State-of-the-art treatment for pancreatic cancer

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Introduction

Cancer of the pancreas is the fourth and sixth most common cancer death in the USA and UK respectively and the peak incidence is at 65–75 years. Most patients present with advanced disease resulting in low resection rates. The late presentation is responsible in part for the overall median survival of less than 6 months and 5-year survival rate of 0.4 to 5%. Between 2.6% and 9% of patients undergo pancreatic resection (Table 1) with a median survival of 11–20 months and a 5-year survival rate of 7–25% but virtually all patients are dead within seven years of surgery. Due to the poor 5-year survival, the incidence and mortality are roughly equivalent; figures for the UK are 6989 new patients in 1999 and 6763 deaths in 2001. The latest data from Europe show 60139 new patients per year, representing 10.4% of all digestive tract cancers and 64801 deaths per year.

The surgical management of pancreatic cancer has undergone a paradigm shift in the past decade that has moved from no active treatment to the standard of care being now defined as potentially curative resection in a specialist centre followed by adjuvant systemic chemotherapy with 5FU/leucovorin. For advanced pancreatic cancer, surgery may be avoided by the use of stents and survival may be improved even further on gemcitabine by the addition of Tarceva or capecitabine.

Table 1
Resection rates for pancreas cancer in population based studies

Study	Period	Number of patients	Region	Resection rate (%)
Bramhall	1977–1987	5672	West Midlands, UK	2.6
NYCRIS	1986–1994	3278	Northern & Yorkshire, UK	4
Hedberg	1977–1991	575	Mälmo, Sweden	4.2
Sener	1985–1995	100,313	USA	9

Risk factors

After smoking (2-fold risk; 30% of cases) the most important risk factor is a familial background (5–10%). In families with at least two first degree relatives with pancreatic cancer, the increased relative risk varies from 18-fold to 57-fold depending on the number of pre-existing affected relatives. European groups have identified rare pancreatic cancer families in which pancreatic cancer appears to be inherited in an autosomal manner and in which germline mutations of BRCA2 appear to be involved in up to 19%. Other families have a combination of pancreatic cancer and melanoma in which there are germline mutations of $p16^{INK4a}$. In addition there are a variety of familial cancer syndromes in which there is a significantly increased risk of pancreatic cancer. Chronic pancreatitis is also an important risk factor for pancreatic cancer with an increased risk of 15- to 25-fold in sporadic chronic pancreatitis, whilst this increases to 70- to 100-fold in hereditary pancreatitis although this latter factor accounts for less than 1% of all patients with pancreatic cancer. High risk groups may undergo secondary screening by modern imaging methods (CT, EUS) and molecular diagnosis of pancreatic juice.

Regionalisation

The development of high volume specialist centres is the main reason for the reduction in peri-operative mortality during the last decade (Table 2). The evidence base around specialist units has grown substantially and now clearly shows a reduced post-operative mortality that is a continuous effect, with no threshold, unaffected by case mix and only a possible single surgeon effect; reduced post-operative morbidity; reduced post-operative length of stay and cost; an increased resection rate; and increased long-term survival. Numerous studies from Europe and the USA demonstrated a clear correlation between caseload and surgical mortality. A survey of 2.5 million complex surgical procedures from the USA showed a large

Table 2
Hospital mortality following resection for pancreatic cancer in 11 studies from the USA and Europe published in 1995–2002, comparing high with low volume centres

	Year	Region	Period	Number of institutions	Number of resections	Mortality (%)	
						High volume hospitals	Low volume hospitals
Studies from the USA							
Lieberman	1995	New York	1984–91	184	1972	5.5	11.8–18.9
Janes	1996	USA	1983–90	978	2263	4.2	7.7
Gordon	1995	Maryland	1988–93	39	501	2.2	13–19.1
Glasgow	1996	California	1990–94	298	1705	3.5	6.9–14.1
Gordon	1998	Maryland	1984–95	43	1093	1.8	14.2
Begg	1998	USA	1984–93		742	5.8	12.9
Birkmeyer	1999	USA	1992–95	1246	7229	4.1	12.7–16.1
Studies from Europe							
Neoptolemos	1997	UK	1976–96	21	1026	5.9	8.3–27.6
Gouma	2000	Netherlands	1994–98		1126	1	16
NYCRIS	2000	Yorkshire, UK	1986–94	17	130	7.8	21
Nordback	2002	Finland	1990–94	33	374	4	13

