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Adjuvant therapy in pancreatic cancer

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Abstract

Pancreatic cancer remains one of the leading causes of cancer related death worldwide with an overall five-year survival of less than 5%. Potentially curative surgery, which alone can improve 5-year survival to 10%, is an option for only 10%-20% of patients at presentation owing to local invasion of the tumour or metastatic disease. Adjuvant chemotherapy has been shown to improve 5-year survival to 20%-25% but conflicting evidence remains with regards to chemoradiation. In this article we review the current evidence available from published randomised trials and discuss ongoing phase III trials in relation to adjuvant therapy in pancreatic cancer.

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Key words: Pancreatic cancer; Adjuvant; Gemcitabine; Chemotherapy; Chemoradiotherapy; Phase III

Core tip: This paper discusses every major trial undertaken in the field of adjuvant therapy in pancreatic cancer. The evolution of chemotherapeutic regimes over the past 25 years and the controversy surrounding chemoradiation are analysed, in addition to looking at the phase III trials currently in progress.

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INTRODUCTION

Despite accounting for only 2.2% of all cancers, pancreatic ductal adenocarcinoma is the fourth most common cause of cancer related death in the world^[1]. In 2008 there were 279000 new cases worldwide with 266000 deaths from the disease, reflecting its dismal prognosis. Owing to the majority of patients presenting with locally advanced and metastatic disease, the overall survival rates at one and five years after diagnosis are 19% and 0.4%-4%^[2] respectively. Surgery is the single most important factor in improving outcome but only 10%-20% of patients are candidates for such treatment which can improve the five-year survival rate to 10%^[3]. This modest survival benefit is due to the high prevalence of both local recurrence and distant metastases due to residual microscopic disease. In recent years, interest has increased exponentially in both neoadjuvant and adjuvant strategies to improve these outcomes.

ADJUVANT CHEMOTHERAPY

A handful of chemotherapy regimens had been utilised in locally advanced and metastatic pancreatic cancer in the 1970s and 1980s with limited success. Response rates of 30%-43%^[4] were reported and though these patients achieved some survival benefit, this evidence was not strong enough to recommend its routine use in all patients. Mallinson *et al*^[5] was amongst the first to publish on the benefit of 5-fluorouracil (5-FU) based chemotherapy in the palliative setting of pancreatic cancer, reporting a median survival of 44 wk in those receiving treatment against only 9 wk in controls. In 1993, a Norwegian group^[6] was first to publish a randomised study assessing

the role of adjuvant chemotherapy in resected pancreatic cancer (Table 1). Sixty-one patients (47 pancreatic and 14 ampullary cancers) were divided into two treatment arms - one to undergo surgery alone and the second to undergo adjuvant chemotherapy. This adjuvant therapy consisted of 5-FU 500 mg/m², doxorubicin 40 mg/m² and mitomycin C 6 mg/m² every 3 wk for six cycles. Median survival was improved to 23 mo with adjuvant chemotherapy in comparison to 11 mo in those undergoing observation alone ($P = 0.04$). One-year survival improved to 70% with chemotherapy as opposed to 45% in the observation group but unfortunately this did not translate into a longer-term survival benefit. A potential explanation may be the high toxicity rate in the treatment group, which resulted in only 56% completing the prescribed chemotherapy course.

The landmark ESPAC-1^[7] (European Study Group for Pancreatic Cancer) study was designed to determine whether adjuvant chemoradiotherapy or adjuvant chemotherapy alone had a role in improving survival following pancreatic cancer resection. This was the first adequately powered randomised trial to assess adjuvant therapy in pancreatic cancer, recruiting 541 patients over a six year period in 61 centres internationally. Inclusion criteria consisted of patients having made a full recovery from a macroscopically resected pancreatic ductal adenocarcinoma, with a life expectancy of over 3 mo. Two hundred and eighty five patients were randomised in a two-by-two factorial design to receive chemoradiotherapy alone, chemotherapy alone, both or observation. In addition to this 2 × 2 design, a further 256 patients were also randomised to receive either chemoradiotherapy, chemotherapy, or observation (Individual treatment groups). Chemotherapy consisted of a 20 mg/m² intravenous bolus of folinic acid, followed by a further intravenous bolus of 5-FU (425 mg/m²) to be administered on days 1-5 of a 28 d cycle, over 6 cycles.

With a median follow-up of 10 mo [range 0-62, interquartile range (IQR) 1-25] for surviving patients, initial results were suggestive of a significant improvement in outcome in those receiving chemotherapy when considering the entire study population. Median survival was 19.7 mo (95%CI: 16.4-22.4) in those receiving chemotherapy, against 14 mo (95%CI: 11.9-16.5) in those not receiving any [hazard ratio (HR) = 0.66, 95%CI: 0.52-0.83, $P = 0.0005$]. However, this significance was lost when analysing those patients in the 2 × 2 design alone (17.8 mo *vs* 15.8 mo, HR = 1.3, 95%CI: 0.96-1.77, $P = 0.09$).

The final analysis of the 2 × 2 ESPAC-1 data^[8] was based on 237 deaths in 289 patients with a median follow up of 47 mo (IQR 33-62 mo). Median survival was 20.1 mo (95%CI: 16.5-22.7) amongst patients who had undergone chemotherapy *vs* 15.5 mo (95%CI: 13-17.7) in those who had not (HR = 0.71, 95%CI: 0.55-0.92, $P = 0.009$). The estimated two and five year survival was 40% *vs* 21% and 21% *vs* 8% respectively in those who received chemotherapy against patients which had not.

Exclusive to the 2 × 2 study design, the cohort of 75

patients that received chemotherapy alone fared significantly better than those who underwent observation ($n = 69$). Median survival was 21.6 mo (95%CI: 13.5-27.3) *vs* 16.9 mo (95%CI: 12.3-24.8) and estimated five-year survival was 29% *vs* 11%. ESPAC-1 established 5-FU and folinic acid as the drug of choice in the adjuvant treatment of pancreatic cancer.

