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• REVIEW •

Adjuvant therapy in pancreatic cancer

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Abstract

The outlook for patients with pancreatic cancer has been grim. There have been major advances in the surgical treatment of pancreatic cancer, leading to a dramatic reduction in post-operative mortality from the development of high volume specialized centres. This stimulated the study of adjuvant and neoadjuvant treatments in pancreatic cancer including chemoradiotherapy and chemotherapy. Initial protocols have been based on the original but rather small GITSG study first reported in 1985**. There have been two large European trials totalling over 600 patients (EORTC and ESPAC-**1**) that do not support the use of chemoradiation as adjuvant therapy. A second major finding from the ESPAC-**1 **trial (**541 **patients randomized) was some but not conclusive evidence for a survival benefit associated with chemotherapy. A third major finding from the ESPAC-**1 **trial was that the quality of life was not affected by the use of adjuvant treatments compared to surgery alone. The ESPAC-**3 **trial aims to assess the definitive use of adjuvant chemotherapy in a randomized controlled trial of** 990 **patients.**

Subject headings pancreatic neoplasms/drug therapy; pancreatic neoplasms/radiotherapy; human; review

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INTRODUCTION

Pancreatic cancer is the 5th most common site of deaths due to cancer among all cancer sites in the Western world. Low cure rates ensure that the mortality is nearly as high as the incidence. It is responsible for 7 000 deaths per year in the UK[1], 40 000 per year in Europe and 28 000 in the USA[2]. The peak mortality ages are estimated to be between 65 and 72 years in Europe and 55 and 75 years in the USA[2]. The incidence of this deadly disease has been rising during the last century. In the past 20 years however, there have been vast improvements in the surgical management of patients with pancreatic cancer. The surgical procedures have been improved and become more standardized between centres and countries. The level of pre- and post-operative support for these patients has been optimized, particularly in established centres with a high throughput[3]. These measures have ensured that the outlook for patients with resectable disease has certainly improved, particularly in the short term. Extending patient survival still remains a problem. The overall five-year survival for all patents with pancreatic cancer is only 0.4%[4]. Patients who are suitable for resection have five-year survival rates of between 10% and 24%[5-8] and are virtually never cured. Therefore, even for the 10% to 15% of patients who undergo surgery, there appears to be no guarantee of cure or indeed long-term survival. These outcomes would suggest a role for the use of additional or adjuvant therapy to attempt to improve patient survival and quality of life.

RADICAL SURGERY

Japanese groups amongst others have been enthusiastic in pursuing radical resection as means of increasing disease free margins and thus hopefully improving patient survival. Radical surgery includes extensive lymph node dissection and retroperitoneal connective tissue clearance as well as pancreatic resection. The Japanese groups have suggested that these approaches are superior to conventional Kausch-Whipple resection but several studies have not shown significant survival advantages when compared with conventional resection[9-13]. Kayahara *et al* found that radical resection in patients with Stage I and II disease (Japanese classification) and clear margins (R0) resulted in a reduction of local recurrence but did not translate into improved survival because of hepatic metastases[14]. Interestingly highly detailed serial section analysis of presumed R0 specimens has revealed microscopic margin disease (R1) in up to 38% of specimens[14].

Difficulties are encountered when comparing survival figures of Western and Japanese studies because of the different staging systems used (UICC *vs* JPS respectively). This is because of the phenomenon of 'staging system migration' that may give apparently better survival for each stage in one system compared to the other even though there is no overall difference in survival. Satake *et al*[15] compared the Japanese and UICC staging systems in a large cohort of patients. Stage for stage the Japanese system revealed a better survival from Stage I to IV compared with UICC system. The overall five-year survival however, was the same (11%) because the systems had been analysed in identical patients.

