Review

The future of surgery for pancreatic cancer

J. Slavin, P. Ghaneh, L. Jones, R. Sutton, M. Hartley & J.P. Neoptolemos
Department of Surgery, University of Liverpool, Royal Liverpool University Hospital, Liverpool, L69 3GA, UK

Summary

Carcinoma of the pancreas has a grim prognosis even following surgical resection. Only a relatively small proportion of patients have a resectable tumour at presentation. At the present time it is uncertain whether the use of radical forms of surgery, or adjuvant therapy improve survival. It is however unlikely that either of these approaches will greatly increase the number of long term survivors. Earlier diagnosis particularly in individuals who are at greater risk of developing carcinoma of the pancreas is one way in which results might be improved. Unfortunately current imaging techniques are inadequate for the diagnosis of early disease. New molecular diagnostics techniques that can identify example mutations in oncogenes such as K-ras or deletions of tumour suppressor genes such as P53 or P16 are being developed. These tumour specific abnormalities are also a target for gene therapy. Surgery alone cannot cure any patient with pancreatic cancer but may in the future in conjunction with these new approaches.

Key words: adjuvant treatment, gene therapy, molecular diagnosis, pancreatectomy, pancreatic cancer, prognosis, surgery.

Historical perspective

Carcinoma of the pancreas is a relatively common, and highly lethal condition. The median survival of patients with unresected disease is 4-6 months and only about 10% of patients live beyond a year. Resection when this is possible, prolongs survival with a good quality of life but cure is rarely, if ever, achieved [1].

Alexander Codvilla undertook the first pancreaticoduodenectomy in 1898 and by 1908, 11 resections had been performed by different surgeons although none of these patients survived beyond the immediate post-operative period [2]. Kausch reported the first successful pancreatectomy in 1912; this operation was performed in two stages, an initial biliary bypass followed by a later resection [3]. In 1934 Whipple described a two-stage procedure [4]. Five years later he performed a one-stage procedure, which included a pancreatojejunal anastomosis; this operation was reported in 1946 [5]. Whipple's procedure, however, was still associated with such a high mortality that many suggested that it had no place in surgical practice. Even relatively recently an epidemiological study in the West Midlands of 13560 patients with pancreatic cancer revealed a post operative mortality approaching 30% in non-specialist units over the period 1978-1987 [6].

A number of series from specialist centres, however, have shown that it is possible to resect with mortality rates below 6% although morbidity remains high at around 40% [7-12]. A major factor in these improved results has been the development of specialist units with high volume throughput. Comparative studies from the United states and latterly Europe show that when the institutional case volume passes a threshold (approximately 12 pancreatic resections per year) pancreatic surgery can be performed with a relatively low mortality (Table 1) and that units performing fewer than this critical threshold are likely to have significantly increased mortality rates [13-16]. Good results can also be obtained in those of advanced age provided they are selected appropriately [17, 18].

Diagnosis

Most patients present with obstructive jaundice and have an endoscopic retrograde cholangiopancreatogram (ERCP) as part of their diagnostic workup, at which time it is relatively easy to establish internal biliary drainage. Most surgeons are

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Resections</th>
<th>Post-operative Mortality</th>
<th>5 year survival</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trede et al [11]</td>
<td>1989</td>
<td>118</td>
<td>0%</td>
<td>24%</td>
<td>-</td>
</tr>
<tr>
<td>Gall et al [7]</td>
<td>1991</td>
<td>138</td>
<td>6%</td>
<td>16%</td>
<td>11 months</td>
</tr>
<tr>
<td>Geer et al [95]</td>
<td>1993</td>
<td>146</td>
<td>3.4%</td>
<td>24%</td>
<td>-</td>
</tr>
<tr>
<td>Nitecki et al [96]</td>
<td>1995</td>
<td>186</td>
<td>3%</td>
<td>7%</td>
<td>-</td>
</tr>
<tr>
<td>Russell et al [97]</td>
<td>1996</td>
<td>61</td>
<td>-</td>
<td>8%</td>
<td>13 months</td>
</tr>
<tr>
<td>Sperri et al [8]</td>
<td>1996</td>
<td>113</td>
<td>15%</td>
<td>12%</td>
<td>-</td>
</tr>
<tr>
<td>UKPACA [16]</td>
<td>1996</td>
<td>421</td>
<td>5.9%</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Mosca et al [98]</td>
<td>1997</td>
<td>221</td>
<td>8.2% (KW)</td>
<td>9.6%</td>
<td>-</td>
</tr>
</tbody>
</table>
confident that in jaundiced patients a period of biliary drainage prior to a major resection of the pancreatic head is beneficial, and reduces postoperative complications. A randomised controlled trial of preoperative endoscopic biliary drainage versus early surgery failed to demonstrate any reduction in mortality (14% vs 14%) or morbidity (41% vs 37%) following surgery but the study was seriously underpowered [19].