Takada *et al*^[9] recruited a total of 508 patients with various resected pancreaticobiliary cancers which included 173 pancreatic malignancies. Though this multicentre randomised controlled trial recruited patients between 1986 and 1992, it was published later than ESPAC-1, in 2002. Patients were randomised in this study to receive either adjuvant mitomycin C (rapid intravenous infusion of 6 mg/m² on the day of surgery) and 5-FU (310 mg/m² for days 1-5 of postoperative weeks 1 and 3, followed by a daily dose of 100 mg/m² from week 5 until disease recurrence) or surgery alone. In the pancreatic subset of patients, this chemotherapy regime showed no significant improvement in 5-year survival or 5-year disease free survival. Unusually, this study utilised oral 5-FU as opposed to the usual intravenous form which may offer a reason for its ineffectiveness.

Kosuge *et al* (JSAP)^[10] published a randomised trial evaluating adjuvant cisplatin (80 mg/m² on day 1) and 5-FU (continuous infusion of 500 mg/m² on days 1-5) with a second cycle of chemotherapy 4-8 wk after the first. As only those having undergone a R0 resection for ductal pancreatic cancer were included, only 89 patients were recruited over 8 years, resulting in an underpowered study. No significant difference was identified in median survival, 5-year survival and 5-year disease-free survival in comparison to patients undergoing surgery alone. It must be mentioned that approximately two-thirds of these patients also underwent 30 Gy of intraoperative radiotherapy on a non-randomised basis, but this therapy proved insignificant as a prognostic indicator in a multivariate analysis.

In 1997, Burris *et al*^[11] published their randomised control trial comparing the nucleoside analogue gemcitabine with 5-FU in advanced pancreatic cancer. In addition to demonstrating a clinical benefit with regards to pain relief, weight and performance status, those receiving gemcitabine achieved a one-year survival rate of 18% as opposed to 2% with 5-FU. These findings resulted in the recruitment of patients for CONKO-001^[12] between 1998 and 2004. This randomised study compared adjuvant gemcitabine (six cycles of a 30 min intravenous infusion at 1000 mg/m² during weeks 1-3 followed by a break at week 4) with observation alone in patients undergoing a curative pancreatic cancer resection. In addition to clinical follow up and serum biochemistry checks, two-monthly ultrasound scans were performed to assess any recurrence. A computed tomography (CT) scan was also performed at the termination of chemotherapy (gemcitabine group) or at six months (observation group). Three hundred and sixty eight patients were recruited with a median follow-up of 53 mo. The main

Table 1 Major adjuvant chemotherapy trials in pancreatic cancer

Year published	Author/group	Treatment arms (n)	Final analysis			Survival (95%CI)					Disease-free survival (DFS)(95%CI)						
			T3	N+	RO	Median survival (mo)	1-yr survival	2-yr survival	3-yr survival	5-yr survival	Median DFS (mo)	1-yr DFS	2-yr DFS	3-yr DFS	5-yr DFS		
1993	Bakkevoild	5-FU/ doxorubicin/ mitomycin (30)	NA	NA	100%	23	-	70%	27%	4%	-	-	-	-	-	-	-
2001	ESPAC-1 (all patients)	Surgery alone (31) 5-FU/folinic acid +/- CRT (238)	NA	53%	82%	11 (P = 0.02) 19.7 (16.4-22.4)	-	45%	30%	8% (P = 0.1)	-	-	-	-	-	-	-
		No chemotherapy +/- CRT (235)				14 (11.9-16.5) (HR = 0.66, 0.52-0.83, P = 0.0005)											
2002	Takada	5-FU/ mitomycin C (89)	NA	85%	58%	NA	-	-	-	11.5%	-	-	-	-	-	-	8.6%
2004	ESPAC-1 (2 x 2 final analysis)	Surgery alone (84) 5-FU/folinic acid (147)	NA	54%	82%	20.1 (16.5-22.7)	-	40%	-	18% (log rank NS)	-	-	-	-	-	-	7.8% (log rank P = 0.84)
		No chemotherapy +/- CRT (142)				15.5 (13-17.7) (HR = 0.71, 0.55-0.92, P = 0.009)		30%		8%							
2006	JSAP (Kosuge)	Cisplatin/5- FU (45)	NA	27%	100%	12.5	-	-	-	26.4%	-	-	-	-	-	-	-
		Surgery alone (44)				15.8				14.9% (P = 0.94)							
2007	CONKO-001 (Oettle)	Gemcitabine (179)	86	72%	83%	22.1 (18.4-25.8)	72.5%	47.5%	34%	22.5%	13.4 (11.4-15.3)	58%	30.5%	23.5%	16.5%	16.5%	16.5%
		Surgery alone (175)				20.2 (17-23.4) (P = 0.06)	72.5%	42%	20.5%	20.5%	6.9 (6.1-7.8) (P < 0.001)	31%	14.5%	7.5%	5.5%	5.5%	5.5%
2008	CONKO-001 Final (Neuhaus)	Gemcitabine (179)				22.8	-	-	36.5	21	13.4	-	-	23.5	16.0	16.0	16.0

Year	Study	Intervention	Control	HR	95% CI	P	9%	19.5%	24%	26.7%	27.2%	8.5%	6.5%
2009	JSAP-2 (Ueno)	Surgery alone (175)	86%	20.2	(16.1-30.7)	0.005	9%	19.5%	24%	26.7%	27.2%	8.5%	6.5%
		Gemcitabine +/- RT (58)	69%	22.3	(16.1-30.7)	0.005	23.9%	-	49%	49%	-	-	-
2009	Collated data ESPAC-1, ESPAC-1 plus, ESPAC-3(v1)	Surgery alone +/- RT (60)	84%	18.4	(15.1-25.3)	0.001	10.6%	48.3%	49%	26.7%	16.7%	-	-
		5-FU/folinic acid (233)	55%	23.2	(20.1-26.5)	0.001	24%	-	-	-	-	-	-
2010	ESPAC-3(v2)	Surgery alone (225)	NA	16.8	(14.3-19.2)	0.003	14%	-	37%	63%	30.7%	-	-
		5-FU/folinic acid (551)	72%	23	(21.1-25)	0.003	-	48.1%	78.5%	56.1%	56.1%	30.7%	-
2010	ESPAC-3(v2)	Gemcitabine (537)	NA	23.6	(21.4-26.4)	0.001	-	49.1%	80.1%	61.3%	29.6%	-	-
		5-FU/folinic acid (551)	72%	23.6	(21.4-26.4)	0.001	-	49.1%	80.1%	61.3%	29.6%	-	-
2013	IASPAC-01	S-1 (187)	87%	46.3	(39.1-55.4)	0.0001	-	70%	53%	29%	49%	-	-
		Gemcitabine (191)	63%	25.5	(21.4-30.7)	0.0001	-	53%	53%	29%	49%	-	-