The majority of radical resection studies have been non-randomized and performed in single institutions. The radical lymph node dissection allows more accurate staging of disease and these tumours will tend to be upstaged because of this. Thus it is necessary to examine overall group survival within the context of randomized studies by an intention to treat analysis. There has been one multicentre prospective randomized trial comparing traditional partial pancreatoduodenectomy with and without a more extensive lymph node dissection[16]. Eighty-one patients were randomized to receive a standard (n=40) or extended (n= 41) lymphadenectomy and retroperitoneal soft tissue clearance. The standard lymphadenectomy included removal of lymph nodes situated at the anterior and posterior

pancreatoduodenal, pyloric, main bile duct, superior and inferior pancreatic head and pancreatic body stations. The extended lymphadenectomy also included the removal of lymph nodes from the hepatic hilum, along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery, laterally to both renal hila and clearance of the coeliac trunk and superior mesenteric artery. There was no significant difference of overall survival between the two groups. Patients who had lymph node positive disease demonstrated better survival following an extended resection compared to those who did not have an extended lymphadenectomy but must be regarded as a statistically invalid manoeuvre as this was a post-hoc subgroup analysis. In light of these findings the ultimate benefit of extended lymphadenectomy surgery still needs to be proven with further critical evaluation.

There appears to be no additional survival benefit associated with total pancreatectomy compared to Kausch-Whipple pancreatoduodenectomy and at the present time the pylorus preserving pancreatoduodenectomy has been shown to produce similar results to the more traditional Kausch Whipple procedure[17,18]. The latter approach is now the procedure of choice in most centres.

The lack of survival benefit associated with radical resection may be due in part to the pattern of disease recurrence in resected pancreatic cancer. Most tumour recurrences are local, peritoneal and hepatic[19-24]. The early appearance of hepatic metastases following resection almost certainly indicates the presence of hepatic micrometastases at the time of surgery. Microscopic peritoneal disease also tends to occur early in contrast to the relatively later presentation of local recurrence. Pancreatic cancer cells tend to spread within a range of peripancreatic tissues. Lymphatic infiltration and perineural invasion may be found in 90%-100% of resected specimens[25]. Reasons for recurrence following an apparently curative resection include residual retroperitoneal disease, perineural invasion, hepatic micrometastases and lymph node involvement. The pattern of relapse after surgery reflects the natural course of the disease without resection. The most commonly affected organs include abdominal lymph nodes (72%-83%), liver (64%-80%), peritoneum (40%-53%) and lung (27%-50%)[14]. An R0 resection in patients with no lymph node metastases cannot be achieved in more than about half of the patients undergoing resection. Kayahara *et al*[14] at post mortem examined 15 patients who had undergone radical resection. The local recurrence rate in this group of patients was 80%. The local recurrences were associated with perineural invasion, lymphatic invasion and soft tissue infiltration. High rates of local recurrence have been confirmed in numerous studies of patients who have undergone pancreatoduodenectomy and the majority occur within 1 to 2 years of surgery[23,24].

Identification of extrapancreatic disease at the pre-operative stage has improved due to accurate imaging techniques[26] and laparoscopy[27]. Peritoneal cytology has been shown to be positive in 58% of patients who may have unresectable tumours or have a limited postoperative survival[27]. The best predictors of outcome following surgery also reflect the causes of disease relapse. These include tumour stage (which also includes the lymph node status), grade of primary tumour and resection margin status[28-32]. Not surprisingly patients with stage I or II disease and negative resection margins tend to demonstrate the best survival.

The poor overall survival of patients with pancreatic cancer, even following optimal surgical intervention, and the pattern of disease progression and recurrence are clear indications for the use of additional treatment modalities.