inverse relationship between the hospital volume and case mortality rates for pancreatic resection. In the UK all pancreas cancer surgery is now confined to large Regional Pancreas Cancer Centres serving populations of at least 2 million.

Staging and treatment of advanced disease (Table 3, Fig. 1)

Advances in imaging mean that a pre-operative staging is becoming increasingly accurate and may be further augmented by selective (CA19-9 levels) laparoscopic staging. Unresectable patients can be managed entirely non-surgically with biliary and duodenal stents and chemotherapy. The evidence base for chemoradiation is largely non-existent. The standard of chemotherapy is monotherapy with gemcitabine but recent trials will probably lead to an important change in 2005 with the addition of Tarceva or capecitabine.

Table 3
2002 UICC staging of pancreatic cancer

Stage	T	N	M
0	is	0	0
IA	1	0	0
IB	2	0	0
IIA	3	0	0
IIB	1–3	1	0
III	4	Any	0
IV	Any	Any	1

Tis: carcinoma *in situ* T1: tumour limited to the pancreas <2 cm
T2: tumour limited to the pancreas >2 cm
T3: tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4: tumour involves coeliac axis or superior mesenteric artery
N0: no regional lymph node metastasis N1: regional lymph node metastasis
M0: no distant metastasis M1: distant metastasis

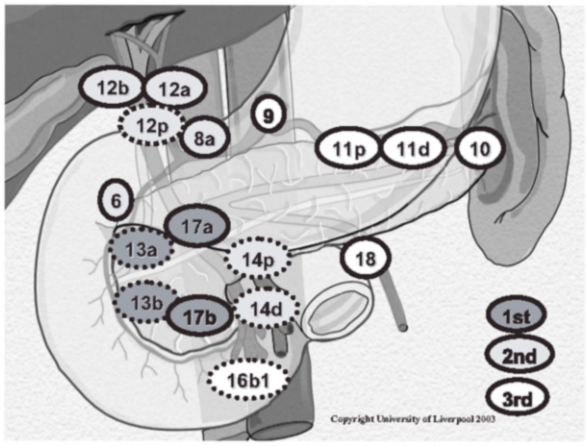

Fig. 1. Japanese Pancreas Society lymph node groups. This shows the first, second and third order lymph node groups. Doted lines indicate posteriorly positioned lymph node stations.

Resection

For patients undergoing resection there is no evidence that pre-operative endoscopic stenting is either of