CRT: Chemoradiotherapy; NA: Not available; NS: Not significant; 5-FU: 5-fluorouracil.

outcome of this study was that gemcitabine significantly improved disease-free survival following pancreatic cancer resection. Median disease-free survival in the gemcitabine group was 13.4 mo (95%CI: 11.4-15.3) as opposed to only 6.9 mo (95%CI: 6.1-7.8) in the observation group ($P < 0.001$). Importantly, this significant disease-free survival benefit was maintained whether patients had undergone an R0 or R1 resection. With regards median overall survival, the gemcitabine benefit was only marginal in comparison to the observation group (22.8 mo *vs* 20.2 mo, $P = 0.005$)^[13]. This minimal difference is potentially explained by the authors by the fact that almost all patients that relapsed in the observation group received gemcitabine or a further line of chemotherapy. However, this study established gemcitabine as the favoured adjuvant chemotherapeutic agent particularly due to its excellent toxicity profile in comparison to 5-FU.

Coincidentally, at the same time as CONKO-001, a further study to compare adjuvant gemcitabine and observation was being undertaken. One hundred and nineteen patients were recruited between 2002 and 2005 for JSAP-2^[14], with a median follow up for surviving patients of over five years. Gemcitabine resulted in a median disease-free survival of 11.4 mo (95%CI: 8-14.5) against 5 mo (95%CI: 3.7-8.9) in the observation group (HR = 0.60, 95%CI: 0.40-0.89, $P = 0.01$). This however did not convert to a significant benefit in overall survival as the study was underpowered. Another factor may be that though this study utilised an identical gemcitabine dosage regimen as used in CONKO-001, only three cycles were administered as opposed to the six used in the European study. It must also be noted that the median number of days between surgery and randomisation was nearly double that of CONKO-001. Just over half of patients in this study (52%) also received intraoperative radiotherapy, though the authors argue that this effect may have been negligible.

Following on from the ESPAC-1 study, the group undertook another randomised controlled trial, ESPAC-3 to compare 5-FU and folinic acid (as per the ESPAC-1 regime),

Table 2 Meta-analyses of adjuvant chemotherapy in pancreatic cancer

Year published	Author	Arm (n)	Survival (95%CI)		
			Median survival (mo)	2-yr survival	5-yr survival
2005	Stocken <i>et al</i> ^[20]	CT (348)	19 (16.4-21.1)	38%	19%
		No CT (338)	13.5 (12.2-15.8)	28%	12%
2007	Boeck <i>et al</i> ^[24]	CT (482)	3 mo (0.3-5.7) survival benefit with CT <i>vs</i> no CT (<i>P</i> = 0.03)	-	3.1% (-4.6%-10.8%) survival benefit with CT <i>vs</i> no CT (<i>P</i> > 0.05)
		No CT (469)			
2008	Butturini <i>et al</i> ^[25]	R0 resections			
		CT (236)	20.8 (17.7-23.2)	42% (35%-48%)	22% (17%-28%)
		No CT (222)	13.8 (12.2-16.4)	27% (21%-33%)	10% (5%-14%)
		R1 resections			
2013	Liao <i>et al</i> ^[26]	CT (109)	15 (11.7-18.1)	29% (20%-38%)	14% (7%-21%)
		No CT (114)	13.2 (10.5-17.6)	31% (22%-40%)	17% (10%-24%)
		Hazard ratio for death (95%CI)			
		Flurouracil (876)	0.62 (0.42-0.88)		
	Observation (670)				
	Gemcitabine (774)	0.68 (0.44-1.07)			
	Observation (670)				
	Gemcitabine (774)	1.1 (0.70-1.86)			
	Flurouracil (876)				

CT: Chemotherapy.

gemcitabine (as per CONKO-001 regime) and surgery alone in resected pancreatic cancer. During recruitment however, the publication of ESPAC-1 proved the undoubted benefit of adjuvant chemotherapy. This resulted in the observation arm being forfeited and the study was renamed ESPAC-3(v2)^[15].

ESPAC-3(v2) was the largest study of its kind, recruiting 1088 patients with pancreatic ductal adenocarcinoma in 159 centres worldwide over a seven year period. With a median follow-up of 34.2 mo (range: 0.4-86.3 mo, IQR 27.1-43.4), no significant difference was shown in overall survival or progression-free survival between the two treatment groups. However, gemcitabine halved the number of serious treatment-related adverse events compared to its opposing arm (14% *vs* 7.5% of patients, *P* < 0.001). It was also noted a more favourable outcome was achieved in patients with node positive disease or an R1 resection when administered gemcitabine. This firmly established the drug as the current gold standard in the adjuvant treatment of pancreatic cancer.

A meta-analysis in 2009^[6] combined data from a subgroup of ESPAC-3(v1) with ESPAC-1 2 × 2 and ESPAC-1 Plus (a subgroup of 192 patients in a randomised comparison between 5-FU and observation +/- chemoradiation). The purpose of this publication was to ascertain the benefit of adjuvant 5-FU and folinic acid (*n* = 233) as opposed to surgery alone (*n* = 225). Median survival was 23.2 mo (95%CI: 20.1-26.5) in the chemotherapy group, in comparison to 16.8 mo (95%CI: 14.3-19.2) in those patients in the observation arm (HR = 0.7, 95%CI: 0.55-0.88, *P* = 0.003). Chemotherapy also improved overall survival at one, two and five years, providing robust evidence for the continued use of 5-FU and folinic acid in the adjuvant setting alongside gemcitabine.

The most recently published randomised controlled trial, JASPAC-01^[17] enrolled 385 patients between 2007

and 2010 to compare adjuvant gemcitabine with fluorinated pyrimidine S-1 in resected pancreatic cancer. The gemcitabine regime was identical to CONKO-001 with an S-1 regime of four cycles of 80 mg/m² per day for four weeks, followed by a fortnight rest. Promising interim results were presented in 2012^[18] with an overall 2-year survival of 53% and 70% in the gemcitabine and S-1 groups respectively (HR = 0.56, 95%CI: 0.42-0.74, *P* < 0.0001). S-1 also proved superior with regards to recurrence-free survival at 2-years with 49% of patients remaining disease-free compared with 29% in the gemcitabine cohort (HR = 0.56, 95%CI: 0.43-0.71, log-rank *P* < 0.0001). S-1's comparatively low toxicity in addition to the fact that S-1 is orally administered, would be partly responsible for the superior quality of life scores in this group (*P* < 0.0001). Though the authors concluded that S-1 should be considered the new standard treatment for resected pancreatic cancer, there is doubt whether this agent will ever be of broad benefit in the West. It has been stated that due to the metabolic differences between Asian and Caucasian populations, gastrointestinal side effects are far greater in the latter leading to lower tolerated doses of S-1^[19].