CHEMOTHERAPY

Advanced pancreatic cancer

There have been many studies of chemotherapy in patients with advanced pancreatic cancer. Single agents and combination regimens have been used. At the present time there is no accepted standard chemotherapeutic agent for the treatment of pancreatic cancer. 5-fluorouracil (5-FU) remains the most effective and most frequently used single chemotherapy agent. 5-FU works partly by interference with enzymes such as thymidylate synthase and partly by incorporation of 5-FU metabolites into DNA and RNA. The response rates of -15% with a median survival of 3-5 months[33]. The addition of the modulator folinic acid has produced marginal survival benefit over 5-FU alone but this has not been a significant increase[33]. The addition of other modulators such as phosphonacetyl-L-aspartate (PALA), and interferon has also not produced significant improvements in survival[34,35]. Comparisons of 5-FU alone and 5-FU with a combination of other agents have not shown any advantage for the combination groups in randomized trials[33].

A new agent, gemcitabine has been compared to 5-FU in a randomized multi-centre phase III clinical trial[36]. Gemcitabine is a deoxycytidine analogue that is phosphorylated to an active form and competes with dCTP for incorporation into DNA. The study, in which over 70% of patients had stage IV disease, randomized 63 patients to receive gemcitabine and 63 patients to receive 5-FU. Median survival in the gemcitabine group was 5.7 months compared to 4.4 months in the 5-FU group but no patient survived beyond 19 months. The clinical benefit response was also significantly higher in the gemcitabine group[36]. Despite the fact that this is the only trial with a straight comparison between the two agents gemcitabine has been recommended as the drug of choice in the USA. Gemcitabine has also been combined with 5-FU in several phase II studies. It is generally well tolerated but can have unpredictable side effects such as neutropaenia, abnormal liver function tests and nausea and vomiting. In patients who have had previous radiotherapy to the mediastinum there have been unpredictable reactions[37].

There is good evidence from several randomized controlled trials comparing chemotherapy with a no treatment group that chemotherapy is of benefit in patients with advanced pancreatic cancer. Mallinson *et al*[38] demonstrated a median survival of 11 months for patients treated with 5-FU, cyclophosphamide, methotrexate, vincristine and mitomycin C compared to 2.2 months for the untreated control group. This regimen did not produce a significantly greater survival when compared to 5-FU alone in a much larger randomized control trial[39]. Another rather poorly controlled study compared 5-FU and carmustine to untreated controls[40]. There was no significant survival benefit associated with this regimen but the majority of patients in this study received only a single treatment and did not finish the course. A further trial of the combination of 5-FU, doxorubicin and mitomycin C (FAM) resulted in median survival of 33 weeks compared with median survival of 15 weeks in untreated control patients[41]. A recent study compared the use of 5-FU + folinic acid (+/- etoposide) with best supportive care and showed that the median survival in the treated group was 6 months compared to 2.5 months in the control group[42]. Moreover there was better overall

quality of life score for the treated patients.

Adjuvant chemotherapy

There have been only a few studies of adjuvant chemotherapy in pancreatic cancer and (up until the ESPAC-1 trial) there was only one randomized controlled trial comparing surgery and chemotherapy with surgery alone (Table 1)[43-46]. Splinter *et al* [43] reported no evidence of improvement or survival using a FAM regimen in 16 patients who had undergone pancreatoduodenectomy with a three year survival of 24% compared to a three year survival of 28% in 36 patients who had undergone surgery only. Patients from different time periods were included in the two groups and there were only nine patients with pancreatic ductal adenocarcinoma in the adjuvant group and 18 in the surgery only group. Baumel *et al*[46] reported adjuvant chemotherapy in 43 selected patients with a median survival of 12 months but there was no difference in median survival from those patients who underwent surgery only (12 months). Bakkevold *et al*[45] randomized 61 patients who had undergone pancreatoduodenectomy for pancreatic cancer or ampullary cancer to receive either six courses of FAM or no chemotherapy. There was a significant difference in the median survival rates between the two groups: 23 months. Unfortunately this did not translate into a significantly improved long-term survival however: the 5-year survival rates were 4% for the treatment arm versus 8% for the surgery only arm. There was also considerable toxicity encountered with the FAM regimen. Only 24 out of 30 patients randomized to treatment actually started therapy. Sixteen patients needed hospitalization after the first chemotherapy course and a total of 13 patients managed to complete all six cycles of FAM.

