With rare exceptions, prolonged survival from carcinoma of the pancreas is dependent on surgical resection. However, even those patients undergoing complete surgical resection can anticipate at best a 15 to 20% five-year survival. Of those who survive five years, at least half will subsequently die of disease [1].

While major developments have occurred in diagnosis and imaging and a proliferation of techniques to evaluate cystic neoplasms, overall prognosis over the last 25 years has changed very little (Figure 1). Advances in imaging, particularly the utilization of dedicated pancreatic computer tomography and MRI (magnetic resonance imaging), have allowed much more precise diagnosis. The primary surgical evaluation of images of the pancreas focuses on the definitions of resectability. Resectability is dominated by the absence of metastatic disease, the lack of major arterial vascular involvement, and limited or minimal venous involvement. Pre-operative imaging adds significant information about aberrant arterial anatomy, the presence or absence of other disease, such as aneurysms or second tumors, all of which contribute to the potential morbidity of a surgical procedure.

Once resectability has been determined, an improvement in absolute resectability is added by the addition of laparoscopy with cytological washings. Depending on the underlying histopathology, laparoscopy adds a variable percentage in laparoscopic yield. The yield is low in duodenal carcinoma and neuroendocrine tumors, and is highest in patients who have a distal pancreatic adenocarcinoma as there is no palliative procedure for the patient with a distal pancreatic adenocarcinoma in the presence of metastatic disease. In our original report in 1996 [2], we evaluated laparoscopy in 115 patients with radiographically resectable peripancreatic tumors and identified 36% as having unresectable disease. The majority had either peritoneal or liver metastasis. More recently, an evaluation of 2,300 patients, of which 61% underwent staging laparoscopy, suggested that the anticipated radiological
Resectability of 80% found 13% to be laparoscopically unresectable, i.e. by the use of diagnostic laparoscopy we came to operation with the probability of 87% of patients as resectable and of those, 85% were resected. The overall yield of identifying unexpected unresectable disease was 2% for ampullary, 17% for pancreatic adenocarcinoma and 6% for duodenal lesions.

We still believe that laparoscopy is valuable in suspected pancreatic adenocarcinoma, as the relative yield over high quality imaging is approximately 15 to 20%. This is usually unidentified peritoneal metastatic disease or, less frequently, small volume liver metastasis.

Technical aspects of pancreatic surgery have improved markedly over the last 15 years, and mortality has diminished considerably from the 20% seen in the late 70s to less than 2% in currently high volume practices. Mortality is highly institution and surgeon volume dependent [3-4]. Morbidity, however, remains high even in the most experienced of hands [5]. Depending on the definition of morbidity, 40 to 60% of patients will have some degree of morbidity with at least 10% having either a defined pancreatic fistula or at least a post resection pancreatic collection with or without infection.

It is now clear that the infections that occur are highly dependent on preoperative instrumentation of the biliary tract, with the organisms anticipated as the usual organisms found in the bile duct at the time of operation [6]. This has practical implications for the use of prophylaxis because the organisms seen in the bile are very different from conventional skin contaminants.

Multiple randomized controlled studies have been done to examine aspects that may or may not improve outcome. The highly controversial use of drains has been addressed in a randomized control trial [7] with no clear benefit identified. In addition, we have performed prospective randomized control trials of enteral [8] and parenteral nutrition [9-10] as an adjuvant, and these have not diminished morbidity or mortality and may have increased infectious morbidity. Extensive studies have been performed as to the use of postoperative octreotide and remain either negative or with minimal benefit. Perioperative management has continued to minimize interventions with nasogastric suction no longer routinely used, and drains used very selectively.

Variations on operative management have included pylorus sparing procedures and variations in pancreatic anastomoses, either as pancreatico-jejunostomy or pancreatico-gastrostomy. Again, these technical refinements have limited long-term impact. With these and other modifications, in-hospital stay in the United States has markedly diminished. When we began our prospective database in 1983, the median stay was approximately 28 days. In 2010 it is seven days. It is important to understand that this early discharge does not mean that patients have minimal complications, and some late readmissions can be anticipated with the development of intra-abdominal collections, either infected or noninfected.