META-ANALYSIS OF ADJUVANT CHEMOTHERAPY IN PANCREATIC CANCER

The first meta-analysis assessing adjuvant therapy in pancreatic cancer was published in 2005 (Table 2). Stocken *et al*^[20] included five randomised trials [Bakkevold *et al*^[6], ESPAC-1^[7], Takada *et al*^[9], EORTC^[21] and Gastrointestinal Study Group (GITSG)^[22,23] to evaluate the effects of both chemotherapy and chemoradiotherapy in the adjuvant setting (*n* = 939). With the exception of GITSG, the authors collected individual patient data from each

of these studies ($n = 875$) to produce as accurate a results as possible. When collating results from the three chemotherapy trials, heterogeneity was affected with the addition of the Japanese results ($\chi^2 = 11.7$, $P = 0.009$ when included, $\chi^2 = 2.5$, $P = 0.29$ without). The authors suggest that this was due to the large number of R1 resections included in that particular study. Nevertheless, analysis of the dataset both including and excluding this study resulted in reductions of 25% (HR = 0.75, 95%CI: 0.64-0.9, $P = 0.001$) and 35% (HR = 0.65, 95%CI: 0.54-0.8, $P < 0.001$) respectively in the risk of death with adjuvant chemotherapy. Median survival was estimated to be 19 mo (95%CI: 16.4-21.1) with chemotherapy and 13.5 mo (95%CI: 12.2-15.8) without.

A later meta-analysis^[24] included the five randomised trials comparing adjuvant chemotherapy to observation (Bakkevold *et al*^[6], ESPAC-1^[7], Takada *et al*^[9], JSAP^[10] and CONKO-001^[12]). Median survival data was available from all studies with the exception of Takada *et al*^[9], with no significant heterogeneity between the remaining four conflicting studies ($P = 0.07$). Meta-analysis indicated a significant survival benefit of 3 mo (95%CI: 0.3-5.7, $P = 0.03$) in patients receiving adjuvant chemotherapy as opposed to observation. However, adjuvant treatment translated into only a 3.1% benefit in 5-year survival which proved insignificant.

A third meta-analysis looked specifically at adjuvant therapy in relation to resection margins^[25]. This meta-analysis was supportive of adjuvant chemotherapy, indicating a 25% reduction in the risk of death with treatment as opposed to observation (HR = 0.75, 95%CI: 0.64-0.9, $P = 0.001$). Patients undergoing a clear-margin resection benefited from a 7-mo survival increase with chemotherapy (median survival of 20.8 mo *vs* 13.8 mo), but the effect was less pronounced in R1 resections (median survival of 15 mo *vs* 13.2 mo). This finding was in agreement with Stocken who noted that chemotherapy was less effective in patients with a positive resection margin.

A recently published network meta-analysis^[26] has examined overall survival in patients receiving adjuvant gemcitabine or 5-FU in comparison to observation. Results suggested that adjuvant therapy with either gemcitabine ($n = 774$) or 5-FU ($n = 876$) showed a survival benefit in comparison with observation alone ($n = 670$) with hazard ratios of 0.68 (95%CI: 0.44-1.07) and 0.62 (95%CI: 0.42-0.88) respectively. No significant survival difference was noted in comparing adjuvant gemcitabine and 5-FU, though grades 3-4 non-haematological toxicity was almost four-times as common in patients receiving the latter drug.

ADJUVANT CHEMORADIOTHERAPY

GITSG^[22] was the first randomised trial evaluating the role of adjuvant therapy in pancreatic cancer (Table 3). In non-resectable patients, previous studies had shown the benefit of both radiotherapy^[27] and 5-FU combined with radiotherapy^[28] and on this basis GITSG compared

adjuvant 5-FU chemoradiation *vs* no adjuvant therapy. Though the study population was small ($n = 43$), final analysis of the data revealed a substantial median survival benefit with treatment (21 mo) in comparison to no treatment (10.9 mo). Following this evidence, chemoradiotherapy became a standard adjuvant treatment option for pancreatic cancer patients in the United States^[29]. A decade later, the findings from GITSG were supported by a prospective, non-randomised study. Yeo *et al*^[30] offered two different chemoradiotherapy regimes (standard or intensive) or observation. Patients undergoing adjuvant treatment reported a median and one-year survival of 19.5 mo and 80%, in comparison to 13.5 mo and 54% in those undergoing observation ($P = 0.003$). Multivariate analysis also supported a survival benefit to those receiving either standard ($P < 0.001$) or intensive therapy ($P = 0.04$).

The EORTC study^[21] was undertaken across twenty nine European centres and included 218 patients who had undergone resection for pancreatic or ampullary lesions. One hundred and fourteen of these were for pancreatic head cancers and those tumours graded as T3 \leq or N1b nodal disease were excluded from the study. Patients were assigned surgery alone or to additionally receive two four-week cycles of adjuvant 5-FU and concurrent radiotherapy. Treatment was commenced within eight weeks of surgery when patients received a daily radiotherapy dose of 2 Gy, five times a week for two weeks followed by a two week break. This cycle was then repeated to make a total absorbed dose of 40 Gy. Alongside the first week of radiotherapy, patients received 25 mg/kg of 5-FU per 24 h up to a maximum daily dose of 1500 mg. The dosage of 5-FU during the second cycle was dependant on any resulting toxicity from the first cycle.

Analysis of the entire study population revealed no statistical difference in overall or disease-free survival. When considering the pancreatic group alone, median survival in the treatment group was 17.1 mo compared to 12.6 mo in those undergoing observation ($P = 0.099$). Two-year survival was 37% and 20%, with five-year survival being 23% and 10% in each group respectively. The pattern of recurrent disease was similar in both treatment groups with both locoregional and distant metastases occurring concurrently in 19%-22% of patients experiencing disease recurrence. 15% of patients from each group experienced local recurrence alone, suggesting that adjuvant radiotherapy is ineffective against pancreatic and ampullary cancer.