The success of endoscopic biliary drainage also means that it is important to avoid an unnecessary laparotomy in patients with advanced disease through the use of preoperative staging protocols. Laparoscopy will identify macroscopic intraperitoneal spread and may reduce the number of unnecessary laparotomies [20]. The use of ultrasound at the time of laparoscopy [21] or endoscopy may improve assessment of resectability and provide improved imaging of the gland and of associated vasculature [22]. Spiral CT however remains the gold standard for the assessment of tumour resectability [23], although there are encouraging reports of MRI [24].

A common diagnostic quandary is the need to differentiate chronic pancreatitis from malignancy. Biopsy carries the risk of intra-peritoneal seeding with intra-abdominal spread [25] and because of this is employed only if a lesion is felt to be irresectable or there is metastatic disease. Resection en bloc with later histological analysis is justified on the basis of a low postoperative mortality. Percutaneous biopsy is required for histological diagnosis in advanced pancreatic cancer if treatment with chemotherapy is contemplated.

Presymptomatic diagnosis

Particular patient groups can now be identified that are at increased risk of pancreatic cancer; these include patients with sporadic chronic pancreatitis and individuals from families with hereditary chronic pancreatitis or familial pancreatic cancer [26, 27]. With current diagnostic modalities by the time a tumor of the pancreas is detected micrometases have occurred. To improve the results of surgery methods of detecting tumours at a far earlier stage are required. The use of molecular markers for the diagnosis and staging of pancreatic disease has shown great promise. K-ras mutations are present in approximately 100% of cases with pancreatic ductal adenocarcinomas. [28, 29]. They have been detected in early lesions (<20mm in size) [30], and also in areas of ductal hyperplasia of the pancreas, suggesting that these mutations occur early in the development of pancreatic ductal adenocarcinoma [31]. K-ras mutations have been detected in free DNA circulating in the peripheral blood of patients with pancreatic ductal adenocarcinomas with a sensitivity of 60-90% and a specificity of 100%; the high detection rate is however only seen in advanced disease [32]. K-ras mutations have also been detected in the stool of patients with pancreatic ductal adenocarcinomas [31]. K-ras mutations of pancreatic duct brushings obtained at ERCP gave a sensitivity of 81% and specificity of 75% for the diagnosis of pancreatic ductal adenocarcinoma [33]. More recent studies using pure pancreatic juice have found that 40% of patients with chronic pancreatitis harbour a K-ras mutation and these patients do not go on to develop pancreatic ductal adenocarcinoma on longer term prospective follow up [34]. Additionally, K-ras mutations have been detected in micro-dissected foci of pancreatic hyperplasia in patients with no pancreatic disease, suggesting that there may be a low background rate of K-ras mutations in normal pancreas glands [35]. In order to improve diagnostic accuracy, other markers will be used in tandem with K-ras. Mutations or deletions that affect p53, p16 and SMAD4 are also commonly found in pancreatic ductal adenocarcinomas but not in tissue from patients with chronic pancreatitis [36-38]. Further work is underway to try and detect these mutations/deletions in pancreatic juice.

Prognosis using molecular markers

Overexpression of growth factors EGF, TGFα, TGFβ 1-3, aFGF, bFGF, and growth factor receptors c-erbB-2, c-erbB-3, TGFβRI-III is common in pancreatic cancers. High levels of mutations are found in genes which control the cell cycle such as p53, p16, p21, DPC4, cyclin D1, abnormal expression of apoptotic genes such as bcl-2, bcl-XL, and bax are also found. In general, no significant correlation between overexpression of growth factors and their receptors and patient survival has been found, although they are associated with poorly differentiated tumours of an advanced stage. Inactivation and loss of expression of tumour suppressor genes p16, p53 and p21 has not been found to be of any prognostic significance [39]. In one study overexpression of cyclin D1 was associated with significantly shorter patient survival but this was not confirmed by another larger study [39, 40]. TGFβ1 expression has been shown to be associated with significantly longer survival in patients with pancreatic cancer [41]. Bax expression has also been shown to be a significant indicator of prolonged survival in one study but was not confirmed in our own and there is no significant relationship between bcl-2 expression and survival [42, 43]. Two studies (including our own) have confirmed bcl-XL expression to be significantly associated with poor outcome and survival in patients with pancreatic cancer [43, 44]. Certain types of K-ras mutation may differentiate between poor and good long-term survival following resection (unpublished data). These results confirm the potential use of molecular markers to predict the outcome of patients with pancreatic cancer.