The European Study Group for Pancreatic Cancer (ESPAC) has commenced the ESPAC-3 trial with the objective of definitively defining the role of adjuvant chemotherapy following curative resection for pancreatic ductal adenocarcinoma. Two adjuvant regimens are being studied against a no chemotherapy control: ① 5-FU + folinic acid for 24 weeks versus ② gemcitabine for 24 weeks versus ③ observation. All patients will have undergone potentially curative resection for pancreatic ductal adenocarcinoma. A total of 990 patients (330 in each arm) will be recruited over the next few years and survival analysis will be completed after two years of follow-up. At the present time recruitment is underway from centres across Europe with further centres in Canada, Australia and New Zealand due to join.

RADIOTHERAPY (CHEMORADIOTHERAPY)

Advanced pancreatic cancer

External beam radiotherapy (EBRT) although used in the treatment of advanced pancreatic cancer, has never been compared with an untreated control arm in any randomized controlled trial. The most commonly used and probably the best radiosensitizer used with EBRT for advanced pancreatic cancer is 5-FU. Many retrospective studies of EBRT, usually in relatively small groups of selected patients report median survival times of 10 - 15 months with good palliation of symptoms[47,48].

The improved local control of disease achieved with EBRT has not translated into significantly longer survival times, so there have been various refinements in an attempt to enhance the effectiveness of radiotherapy. Wide field irradiation has been used to address the problem of hepatic micrometastases. A Radiation Therapy Oncology Group (RTOG) study of 79 patients who received pancreatic and hepatic irradiation resulted in a median survival of 8.4 months but at the expense of considerable toxicity[49]. Intraoperative radiation therapy (IORT) aims to deliver higher doses of radiation with greater precision and thus reducing the exposure of neighbouring organs. Experimentally, its effectiveness may be as high as five times the equivalent dose given by EBRT. In advanced pancreatic cancer the survival times achieved using IORT have not been encouraging (median survival -6 months) and it has been mainly used to boost EBRT[50,51]. A study comparing EBRT + IORT + 5-FU with EBRT +5-FU demonstrated no significant survival difference (12 and 13 months respectively)[50,51]. Complications encountered during IORT include, duodenal and gastric ulceration, vascular sclerosis and pancreatic abscess[52]. IORT offers good local control and pain relief but cannot be recommended as a standard treatment as it has not been possible to demonstrate any advantages over conventional therapy.

Adjuvant radiotherapy (chemoradiotherapy)

Adjuvant EBRT and IORT have been used alone and in combination in the adjuvant setting (Table 2)[21,32,53-60]. The majority of studies indicate that EBRT alone or in combination with IORT has a significant survival advantage over the use of IORT alone. In a randomized trial IORT was observed to reduce the local recurrence rate by 50% following surgery, but this did not translate into a significant survival advantage (3-year survival with IORT=7% *vs* no IORT 3%)[21]. In selected patients IORT and resection produced 3 and 5-year survival rates of 53% and 29%[61,62]. The use of IORT however requires specialised facilities and can be associated with severe complications.

EBRT (with concomitant chemotherapy) following resection is generally well tolerated but the degree of survival advantage, if any, is uncertain. To address this issue a multicentre Phase III trial organized by the European Organisation for Research and Treatment of Cancer (EORTC) compared chemoradiotherapy in patients following potentially curative surgery for pancreatic cancer with surgery alone[58]. Between 1987 and 1995, 218 patients were randomized to receive either chemoradiotherapy or no chemoradiotherapy following curative surgery for pancreatic or ampullary cancer. Ninety-three out of 110 patients randomized to treatment received a total of 40 Gy with concomitant continuous infusion of 5-FU. There were a total of 54 patients in the observation group and 60 patients in the treatment group with pancreatic ductal adenocarcinoma. There was no significant difference in median survival (with treatment 17.1 months *vs* 12.6 months with observation) and in five year survival [with treatment 20 (95% CI, 5-35)% *vs* 10 (0-20)% with observation]. Similarly there was no significant difference in survival between the treatment and observation groups in patients with ampullary cancer. This study showed that there was no survival advantage for adjuvant chemoradiotherapy for pancreatic and ampullary cancer but has been criticized because it was almost certainly underpowered.