In the ESPAC-1 trial, chemoradiotherapy consisted of 20 Gy in ten daily fractions over a fortnight with a 500 mg/m² intravenous bolus of 5-FU on days 1-3 to be repeated two weeks later. For those patients assigned to receive both chemoradiotherapy and chemotherapy, the above regime was combined with the chemotherapy regime previously described. Initial results from ESPAC-1 showed no survival benefit in those receiving chemoradiotherapy. Chemoradiotherapy incurred a median survival of 15.5 mo (95%CI: 13.5-17.4) compared to

Table 3 Major adjuvant chemoradiotherapy trials in pancreatic cancer

Year published	Author/group	Treatment arms (n)	Final analysis			Median survival (mo)	Survival (95%CI)				Disease-free survival (DFS) (95%CI)	
			T3	N*	R0		2-yr survival	3-yr survival	5-yr survival	Median DFS (mo)	2-yr DFS	
1985	GITSG	CRT (21)	37	28	100	21	43% (0.25%-0.63%)	-	-	-	-	-
1999	EORTC	Surgery alone (22)	21	46	77	10.9	18% (0.08%-0.36%)	-	-	-	-	-
		5-FU/RT (104)				24.5	51% (41%-61%)	-	-	28% (17%-39%)	17.4	38% (28%-48%)
		Surgery alone (103)				19 (log rank $P = 0.208$)	41% (31%-51%)	-	-	22% (12%-32%)	16 ($P = 0.643$)	37% (27%-47%) ($P = 0.643$)
2001	ESPAC-1 (all patients)	5-FU/RT (60)	0	51	NA	17.1	37% (24%-50%)	-	-	-	-	-
		Surgery alone (54)	NA	56	82	12.6 (log rank $P = 0.099$)	23% (11%-35%)	-	-	-	-	-
		CRT +/- 5-FU/folinic acid (175)	NA	56	82	15.5 (13.5-17.4)	-	-	-	-	-	-
2001	ESPAC-1 (2 x 2 design only)	No CRT +/- 5-FU/folinic acid (178)	NA	NA	NA	16.1 (13.1-20.1) (HR = 1.18, 0.9-1.55, $P = 0.24$)	-	-	-	-	-	-
		CRT +/- 5-FU/folinic acid (142)	NA	NA	NA	15.8 (13.5-19.4)	-	-	-	-	-	-
2004	ESPAC-1 (2 x 2 final analysis)	No CRT +/- 5-FU/folinic acid (143)	NA	53	82	17.8 (14.2-23.6) (HR = 1.3, 0.96-1.77, $P = 0.09$)	29%	-	10%	-	-	-
		CRT +/- 5-FU/folinic acid (145)	NA	53	82	15.9 (13.7-19.9)	-	-	-	-	-	-
2006	RTOG 97-04	No CRT +/- 5-FU/folinic acid (144)	75	66	66	17.9 (14.8-23.6) (HR = 1.28, 0.99-1.66, $P = 0.05$)	41%	-	-	-	-	-
		5-FU/folinic acid (75)	NA	NA	NA	21.6 (13.5-27.3)	-	-	29%	-	-	-
		CRT + 5-FU/folinic acid (72)	NA	NA	NA	19.9 (14.2-22.5)	-	-	13%	-	-	-
2011	RTOG 97-04 (5-yr analysis)	Observation (69)	75	66	66	16.9 (12.3-24.8)	-	-	11%	-	-	-
		CRT (73)	75	66	66	13.9 (12.2-17.3)	-	-	7%	-	-	-
		CRT + 5-FU (230)	NA	NA	NA	No significant difference	-	-	-	-	-	-
2011	RTOG 97-04 (5-yr analysis)	CRT + gemcitabine (221)	75	66	66	16.9	-	-	22%	-	-	-
		CRT + 5-FU (201)	NA	NA	NA	20.5 (HR = 0.82, 0.65-1.03, $P = 0.09$)	35%	-	-	-	-	-
		CRT + gemcitabine (187)	75	66	66	No significant difference	-	-	19%	-	-	-
2012	CapRI (Schmidt)	CRT + gemcitabine (221)	NA	NA	NA	HR = 0.933, 0.76-1.145, $P = 0.51$	40%	27%	19%	-	-	-
		CRT + 5-FU (201)	97	79	61	17.1	34%	21%	18% (13%-24%)	-	-	-
		CRT + gemcitabine (187)	97	79	61	20.5	42%	28%	22%	-	-	-
2012	CapRI (Schmidt)	5-FU/cisplatin/interferon α -2b → RT → 5-FU (53)	97	79	61	32.1 (22.8-42.2)	-	-	-	-	-	-
		5-FU/folinic acid (57)	NA	NA	NA	28.5 (19.5-38.6) (HR = 1.2, 0.49-2.95, $P = 0.49$)	-	-	-	11.5 (9.8-17.6) ($P = 0.61$)	-	-

CRT: Chemoradiotherapy; NA: Not available; 5-FU: 5-fluorouracil.

16.1 mo (95%CI: 13.1-20.1) in patients which had not received any (HR = 1.18, 95%CI: 0.9-1.55, $P = 0.235$). These findings were echoed when evaluating patients in the 2 x 2 study design alone with those patients receiving chemoradiotherapy alone achieving a median survival of 15.8 mo (95%CI: 13.5-19.4) vs 17.8 mo (95%CI: 14-23.6) in those not. Again, these findings did not reach statistical significance with $P = 0.086$.

Final analysis of the 2×2 data showed that chemoradiotherapy had a negative effect on patient survival. Median survival was 15.9 mo (95%CI: 13.7-19.9) in those that received chemotherapy whilst patients that received none survived for a median of 17.9 mo (95%CI: 14.8-23.6), $P = 0.05$. Estimated 5-year survival was 10% in the chemoradiotherapy cohort in comparison to 20% in those patients who received none. In those patients randomised outside the 2×2 study design, median survival was only 13.9 mo (95%CI: 12.2-17.3) amongst the 73 patients who had received chemoradiotherapy. This was in comparison to a median survival of 16.9 mo (95%CI: 12.3-24.8) in those who underwent surgery alone and 21.6 mo (95%CI: 13.5-27.3) in those who underwent adjuvant chemotherapy without any chemoradiation. Estimated 5-year survival in these individual treatment groups was 7%, 11% and 29% respectively. Though this is strongly suggestive that adjuvant chemoradiation has a negative impact on survival, ESPAC-1 was underpowered to directly assess these smaller cohorts outside the 2×2 design. The authors suggest that the lack of survival benefit with chemoradiation may be due to a delay in administering the treatment to patients who were also receiving chemotherapy. Some have argued that the radiotherapy given during ESPAC-1 was substandard and not subject to rigorous quality control, though the survival rates achieved in the individual groups were similar to those achieved in other major studies^[31].