Surgical palliation

With the development of endoscopic techniques of biliary bypass and improved preoperative staging the role of open surgical palliation has decreased. Three randomised clinical trials have compared open surgical bypass and endoscopic drainage in patients with distal bile duct obstruction [45-47]. The two methods have a similar initial success rate and overall survival of patients does not seem to differ. The advantages of the endoscopic route are decreased morbidity and possibly mortality in the period immediately following the drainage procedure and a decreased hospital stay with cost savings following stenting [48]. Stent blockage that requires re-ERCP and stenting occurs in a proportion of patients, particularly in those living longer than six months when the alternative is to use the self-expanding metal stents [49]. Randomised controlled studies from Europe [50, 51] and the USA [52] showed that self-expanding metal stents...
remained patent for longer than plastic stents. Metal stents must be avoided if there is a possibility of tumour excision, s resection then becomes hazardous or impossible.

Patients with gastric outlet obstruction have previously required an open surgical bypass; insertion of a metal stent into the duodenum obviates the need for surgery [53]. Laparoscopic cholecystectomy offers another treatment strategy, but cholangiography is essential to confirm that the cystic duct is patent and that the point of insertion into the common bile duct is well away from the tumour [54]. Gastric bypass also may be performed laparoscopically [55].

**Standard Kausch-Whipple pancreatectomy**

There has been confusion about what constitutes a standard Kausch-Whipple operation. A consensus conference attended by a number of international experts was held at Castelfranco Veneto in Italy to resolve this issue in May 1998 [56]. In the standard operation the resected specimen consists of the distal stomach, the duodenum and proximal jejunum, attached bile duct and gallbladder, as well as the head of the pancreas. Lymph nodes (according to the Japanese Pancreatic Society classification) which are removed en bloc during the standard Kausch-Whipple procedure include the anterior pancreaticoduodenal nodes, (13a, 13b); lymph nodes on the right side of the hepatoduodenal ligament (12b1, 12b2, 12c); the nodes to the right side of the superior mesenteric artery, from the origin of the superior mesenteric artery at the aorta to the inferior pancreaticoduodenal artery (14a,14b); and the anterior pancreaticoduodenal nodes (17a,17b). The outcome from the Standard Kausch-Whipple pancreaticoduodenectomy is shown in Table 1. Portal vein involvement does not necessarily preclude resection as part of it may be resected [57]. Similarly portal vein involvement does not necessarily indicate a more aggressive tumour as survival following portal vein resection is similar to other tumours of similar stage [58]. Involvement of the mesenteric artery is usually considered to indicate irresectability but combined resection of the coeliac artery with a distal pancreatectomy has been shown to increase the resectability rate with an acceptable post-operative mortality [59]. The exact definition of a resectable tumour is thus to some extent surgeon dependent.

Pylorus preserving pancreaticoduodenectomy (PPPD) first described by Watson in 1944 [60] does not compromise longer term survival, despite initial fears that this might be the case [61-63]. PPPD may shorten operative time and reduce blood loss [62]. Although preservation of the pyloric sphincter should allow for more controlled emptying of the upper gastrointestinal tract and reduce biliary reflux, whilst preservation of the duodenal packer should reduce delayed gastric emptying and improve late gastro-intestinal functions, clinical studies are inconclusive [62,64].

Total pancreatectomy was advocated at one time in an attempt to reduce recurrence rates and postoperative morbidity, particularly leakage from the pancreatic anastomosis [65-67]. Unfortunately following total pancreatectomy patients become diabetic and a number of studies have failed to confirm the procedure’s oncological benefits, reduced morbidity or mortality. It is now used infrequently [68, 69].