REGIONAL THERAPY

Advanced pancreatic cancer

Regional therapy has been developed with the objective of

delivering high doses of cytotoxic drug to the tumour. The systemic side effects should be reduced with this approach. The coeliac and hepatic arteries and portal vein have all been used to deliver chemotherapeutic drugs to the tumour bed. Good control of hepatic metastases has been reported, with disease progression mainly due to local progression or peritoneal deposits. The combination of 5-FU, folinic acid and cisplatin produced median survival times of 9-14 months in selected patients[63,64]. It has also been reported that some apparently irresectable tumours have become resectable following regional therapy[64].

Adjuvant regional therapy

There have been several studies which have demonstrated improved survival in patients receiving regional chemotherapy following pancreatic resection largely in comparison with historical controls (Table 3)[65-68]. Link *et al*[69] found a median survival of 21 months in 18 patients who had undergone pancreatoduodenectomy for pancreatic ductal adenocarcinoma and then coeliac artery infusion of 5-FU, folinic acid, mitoxantrone and cisplatin compared to 9.3 months for historical controls. Disease progression occurred principally locally or in the peritoneum and was rarely detected in the liver. The rate of hepatic recurrence was greatly reduced using a combination of hepatic artery and portal vein infusion in patients with resected pancreatic, which in one study cancer produced a 54% three-year survival compared to 34% in historical controls[65]. Ozaki *et al*[66] found a 5-year survival rate of 32% patients treated with extended resection, IORT and hepatic artery and portal vein. The encouraging results of these small studies have prompted the ESPAC-2 trial, which is a multicentre, prospective randomized controlled Phase III trial. This study will compare adjuvant intra-arterial chemotherapy (cisplatin, 5-FU, folinic acid and mitoxantrone) and radiotherapy (Arm A) with surgery alone (Arm B) in patients who have undergone potentially curative resection for pancreatic ductal adenocarcinoma or ampullary carcinoma. The trial will recruit 110 patients into each arm and will be completed by 2007 aiming to provide a definitive answer to the role of adjuvant regional therapy for pancreatic cancer.

Table 1 Survival following surgery and adjuvant chemotherapy for pancreatic cancer

Series	Period	Number		Regimen	Median survival (months)	Actuarial survival (%)		
		Total	PDAC			1 year	3 year	5 year
Splinter *et al*[43]	1977-1984	36	18				28	
	1980-1984	16	9	5-FU / DOX / MMC			24	
Livingstone *et al*[44]	N / A	285	285	N / A				9
Bakkevold *et al**[45]	1984-1987	30	23	5-FU / DOX / MMC	23	70	70	4
		31	24		11	45	30	8
Baumel *et al*[46]	1982-1988	43	43	Not specified	12			
	1982-1988	527	527		12			

5-FU = 5-fluorouracil; DOX = doxorubicin; MMC = mitomycin C; * randomised cont rolled trial, PDAC = pancreatic ductal adenocarcinoma.