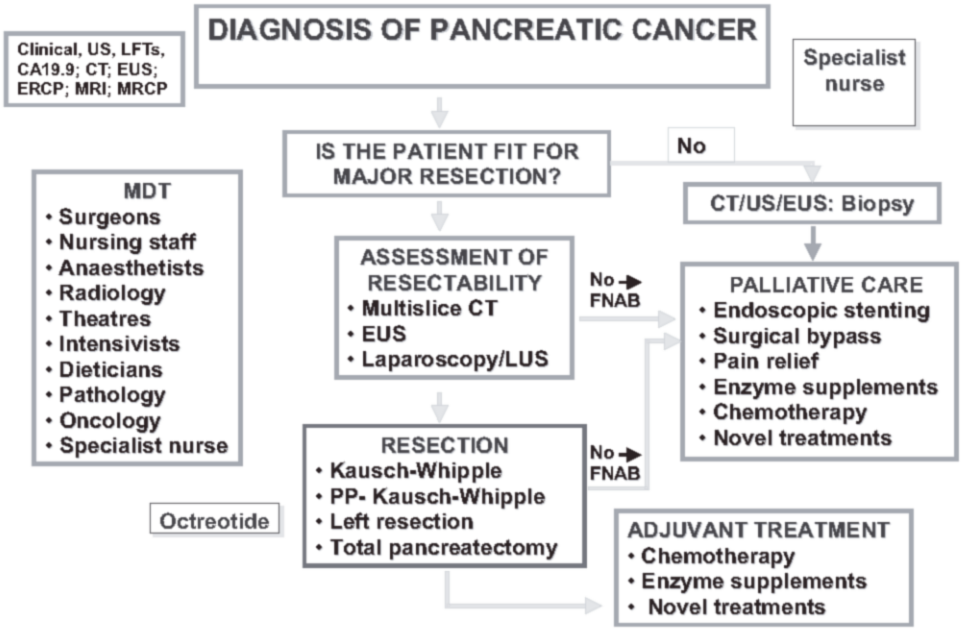

Fig. 2. A summary algorithm for the modern management of pancreatic cancer. US: ultrasonography; LFTs: liver function tests; CT: computed tomography; EUS: endoluminal ultrasonography; ERCP: endoscopic retrograde cholangiopancreatography; MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; MDT: multidisciplinary team; FNAB: fine needle aspiration for cytology; LUS: laparoscopy, including laparoscopic ultrasound; PP: pylorus-preserving.

benefit or harmful in terms of surgical outcome and continues to be widely used for logistical reasons enabling careful work-up and assessment by the (Regional) Multi-Disciplinary Team (Fig. 2). The more conservative pylorus preserving Kausch-Whipple procedure produces as good long-term results as the standard procedure in expert hands and there is no benefit to be derived from extended lymphadenectomy. Resection of the hepatic portal and superior mesenteric vein is an appropriate means of ensuring resection with gross tumour-free margins (R0 or R1) and does not appear to increase operative morbidity or mortality. Current peri-operative mortality in high volume centers varies from 1% to 4%. More patients die of systemic complications than from surgical complications. Nevertheless breakdown of the pancreatic anastomosis continues to be a major problem. A recent meta-analysis has conclusively shown the value of peri-operative somatostatin analogues in the prevention of pancreatic fistulae (Table 4) and other complications following pancreatoduodenectomy.

Table 4
Four different classifications of post-operative pancreatic fistula applied to a consecutive series of 242 patients from Verona 1996–2000

Classification	Definition of pancreatic fistula	Post-operative fistula rate	
		N	%
#1	>10 ml/day ⩾5 days post-op	69	28.5%
#2	>10 ml/day ⩾8 days post-op	44	18.5%
#3	>25 ml/day ⩾8 days post-op	40	16.5%
#4	>50 ml/day ⩾11 days post-op	24	9.9%

Adjuvant treatment (Table 5)

Up until recently, strong evidence for the routine use of adjuvant therapy was lacking although the use of

Table 5
Details of adjuvant treatment received and the five year survival results in 9044 patients who underwent a resection for pancreatic cancer in the joint study by the American College of Surgeons Commission on Cancer and the American Cancer

Treatment Received	Patients		Five year survival rate
	N	(%)	
Pancreatectomy only	5431	(60.1)	23.3%
Pancreatectomy plus adjuvant chemoradiation	591	(6.5)	13.0%
Pancreatectomy plus adjuvant chemotherapy	465	(51.4)	17.4%
Pancreatectomy plus adjuvant chemoradiation and maintenance chemotherapy	2557	(28.3)	17.0%