**Extended lymphadenectomy**

Following the finding by Cubilla et al in 1978 [70] that up to one third of patients had metastases in lymph nodes not usually removed with the standard operation the concept of a radical extended pancreatectomy was introduced by Fortner [71]. Japanese pancreatic surgeons in the 1980s also developed aggressive strategies to treat pancreatic cancer and developed surgical approaches including extended lymph node and connective tissue clearance with autonomic nerve dissection around the coeliac and superior mesenteric arteries [72]. The results following extended resection from a number of series are shown in Table 2. The radicality of the operation varies from centre to centre and thus it is often difficult to compare results. Most of the series are retrospective, lacking even the dubious benefit of a within-centre comparison of a historical control set - an exception being the study of Ishikawa et al (1988). Moreover, group migration using retrospective data accounts for an apparently better survival in one group compared to another, yet the overall survival is the same. In the case of extended resection there are increased numbers of lymph nodes for histological analysis and the tendency therefore for cases to migrate to a higher stage. This produces an apparent improvement in the survival of early cases which is illusory since the overall survival is the same. Recent large retrospective studies from Japan have shown no benefit following extended lymphadenectomy in patients with more advanced tumours [73-75]. As can be observed from the comparative results in Tables 1 and 2, that extended resections are unlikely to result in longer patient survival compared to a standard resection.

Only two randomised-controlled studies have examined the role of extended lymphadenectomy in this condition. The first is a single centre study, with only a few patients accrued [76]. A randomised controlled study comparing extended lymphadenectomy added to the conventional Kausch-Whipple procedure involving five centres in Italy and one in the USA showed no significant survival benefit nor in post-operative morbidity or mortality. Analysis of the subgroup of patients who were found to be lymph node positive showed a small significant survival benefit with extended lymphadenectomy. Unfortunately this post-hoc analysis has little scientific meaning [77]. A definitive multi-centre randomised study is required to adequately address the role of extended lymphadenectomy in pancreatic carcinoma [78].

**Adjuvant therapy**

Even after resection survival is short for patients with pancreatic cancer. Any extra gain must not be outweighed excessive to morbidity. Radiotherapy is generally felt to give the best local control in advanced disease but there has never been a randomised controlled study [78]. The use of a 5 fluorouracil (5-FU) as a chemosensitising agent with radiotherapy significantly improves survival of patients with advanced disease compared to radiotherapy alone [79]. Polychemotherapy regimens in advanced pancreatic cancer do not have any survival benefit over 5-FU alone but are associated with increased morbidity [80]. The use of systemic 5-FU given as a weekly bolus after radiochemotherapy however was shown to improve survival in advanced pancreatic cancer compared
to radiotherapy alone [81]. Subsequently, a randomised controlled trial of adjuvant chemo-irradiation with follow-on chemotherapy (weekly injections of 5-FU for two years) in patients undergoing potentially curative resection of the pancreas was performed. The control group received no treatment. The trial was eventually terminated because of poor recruitment. At this time results showed a doubling in the median and 2 year survival in the treatment group but there were only 43 patients in the whole study. A further group of 30 patients were subsequently recruited to the same treatment protocol; although survival was similar to that seen in the original treatment group the problems of an unconvincing underpowered study remained [82].

A number of studies using similar protocols of chemotherapy/radiation have since been undertaken in an attempt to confirm these findings. The European Organization for Research and Treatment of Cancer (EORTC) randomised study of postoperative radiotherapy showed a non-significant benefit in the treated group, although survival was similar to that seen in the original treatment group the problems of an underpowered study remained [82].

<table>
<thead>
<tr>
<th>Series</th>
<th>Period (19)</th>
<th>Number of resections</th>
<th>Resection Type</th>
<th>Operative mortality</th>
<th>Median Survival</th>
<th>1 year survival</th>
<th>3 year survival</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Former [99]</td>
<td>72-78</td>
<td>35</td>
<td>Regional</td>
<td>9 (26%) 3 (9%)</td>
<td>15 months</td>
<td>-</td>
<td>-</td>
<td>37%</td>
</tr>
<tr>
<td>Manabe et al [100]</td>
<td>66-87</td>
<td>42</td>
<td>S</td>
<td>4 (10%) 2 (6%)</td>
<td>-</td>
<td>27%</td>
<td>65%</td>
<td>0%</td>
</tr>
<tr>
<td>Hiraoka et al [101]</td>
<td>66-75</td>
<td>19</td>
<td>S</td>
<td>3 (16%) 1 (11%)</td>
<td>-</td>
<td>27%</td>
<td>44%</td>
<td>0%</td>
</tr>
<tr>
<td>Ishikawa et al [102]</td>
<td>71-81</td>
<td>45</td>
<td>E</td>
<td>6 (13%) 3 (4%)</td>
<td>-</td>
<td>39%</td>
<td>59%</td>
<td>10%</td>
</tr>
<tr>
<td>Henne-Bruns et al [76]</td>
<td>88-91</td>
<td>11</td>
<td>S</td>
<td>-</td>
<td>-</td>
<td>25%</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>Hanyu et al [103]</td>
<td>68-95</td>
<td>67</td>
<td>E</td>
<td>8 (12%) 10 (4%)</td>
<td>-</td>
<td>41%</td>
<td>42%</td>
<td>10%</td>
</tr>
<tr>
<td>Naganuma et al [104]</td>
<td>76-96</td>
<td>11</td>
<td>S</td>
<td>0 (%) 1 (1.4%)</td>
<td>-</td>
<td>27%</td>
<td>48%</td>
<td>9%</td>
</tr>
<tr>
<td>Pedrazzoli et al [77]</td>
<td>91-94</td>
<td>40</td>
<td>S</td>
<td>2</td>
<td>18.4 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