Table 2 Survival following surgery and radiotherapy for pancreatic cancer

Series	Year	Number	EBRT(Gy)	IORT(Gy)	Median survival (months)	Actuarial survival (%)		
						1 year	3 year	5 year
Willett *et al*[32]	1993	16 (nm)	40-50		21			29
		23 (pm)	40-50		11			0
Johnstone *et al*[53]	1993	26	45-55	20	18			
Zerbi *et al*[21]	1994	43		12.5-20	19	71	7	
		47			12	49	10	
Di Carlo *et al*[54]	1997	27			14			
		27		12.5-2017				
Dobelbower *et al*[55]	1997	14			6.5	15	0	0
		6		10-20	9	50	35	33
		14	50-67		14.5	64	28	0
		10	27-54	10-25	18	70	10	0
Farrell *et al*[56]	1997	14	60	12-25	16	62	22	15
Hishinuma *et al*[57]	1998	34	24 EBRT	13 EBRT + IOR	13	59		19
Klinkenbijl *et al**[58]	1999	54pdc			12.6			10
		60pdc	40		17.1			20
Mehta *et al*[59]	2000	52	45-54	8 IORT	32	75	38	
Lee *et al*[60]	2000	22					47	
		13	49				81	

EBRT = external beam radiotherapy; IORT = intraoperative radiotherapy; nm = nega tive resection margin; pm = positive resection margin; pdc = pancreatic ductal adenocarcinoma.

Table 3 Adjuvant regional therapy for pancreatic cancer

Series	Year	Number	Regimen	Median survival (months)	Actuarial survival (%)		
					1 year	3 year	5 year
Ishikawa *et al*[65]	1994	20	HAI + PVI			54	
Ozaki *et al*[66]	1994	24	IORT + HAI +/- PVI				32
Link *et al*[67]	1997	20	CAI	21			
		29		9.3			
Beger *et al*[68]	1999	24	CAI	23			54 (4 year)
		nd		10.5			9.5 (4 year)

HAI = hepatic arterial infusion; PVI = portal vein infusion; CAI = coeliac artery infusion

NEOADJUVANT THERAPY

The rationale for pre-operative therapy includes (a) the avoidance of long delays following surgery before starting adjuvant therapy and (b) an attempt to downstage the tumour and thereby increase the prospect of resection (Table 4)[70-77]. Pre-operative radiotherapy produced only modest increases in resectability and so chemotherapy was added in an attempt to improve the efficacy of this approach. Recent studies have reported resection rates as high as 60%[70-77] but not surprisingly those tumours >4cm-cm, encase the superior mesenteric artery or obstruct the superior mesenteric/ hepatic portal vein are less likely to be resected[71,73]. Pre-operative chemoradiotherapy may also increase the incidence of clear resection margins to as high as 90%, compared to the accepted norm of 60%-80%.

The effect of any long-term survival benefit from neoadjuvant treatment, if any, is not known due to the lack of randomized controlled studies. Twenty- four out of 53 patients with pancreatic ductal adenocarcinoma initially treated with 5-FU, mitomycin C and 50.4 Gy were able to undergo resection with a medi an survival of 15.7 months[74]. There was a significant level of toxicity associated with this regimen with two treatment related deaths. Another recent non-randomized study found a median survival of 19.2 months for patients with pancreatic cancer treated by pre-operative chemoradiation compared to 22 months for those treated by post-operative chemoradiation. Neither survival nor the pattern disease of recurrence was significantly different between the two groups[73].

COMBINATION THERAPY

Advanced pancreatic cancer

The combination of chemoradiation and follow-on chemotherapy may enable good local control with systemic destruction of the disease. The Gastrointestinal-Tumour Study Group (GITSG) randomized patients with advanced pancreatic cancer to receive either 60Gy EBRT (with radiosensitizing 5-FU) with or without follow-on 5-FU versus 40Gy EBRT with radiosensitizing 5-FU and follow-on 5-FU. The median survival times were 40, 23 and 42 weeks respectively, indicating a- likely valuable role for radiosensitizing (± follow-on)chemotherapy but not for increased radiotherapy[78]. Other combinations have been evaluated in the palliative setting[79]. A randomized trial of IORT versus IORT and methotrexate/5-FU produced a median survival of 4.8 and 8.5 months respectively[80].