Following the publication of their interim findings in 2008^[32], the final 5-year analysis of the RTOG 97-04 study was published in 2011^[33]. Patients were stratified into two arms - each to receive either gemcitabine or 5-FU both prior to, and after 5-FU based chemoradiation. In the gemcitabine group ($n = 221$), one cycle was administered (1000 mg/m² for 3 wk followed by a 1 wk break) prior to chemoradiotherapy, after which a further 3 cycles was undertaken. Patients in the 5-FU arm ($n = 230$) were administered a continuous infusion of 250 mg/m² per day for 3 wk prior to the commencement of chemoradiation. 5-FU was then administered for two six-week cycles of 5-FU (4 wk on plus 2 wk off). Chemoradiation consisted of 50.4 Gy of radiation in divided fractions, in association with a continuous infusion of 5-FU at the previously stated dose over the duration of the radiation therapy. No significant difference was identified in overall or disease-free survival in the final analysis. Worth noting, is though completion rates for designated treatments were equally high (87% in the 5-FU group and 90% in the gemcitabine group) those in the latter group experienced greater numbers of haematological ($P < 0.001$) and Grade 4 events ($P < 0.001$) secondary to acute toxicity.

A subgroup analysis from RTOG was undertaken observing those with pancreatic head tumours. The difference in median survival between both groups was not statistically significant, being 17.1 mo in the 5-FU group and 20.5 mo in the gemcitabine group (HR = 0.933, 95%CI: 0.76-1.15, log rank $P = 0.51$). However, following adjustment for stratification variables including nodal

status, tumour size and surgical margins, multivariate analysis suggests a benefit with gemcitabine over 5-FU (HR = 0.80, 95%CI: 0.63-1.00, $P = 0.05$).

The most recently published phase III randomised trial compared adjuvant chemoradiation, including 5-FU, cisplatin and interferon Alfa-2b (Group 1) with adjuvant 5-FU and folinic acid without chemoradiation (Group 2). CapRI^[34] followed a similar phase II trial which reported a promising 5-year survival rate of 55%^[35]. Patients in group 1 received a 200 mg/m² continuous infusion of 5-FU, 30 mg/m²/wk of cisplatin and 3 million units of interferon α -2b three times a week. This treatment continued for 5.5 wk and was given alongside 50.4 Gy of radiation in 28 fractions. Following chemoradiotherapy, patients underwent a further two cycles of 5-FU. Those in group 2 were treated for six cycles of chemotherapy with 20 mg/m² of folinic acid and 425 mg/m² of FU on days 1-5 of a 28-d cycle without any radiotherapy. Patients underwent regular clinical follow-up in addition to receiving a CT at 6-monthly intervals, or whenever clinically indicated. Though 132 patients were initially randomised, only 110 of these received at least one dose of a study treatment and were described as the per-protocol population.

Overall survival and disease free survival was not significantly different between the two groups. However, the median survival data from the per-protocol population are amongst the best published, being 32.1 mo (95%CI: 22.8-42.2) in group 1, and 28.5 mo (95%CI: 19.5-38.6) in group 2 (HR = 1.2, 95%CI: 0.49-2.95, $P = 0.49$). Selection bias was unlikely, given that 97% of tumours were T3 and above, 79% of patients had nodal disease and only 61% of patients underwent a R0 resection. The authors concede that these impressive survival figures are unlikely to be secondary to adjuvant therapy alone, and acknowledge that the vast majority of patients underwent an aggressive soft tissue clearance during their resection in Heidelberg. Nevertheless, these results seem to have been achieved at the expense of very high levels of toxicity, with 85% of patients receiving chemoradioimmunotherapy experiencing grades 3 or 4 toxicity which were mainly haematological in origin. In a separate study^[36] this controversial chemoradioimmunotherapy regime led to a 93% grade 3 and 4 gastrointestinal toxicity rate, leading to its abandonment.

In addition to these randomised trials which have produced conflicting results, a handful of large retrospective reviews have also been published^[37]. A prospectively collected database from John Hopkins Hospital in Baltimore compared those who received adjuvant chemoradiotherapy ($n = 271$) to those who did not ($n = 345$). Chemoradiotherapy consisted of a continuous infusion of 5-FU with 50 Gy of radiation in divided fractions, followed by maintenance 5-FU for a further 2-6 mo. Chemoradiation improved survival compared to those who received no adjuvant therapy, with a median survival of 21.2 mo as opposed to 14.4 mo (HR = 0.72, 95%CI: 0.6-0.86, $P < 0.001$). Even after adjusting for confounding factors in-

Table 4 Meta-analyses of adjuvant chemoradiotherapy in pancreatic cancer

Year published	Author	Arm (n)	Survival (95%CI)		
			Median survival (mo)	2-yr survival	5-year survival
2005	Stocken <i>et al</i> ^[20]	CRT	15.8 (13.9-18.1)	30%	12%
		No CRT	15.2 (13.1-18.2)	34%	17%
2008	Butturini <i>et al</i> ^[25]	R0 Resections			
		CRT (188)	15.9 (14-18.5)	30% (23%-36%)	10% (5%-15%)
		No CRT (183)	15.8 (13.4-20.1)	38% (31%-45%)	20% (13%-26%)
		R1 Resections			
2013	Liao <i>et al</i> ^[26]	CRT (53)	14.7 (11.5-20.5)	30% (17%-42%)	18% (7%-29%)
		No CRT (53)	11.2 (9.4-16.7)	19% (8%-31%)	8% (0%-16%)
		Hazard ratio for death (95% CI)			
		Chemoradiation (169)	0.91 (0.55-1.46)		
		Observation (670)			
		Chemoradiation + 5-FU (323)	0.87 (0.27-2.69)		
		5-FU (876)			
		Chemoradiation + 5-FU (323)	0.59 (0.19-1.74)		
2013	Liao <i>et al</i> ^[26]	Chemoradiation (169)			
		Chemoradiation + gemcitabine (221)	0.82 (0.4-1.71)		
		Chemoradiation + 5-FU (323)			

CRT: Chemoradiotherapy; 5-FU: 5-fluorouracil.

cluding comorbid disease and surgical complication rate amongst others, chemoradiation continued to show a survival benefit (relative risk = 0.74, $P < 0.001$). Multivariate analysis revealed a significant survival benefit to chemoradiotherapy in those patients who had either positive ($P = 0.002$) or negative ($P = 0.035$) resection margins.