A most challenging problem is the high prevalence of identified cystic neoplasms of the pancreas. These can provide a diagnostic challenge, and the concern is for their risk of malignancy. It is now clear [11-12] that nonoperative management of many of these cystic lesions is appropriate. We believe primary indications for operative management of cystic neoplasms involve the presence of
symptoms: a size > 3 cm, the presence of a solid component to the lesion, or evidence of pancreatic main duct dilatation. It is important to identify the risk of malignancy in these lesions, as for many cystic lesions the risk of mortality from operation exceeds the risk of the presence of an underlying malignancy.

A most recent update of our cystic pancreatic registry suggests that we have evaluated 1,425 patients with 423 undergoing an initial operation and 1,002 undergoing initial nonoperative management. With time, the size of the lesions we are asked to evaluate has progressively declined as we see more asymptomatic patients. Overall, less than 30% of patients with these lesions currently have come to operative management. If we contrast the operative mortality in those undergoing resections, 0.7%, with the risk of development of adenocarcinoma in the 1,000 patients followed, this was 0.8%. Of the 1,000 patients, only 47 developed changes that indicated any operation at one to 10 years.

As a consequence of the large databases that we have, we have been able to develop nomograms. With over 5,000 admissions for peripancreatic cancer, we have clearly established the relative prevalence of those patients who are to undergo resection. With postoperative information, prognostic data can be accumulated and a nomogram to predict individual survival clearly calculated [13]. Postoperative predictors of poorer outcome are the presence of positive nodes and the presence of positive microscopic margins. But these have small impact on the overall poor survival, and while statistically significant (Figure 2), are relatively limited in practical outcome. It is important to appreciate that survival is histopathology dependent, i.e. that patients with ampullary and duodenal lesions can be expected to have a considerably better outcome than those with distal bile duct and pancreatic adenocarcinoma (Figure 3). Once corrected for resection, the outcome of whether a lesion is situated in the body or tail is not a determinant. However, it is clear that patients
with distal pancreatic lesions are more likely to have metastasis at the time of laparoscopy and/or operation, and so their resectability rate is considerably less than those who present with clinical jaundice.

Studies comparing resection alone to radiation and chemotherapy alone are very limited and of very small sample size. However, in one randomized trial, one year survival is approximately double when resection is contrasted to radiation and chemotherapy as a primary entity [14]. Extended resections, again in randomized trials, have not proven beneficial in long-term disease specific outcome.

Adjuvant therapy has been studied but has been of limited value. A randomized trial of adjuvant gemcitabine [15] has suggested a significant benefit to disease free survival (13.4 versus 6.9 months) with limited overall survival benefit (22.1 versus 20.2 months). Subsequent studies examining comparison of adjuvant chemotherapy with fluorouracil plus folinic acid versus gemcitabine after potentially a curative resection [16] did not show a benefit, and when 69% of the patients were deceased, median survival was 23.0 months for patients treated with fluorouracil plus folinic acid and 23.6 for those treated with gemcitabine, an insignificant difference. Fourteen patients with fluorouracil and folinic acid had serious adverse events contrasted to 7.5% receiving gemcitabine alone.

Marginally resectable pancreatic adenocarcinoma is usually approached by preoperative chemotherapy and then explored for potential resectability, reserving radiation therapy for those who are not resectable. Others prefer the utilization of combination radiation and chemotherapy prior to consideration of resection, but absolute benefit is unproven. Certainly preoperative therapy has the advantage of greater treatment compliance and the avoidance of non-therapeutic operation in those with early progression.
Conclusions

Adenocarcinoma of the pancreas remains a lethal disease, with the majority of treatments ultimately palliative. New ideas are desperately needed.

References