Adjuvant combination therapy

The regimen originally adopted by the GITSG for patients with advanced pancreatic cancer was used in the adjuvant setting for a randomized trial in the 1970's . Forty-three patients were randomized to receive either 40Gy (with radiosensitizing 5-FU) then weekly 5-FU or surgery alone. The median survival in the treated group was 20 months compared to 11 months in the surgery only group and the two year survival rates were 42% and 15% respectively[81]. To increase numbers in the treatment group a further 30 patients received adjuvant therapy. The median survival was 18 months with a two year survival of 46%[82]. The number of patients that received treatment as part of the randomized study however was far too small for convincing conclusions to be drawn. The results were encouraging enough for other studies to adopt this protocol and investigate its role in the treatment of pancreatic cancer (Table 5)[81-88]. Yeo *et al*[84]compared three different regimens in selected patients who had undergone pancrea toduodenectomy: ① 40-45Gy EBRT plus follow-on 5-FU for 4 months (standard); ② 50-57Gy EBRT plus hepatic radiation plus 5-FU + folinic acid for 4 months (intensive); ③ no adjuvant treatment. The median survival was 21 months and the two-year survival was 44% for the group given standard adjuvant treatment, significantly better compared to 13.5 months and 30%, respectively in the no treatment group. There was no significant survival difference however between patients that had received the intensive treatment and those that had received no treatment. The main drawbacks to this study are the retrospective data that suffer from patient selection bias and no specification of patient performance status, which is an extremely important independent prognostic factor.

A phase III randomized controlled study organised by the Radiation Therapy Oncology Group (RTOG) in the USA is currently recruiting patients who have undergone resection for pancreatic adenocarcinoma. This study aims to compare 5-FU versus gemcitabine pre- and post- chemoradiotherapy all following surgery. The trial has already accrued the original 330 patient target but is still recruiting, presumably because of a lack of a significant therapeutic effect so far.

The UK Pancreatic Cancer Trials Group (UKPACA)[85] utilized the GITSG protocol for an open phase II study of 40 patients (34 with pancreatic ductal adenocarcinoma and 6 with ampullary tumour) who had undergone-pancreatoduodenectomy between 1987 and 1993 were recruited. Patients received 40Gy (with 5-FU as a radiosensitizer) plus 5-FU weekly for a maximum of 24 weeks. After a median of eight treatments there were no treatment related deaths and no hospitalizations even with a prolonged course of post-operative chemotherapy. The median survival for patients with pancreatic ductal adenocarcinoma was 13.2 months and the five-year survival rate was 15%.

The findings of these studies were instrumental in the design of the ESPAC-1 trial, which commenced in 1994. This trial was established to compare the effects of three adjuvant treatments with a control group. The four groups were: ① chemoradiotherapy (40Gy with radiosensitizing 5-FU); ② chemotherapy (5-FU plus folinic acid for six months); ③ combination chemoradiotherapy followed by chemotherapy; and ④ best supportive care. Patients were eligible following potentially curative resection for pancreatic ductal adenocarcinoma. Between February 1994 and April 2000 a total of 591 patients were randomized of which 541 had pancreatic ductal adenocarcinoma. A total of 61 centres recruited patients from UK, Ireland, France, Sweden, Spain, Italy, Germany, Switzerland, Greece, Hungary, Belgium and Austria. Randomization was stratified by resection margin status. Clinicians could randomize patients into a 2×2 factorial design (obse rvation, chemoradiation, chemotherapy or combination) or into one of the main treatment comparisons (i.e. chemoradiation *vs* control or chemotherapy *vs* control). Two-hundred and eighty five patients were randomized to the 2×2 factorial design, a further 68 patients were randomized to chemoradiation *vs* no chemoradiation and 188 patients were randomized to chemotherapy *vs* no chemotherapy. Tumour grade, size, nodal status and resection margin status were all significantly associated with survival. The overall results showed no benefit for chemoradiation *vs* no chemoradiation (median survival 15.5 months *vs* 16.2 months respectively). There was evidence of a survival benef it for

chemotherapy (median survival 19.7 months) compared to those patients who did not receive chemotherapy (median survival 14 months). The effect was reduced when taking into account whether patients had also received chemoradiation suggesting that chemoradiation may decrease the benefit of chemotherapy[89]. Moreover quality of life analysis showed no significant difference between any of the groups indicating that adjuvant therapy in pancreatic cancer is worthwhile, provided there is a significant prolongation of life[90].