The Mayo Clinic published their 1975-2005 experience^[38], also supporting the use of adjuvant chemoradiotherapy. Their retrospective study ($n = 454$) included only R0 resections. Ninety-eight percent of the 274 patients that received radiotherapy (median dose 50 Gy in 28 fractions) also received concurrent 5-FU based chemotherapy, and only 10% of these received any additional chemotherapy following chemoradiation. Median survival was improved with adjuvant treatment as opposed to surgery alone, with rates of 25.2 and 19.2 mo respectively. Chemoradiotherapy improved survival in various disease subgroups including node positive disease ($P < 0.001$), high-grade tumours ($P < 0.001$), or both together ($P < 0.001$).

Numerous publications have recently originated from the US-based Surveillance, Epidemiology and End Results (SEER) database supporting the use of adjuvant radiotherapy. Artinyan *et al*^[39] analysed 1930 patients that had undergone curative node-negative resections for pancreatic cancer during 1988-2003. Multivariate analysis revealed adjuvant radiotherapy to be a significant factor in improving overall survival (HR = 0.72, 95%CI: 0.63-0.82, $P < 0.001$). Greco *et al*^[40] presented 2636 pancreatic resections, of which 1123 received adjuvant radiotherapy with a median survival of 18 mo, *vs* 11 mo in those who received no radiotherapy ($P < 0.01$). Moody *et al*^[41] further supported these claims with his series, also concluding that adjuvant radiotherapy improved survival compared to no radiotherapy ($P = 0.004$). However, on subgroup analysis statistical significance was only maintained in patients with Stage 2B disease ($P < 0.0001$).

Hazard *et al*^[42] also supports the use of radiotherapy with her publication, though specific conclusions in relation to adjuvant therapy cannot be made as most patients received both neoadjuvant and adjuvant radiation. Though the SEER database has the advantage of possessing the details of an impressive volume of patients, concerns have been raised. As the data collection is retrospective, now-important prognostic information such as margin status, lymphovascular and perineural invasion, patient comorbid status and performance status details have not been collected. This may have produced a treatment bias in these patient cohorts which cannot be adjusted for during statistical analysis.

META-ANALYSIS OF ADJUVANT CHEMORADIOOTHERAPY IN PANCREATIC CANCER

In addition to the analysis of adjuvant chemotherapy data, Stocken *et al*^[20] also pooled individual patient data from ESPAC-1 2×2 ^[8], ESPAC-1 Plus^[16] and EORTC^[21] to assess the benefit of adjuvant chemoradiotherapy (Table 4). Despite borderline heterogeneity ($\chi^2 = 6.1$, $P = 0.05$), no significant difference in the risk of death was observed with chemoradiotherapy (HR = 1.09, 95%CI: 0.89-1.32, $P = 0.43$). The GITSG trial^[22] was unfortunately unable to provide individual patient data and therefore summary data was utilised. Though heterogeneity was increased ($\chi^2 = 10$, $P = 0.02$) by the addition of the GITSG summary data to the individual data from other studies, the pooled HR again showed no difference in the risk of death between those receiving chemoradiotherapy and those not (HR = 1.02, 95%CI: 0.85-1.24, $P = 0.81$).

Butturini's meta-analysis^[25] on adjuvant therapy and resection margins noted no significant survival advantage with chemoradiation in R0 resections (median survival

Table 5 Current phase III trials investigating adjuvant therapy in pancreatic cancer

Trial number	Co-ordinating country	First enrolment	Target sample size (<i>n</i>)	Adjuvant treatment arms	Primary outcome	Secondary outcomes (clinical only)
ISRCTN96397434 (ESPAC-4)	United Kingdom	2008	1396	(I) Gemcitabine (II) Gemcitabine plus capecitabine	OS	Toxicity Quality of life OS at 2 and 5 yr DFS at 5 yr
DRKS00000247 (CONKO-005)	Germany	2008	436	(I) Gemcitabine (II) Gemcitabine plus erlotinib	DFS	OS Toxicity
NCT01013649 (RTOG 0848)	United States	2009	950	(I) Gemcitabine (II) Gemcitabine plus erlotinib If DFS at end of treatment (I) or (II), further randomisation to: (III) A further course of (I) or (II) as previously received plus Capecitabine CRT (IV) A further course of (I) or (II) as previously received plus 5-FU CRT	OS	DFS Toxicity Correlation between baseline fatigue and survival
NCT01072981	United States	2010	722	Gemcitabine +/- 5-FU CRT +/- HyperAcute@-Pancreas (algenpantucel-L) immunotherapy	OS	
NCT01526135	France/Canada	2012	490	(I) Gemcitabine (II) mFolfinox (5-FU, folinic acid, irinotecan, oxaliplatin)	DFS at 3 yr	OS at 3 yr
NCT01077427	Germany	2012	336	(I) Gemcitabine (II) Gemcitabine plus cisplatin plus regional hyperthermia	DFS	OS
NCT01964430	United States	Not yet active	-	(I) Gemcitabine (II) Gemcitabine plus nab-paclitaxel	DFS/OS	

OS: Overall survival; DFS: Disease-free survival; CRT: Chemoradiotherapy; 5-FU: 5-fluorouracil.

15.8 and 15.9 mo). Though remaining statistically insignificant, there was evidence of a small survival benefit with adjuvant chemoradiation in patients receiving a R1 resection (median survival 11.2 and 14.7 mo). Significant heterogeneity was noted in the effect of chemoradiation dependent on resection margin ($\chi^2 = 4.2$, $P = 0.04$). Adjuvant chemoradiotherapy was estimated to reduce the risk of death by 28% (HR = 0.72, 95%CI: 0.47-1.10) in patients with positive margins, but was estimated to increase the risk by 19% (HR = 1.19, 95%CI: 0.95-1.49) in patients with clear margins.