S standard, E extended, R radical

Table 2: Results of radical surgery and extended lymphadenectomy for pancreatic adenocarcinoma

in comparison to control the group.

Novel approaches are required as the benefits of conventional cytotoxics in pancreatic cancer are limited. Matrix metalloproteinases (MMPs) are a family of zinc-containing proteolytic enzymes that breakdown extracellular matrix proteins (ECM) essential for tumour invasion [86, 87] Disruption in the regulation and expression of MMPs indicates an important role of MMPs in the spread of pancreatic cancer [88-90]. Marimastat is a highly potent but reversible inhibitor of MMP2, with weak activity against unrelated MMPs. Patients with unresectable stage II or III disease treated with marimastat had a median survival of seven months compared to less than three months with stage IV disease [89, 91]. Phase III trials of marimastat and other MMP inhibitors are underway in advanced disease and as adjuvant therapy post resection. These studies include a double-blind randomised study comparing adjuvant chemoradiotherapy with or without marimastat in patients with resectable cancer, and a double-blind randomised study comparing gemcitabine with or without marimastat in patients with non-resectable pancreatic cancer.

Gene therapy

There are several approaches being tested for the treatment of pancreatic cancer. Gene replacement therapy restores the function of genes such as tumour suppressor genes. In appropriate cells this is pro-apoptotic or promotes cell cycle arrest. The wild type p53, p16, p21 and retinoblastoma genes have been replaced in pancreatic cancer using either retrovirus or adenovirus vectors [92]. Anti-sense oligonucleotides directed at oncogenic ras have been shown to reduce tumorigenicity and anti-sense oligonucleotides directed at c-ErbB-2 decrease cancer cell growth. Genetic produg activation therapy (GPAT) involves transferring a gene encoding a specific enzyme into cancer cells which will convert a non-toxic produg into a cytotoxic metabolite. Neighbouring tumour cells and also distant tumour cells that do not express the enzyme may also die due to bystander effects. Several systems have been assessed such as the combination of β-nitroreductase and treatment with CB1954 (which is converted to powerful alkylating agents) [93]. Immunochemistry approaches, which utilise cytokine genes
such as IL2 or IL12, have been used alone or in combination with GPAT [94].

The principal limitation of gene therapy at present is targeting vectors to the appropriate tissue. The best way to introduce genes into mammalian cells is using disabled viruses. Unfortunately this often provokes an immune response. Tumour-specific targeting is not possible at present although the development of modified viruses or ‘synthetic’ viruses is ongoing. Tumour-specific expression is however possible by linking the promoter of a tumour-specific gene (such as CEA) in the gene constructs. Refinement of these strategies in conjunction with the development of novel techniques of delivery will allow the selective targeting of tumour cells.

Surgery for pancreatic cancer in the new millennium

At the present there are nearly 200,000 new cases of pancreatic cancer each year in the world. Most are dead within one year and surgery cures no patient. Outside of specialist centres the resection rates are less than 3% and the mortality is at least 20-30%. The type of surgery is poorly documented and there is no agreed standard of pathological reporting. Advanced cancer or adjuvant therapies have yet to be shown to be of benefit.

In the New Millennium surgery will become a key component of treatment.

- Management of cases will be in regional centres achieving resection rates of 30-50%.
- The type of surgery and pathological reporting will be standardised.
- Treatment will be multimodal hinging on a variety of gene therapies.
- Molecular diagnosis will be in routine use and molecular prognosis will determine the type of treatment to be given to an individual patient.

References


Correspondence to: Professor J.P. Neoptolemos
Department of Surgery
University of Liverpool
5th floor UCD
Dalby Street
Liverpool, L69 3GA
United Kingdom