The results of ESPAC-1 have provided for the first time a clear indication of a potential benefit for the use of chemotherapy in the treatment of pancreatic cancer. Even more importantly both ESPAC-1 and the EORTC trials have rejected the use of chemoradiation as adjuvant therapy in pancreatic cancer. Thus the focus of future studies such as ESPAC-3 will be on new and efficacious chemothe rapy regimens. This study is randomizing patients to three arms: 5-FU+folinic acid, gemcitabine and observation. The power of the study is such to detect a 10% difference in 2-year survival between any of the groups. Thus ESPAC-3 will establish (a) the benefit of adjuvant chemotherapy for pancreatic cancer and (b) if such, then the best form of chemotherapy.

Table 4 Neoadjuvant therapy for pancreatic cancer

Series	Year	Number	Regimen	Resection rate		Positive resection margin (*n*)	Median survival (months)	Actuarial survival (%)	
				n	%			3 year	5 year
Ishikawa *et al*[70]	1994	23	EBRT	17/23	74				22
Coia *et al*[71]	1994	27	EBRT + 5-FU + MMC	13/27	48	0/13	16	43	
Staley*et al*[72]	1996	39	EBRT + 5-FU + IORT	39/39	100	7/39	19		19 (4 year)
Spitz *et al*[73]	1997	41	EBRT + 5-FU	41/91	51	5/41	19.2		
Hoffman *et al*[74]	1998	53	EBRT + 5-FU + MMC	24/53	45		15.7		
White *et al*[75]	1999	25	5-FU + EBRT + MMC +CPP	5/25	20				
Wanebo *et al*[76]	2000	14	5-FU + EBRT +CPP	9/14	64				
Snady *et al*[77]	2000	68	EBRT+5-FU+STREP+CPP	20/68	29		32	32	
				48 NR	71		21	13	

EBRT = external beam radiotherapy; 5-FU = 5-fluorouracil; MMC= mitomycin C; IORT = intraoperative radiotherapy; STP = streptozocin; CDDP = cisplatinum; FA = folinic acid; DPD = dipyridamole; n = number; CPP=cisplatin; NR = not resectable.

Table 5 Results of combination therapy in patients who have undergone resection for pancreatic cancer

Series	Year	Number	Radiotherapy (Gy)	Chemotherapy	Median survival (months)	Actuarial survival (%)			
						1 year	2 year	3 year	5 year
Kalser *et al**[81]	1985	21	EBRT 40	5-FU	20	67	42	24	18
		22			11	50	15	7	8
GITSG[82]	1987	30	EBRT 40	5-FU	18		46		
Conlon *et al*[83]	1996	56	EBRT 45	5-FU	20		35		
Yeo *et al*[84]	1997	53			13.5		30		
		99	EBRT 40-45	5-FU	21		44		
		21	EBRT 50-57	5-FU + FA	17.5		22		
UKPACA[85]	1998	35	EBRT 40	5-FU	13	56	38	29	15
Abrams *et al*[86]	1999	23	EBRT	5-FU + FA	15.9				
Paulino *et al*[87]	1999	30	EBRT	5-FU	26				
		8	EBRT		5.5				
André *et al*[88]	2000	10	EBRT	5-FU + FA + CPP	17				

EBRT = external bean radiotherapy; 5-FU = 5-fluorouracil; FA = folinic acid; CPP = cisplatin

CONCLUSION

This is a very encouraging time for the treatment of pancreatic cancer. The results of these large European trials have at last given clear indications for future therapies of pancreatic cancer. By using this information, reasoned approaches are being developed to improve the treatment of patients with pancreatic cancer without sacrificing quality of life.

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