Table 6
Final results of the ESPAC-1 trial

Series	Year	Number of cases	Regimen	Median survival (months)	Actuarial survival (%)			
					1 year	2 year	3 year	5 year
Overall	**2001**	**595**	–	–	–	–	–	–
Overall: chemotherapy question	2001	237	No 5FU/LV	14.8	–	28.7	–	9.9
		244	5FU/LV	21.6		43.3		23.3
Overall: chemoradiation question	2001	180	No 40 Gy	16.7	–	37.9	–	19.5
		178	40Gy	15.5		27.7		10.3
Factorial 2×2: chemotherapy question	2004	142	No 5FU/LV	15.5	–	30	–	8
		147	5FU/ LV	20.1		40		21
Factorial 2×2: chemoradiation question	2004	144	No 40 Gy	17.9	–	41	–	20
		145	40 Gy	15.9		29		10
Individual groups Factorial 2×2	2004	289	–	–	–	–	–	–
Control	2004	69	–	–	–	–	–	10.7
Chemoradiation	2004	73	40 Gy	–	–	–	–	7.3
Chemoradiation plus chemotherapy	2004	72	40Gy 5FU/LV	–	–	–	–	13.2
Chemotherapy	2004	75	5FU/LV	–	–	–	–	29.0

5FU: 5-Fluorouracil; FA: leucovorin.

combination therapy comprising chemoradiotherapy and maintenance chemotherapy has been common in the USA. A joint study by the American College of Surgeons Commission on Cancer and the American Cancer Society analysed the results of 100,313 patients from 2100 hospitals diagnosed with pancreatic adenocarcinoma from 1985 to 1995 of whom 9044 (9%) underwent a resection. Adjuvant treatment was administered to 3613 (40%) patients and the five year survival results after resection alone, adjuvant chemoradiation, chemoradiation and chemotherapy and chemotherapy alone were 23.3%, 13.0%, 17.0% and 17.4% respectively. All adjuvant trials up to date have been underpowered with the exception of the ESPAC-1 Trial. The ESPAC group recruited 550 patients with pancreatic ductal adenocarcinoma and assessed the roles of adjuvant chemoradiation (40 Gy delivered over six weeks including a 2 week rest period with 500 mg/m^2 5FU intravenous bolus on the first three days of each 20 Gy fraction) and maintenance chemotherapy (intravenous bolus 5FU, 425 mg/m^2 daily for 5 days, with folinic acid, 20 mg/m^2, monthly for six months). The core design was a 2×2 factorial randomisation procedure (observation, chemoradiation alone, chemotherapy alone or combination of the two) but additional patients could be randomised into only one of the main treatment comparisons (chemoradiation versus no chemoradiation or chemotherapy versus no chemotherapy). There were 289 patients randomised to the 2×2 factorial design. The initial results after a median follow-up of 10 months conclusively showed a lack of survival benefit from chemoradiation and further recruitment was therefore stopped. After a median of 47 (inter-quartile range 33–62) months follow-up, the results showed an overwhelming advantage for chemotherapy. There appeared to be a detrimental effect of chemoradiation when combined with maintenance chemotherapy, the simplest explanation being the delay in delivering effective systemic chemotherapy. The role of neoadjuvant chemoradiation on down-staging locally advanced disease to permit potentially curative resection has been addressed in a number of retrospective studies. This approach has been rarely effective in increasing the resection rate in these patients.

Breaking news

The results of ESPAC-1 (Table 6) have been confirmed in a recent meta-analysis of the IPD from all five published adjuvant trials, which also revealed a possible reduced effect from chemotherapy for R1 resections and a possible benefit for R0 resections. A German/Lilly study indicated increased disease-free survival for adjuvant gemcitabine but the data do not indicate superiority over adjuvant 5FU/folinic acid used in ESPAC-1. The ESPAC-3 trial has recruited nearly 1000 patients in order to address this question in a direct comparison (trial will close in December 2005). ESPAC-4 will specifically examine

patients with R1 resections and directly compare best chemotherapy with best chemoradiation in an adequately powered trial.

Conclusions

In the past decade there has been a substantial sharpening of the standard approaches to treatment of pancreatic cancer. Resection provides the only meaningful chance for possible cure and increased survival. Nevertheless, surgery has reached its limits. Current and future developments in tumour biology and genetics, in imaging, in epidemiology and in adjuvant therapies may improve survival even more. There are now numerous ongoing adjuvant trials and trials in advanced pancreas cancer and the first major gene therapy trial has just been launched in the UK. The standard of care is now clearly defined as resection followed by adjuvant chemotherapy with 5FU/folinic acid.