PC [61, 76].

Laparoscopy for Pancreatic Carcinoma

Although technically feasible, [77–80], at present there is no high-level evidence to suggest that laparoscopic PD is equal or superior to open surgery in terms of overall survival. In the case of a complex procedure like PD, the appreciation

Fig. 1 Intraoperative photograph of SMA-first approach for a borderline-resectable pancreatic head cancer. Primary resection and anastomosis of the SMV–portal vein have been performed. The SMA is looped with red tape

that the morbidity of PD (pancreatic leak, haemorrhage, delayed gastric emptying) is not related to the length of the abdominal incision, but to the extensive nature of the actual intra-abdominal surgery [81] deserves due consideration.

Laparoscopic distal pancreatectomy has also been demonstrated to be technically feasible with acceptable perioperative outcomes [82]. The perceived short-term benefits of accelerated recovery have recently been questioned in a well-conducted trial looking at readmission rates [83]. The perceived benefit of reduced hospital stay appears to be completely offset by the high readmission rates following laparoscopic distal pancreatectomy. There is no long-term data demonstrating an improvement in survival of laparoscopic surgery over open surgery for carcinomas of the pancreas.

Fast-Track Protocols/Enhanced Recovery

Fast-track surgery (or enhanced recovery after surgery), an interdisciplinary, multimodal concept designed to accelerate postoperative recovery by combining various techniques used in the care of patients undergoing elective surgery has been trialed in patients undergoing pancreatic surgery [84]. Although the feasibility of such protocols has been demonstrated [85], conflicting evidence on the physiological mechanisms that contribute to accelerated patient recovery as well as certain safety issues associated with postoperative morbidity (higher overall complication rates) [86] have been flagged.

Role of Chemotherapy and/or Radiotherapy

Chemotherapy plays an important role in the adjuvant setting for patients with margin-positive disease following surgical resection and for lymph node metastases.

For non-resectable pancreatic carcinomas—locally advanced or metastatic, neoadjuvant therapies including chemotherapy or a combination of chemotherapy and radiotherapy are being extensively used with an aim to either downstage the tumour, thereby rendering them amenable to surgical resection, or keeping tumour growth under control with an aim to prolonging life.

Salient features on the role of chemotherapy and radiotherapy in pancreatic carcinoma include the following:

- Gemcitabine and 5-fluorouracil constitute the two most important chemotherapeutic drugs available in the treatment of pancreatic carcinomas [10]. The European Study Group for Pancreatic Cancer (ESPAC-3) trial confirmed the lack of benefit of gemcitabine over the current standard treatment regimen—5-fluorouracil/folinic acid in terms of overall survival in patients with completely resected PC [87].
- There is little evidence to support the use of intra-operative radiotherapy either alone or in combination [10].
- A recent meta-analysis has demonstrated improved 12-month survival rates in protocols utilizing gemcitabine and radiotherapy for locally advanced pancreatic carcinomas [88]. However, drug toxicity was noted to be higher.
- In patients with metastatic PC but with a good performance status, a recent randomized controlled trial has demonstrated improved survival in patients randomized to receive a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) as compared with gemcitabine [89].

Conclusions

Newer imaging modalities have facilitated improved preoperative staging of carcinomas of the pancreas. This has enabled better identification of patients likely to benefit from surgical exploration, and thus, possibly, even reducing the number of non-resectable explorations. Surgery remains the modality of choice in achieving longer survival in patients with PC as long as a R0 can be achieved. Refinements in surgical techniques have helped improve perioperative outcomes. The role of laparoscopy remains experimental in the management of pancreatic carcinoma. The development of newer adjuvant and neoadjuvant therapies alone and in combination has witnessed a modest improvement in survival on the balance of increased risk of toxicity.

Conflict of interest None

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