Liao *et al.*^[26]'s recent meta-analysis has been the first to directly compare chemoradiation combined with either 5-FU or gemcitabine with each treatment in isolation. No survival advantage was demonstrated by adding chemoradiation to either adjuvant 5-FU or gemcitabine with all hazard ratios approaching 1. However, the addition of chemoradiation to 5-FU (HR = 2.85, 95%CI: 0.15-61.44) or gemcitabine (HR = 36.49, 95%CI: 0.34-3235.7) dramatically increases toxic events in comparison to the use of the chemotherapeutic agent alone. The authors conclude that on the basis of their results, future trials with chemoradiation are not required citing toxicity, resistance and early tumour dissemination as possible reasons why chemoradiotherapy to the tumour bed may be ineffective in pancreatic cancer.

CURRENT PHASE III TRIALS

It is extremely encouraging to see several phase III trials

currently recruiting for patients to further investigate the role of adjuvant therapy in pancreatic cancer (Table 5). Capecitabine is a fluoropyrimidine which has been shown to exert synergistic antitumour activity when combined with gemcitabine^[43]. A meta-analysis of three randomised controlled trials ($n = 935$)^[44] compared gemcitabine with gemcitabine plus capecitabine (Gemcap) in advanced pancreatic cancer. This showed an overall survival benefit with the latter treatment (HR = 0.86, 95%CI: 0.75-0.98, $P = 0.02$) with no intertrial heterogeneity. The ESPAC group is currently recruiting to trial this therapy in the adjuvant setting with the aim of recruiting nearly 1400 patients by the end of 2014^[45].

Folfinox is another chemotherapeutic regimen that has been subjected to a randomised controlled trial in those with metastatic pancreatic cancer^[46]. In comparison to gemcitabine ($n = 171$), Folfinox ($n = 171$) improved both median overall survival from 6.8 to 11.1 mo (HR = 0.57, 95%CI: 0.45-0.73, $P < 0.001$) and median progression-free survival from 3.3 mo to 6.4 mo (HR = 0.47, 95%CI: 0.37-0.59, $P < 0.001$). However, Folfinox resulted in significantly more grades 3 and 4 adverse events than gemcitabine including neutropenia, febrile neutropenia, thrombocytopenia, diarrhoea, and sensory neuropathy. To the contrary of these findings, further data published from this study^[47] disclosed that quality of life impairment was significantly reduced in the Folfinox group compared to gemcitabine indicating its acceptability to patients. Folfinox is currently subjected to a two armed phase III trial in opposition to gemcitabine in

resected pancreatic cancer^[48].

The tyrosine-kinase inhibitor Erlotinib, used in combination with gemcitabine has been shown to improve overall survival and progression-free survival compared to gemcitabine alone in advanced pancreatic cancer in a large phase III trial ($n = 569$)^[49]. Bao *et al*^[50] utilised these two compounds in the adjuvant setting in a phase II trial achieving a respectable median disease-free survival of 14.0 mo (95%CI: 8.2-24.5). Furthermore, a single-institution phase II trial ($n = 48$) has also shown that erlotinib can be safely utilised alongside capecitabine and chemoradiotherapy^[51]. Currently, erlotinib is being trialled both in combination with gemcitabine *vs* gemcitabine alone^[52] and in a separate trial this will be followed by a course of either capecitabine or 5-FU chemoradiotherapy^[53].

Platinum compounds have been safely used in various pancreatic cancer trials, though particularly encouraging results have been achieved in the neoadjuvant setting. Heinrich *et al*^[54] prescribed 28 patients a two month neoadjuvant course of gemcitabine and cisplatin. In addition to evidence of a histological response in over half of patients, surgery following this neoadjuvant regimen was safe, leading to a median survival of 26.5 mo. A separate phase II study^[55] administered neoadjuvant gemcitabine plus the platinum agent oxaliplatin to 33 patients - 18 with unresectable disease and 15 with borderline resectable disease. Following treatment 13/33 underwent resection with over two-thirds of these patients undergoing an R0 resection. Resection improved median overall survival to 22 mo (95%CI: 14-30) compared to 12 mo (95%CI: 9-15) in those treated non-surgically ($P = 0.046$).

On the basis of these encouraging results, phase III trials are now incorporating platinum agents into their chemotherapy regimens. The Hyperthermia European Adjuvant Trial (HEAT) study^[56] will compare adjuvant gemcitabine to adjuvant gemcitabine plus capecitabine plus regional hyperthermia treatment - a regime that has previously been utilised with low reported toxicity. It has been shown that heat can increase the cytotoxicity of certain chemotherapeutic agents^[57] including gemcitabine^[58] in *in vitro* experiment with pancreatic cancer cell lines. One phase II study^[59] combined gemcitabine with regional heat treatment in the treatment of both metastatic and locally advanced disease. Median survival was 8 mo in the entire study population, but extended to 17.7 mo in those with localised disease. More recently, a retrospective analysis of 23 patients with gemcitabine refractory inoperable disease was published^[60] whereby patients received gemcitabine plus cisplatin alongside regional hyperthermia biweekly for four months. Though 21/23 patients suffered from metastatic disease at recruitment, a median overall survival of 12.9 mo was achieved (95%CI: 9.9-15.9).

One of the more recent phase III studies to be approved is to trial adjuvant gemcitabine *vs* a combination of gemcitabine and the taxane, nabpaclitaxel^[61]. This combination has already been shown to be superior to gemcitabine alone in advanced pancreatic cancer in a

large phase III trial^[62] ($n = 861$), where progression free survival improved from 3.7 to 5.5 mo and overall survival growing from 6.7 to 8.5 mo (HR for disease progression or death 0.69, 95%CI: 0.58-0.82, $P < 0.001$). Though not yet active, the results of this promising large international multicentre trial are already much anticipated.

CONCLUSION

Pancreatic cancer remains a substantial challenge for surgeons and oncologists alike. Surgical resection remains the foundation for any patient with resectable disease. There is now irrefutable evidence that adjuvant chemotherapy improves both overall and disease-free survival and several phase III trials are currently in progress aiming to challenge gemcitabine as the gold standard adjuvant drug. The evidence for adjuvant chemoradiotherapy in large phase III trials is lacking and can therefore not be recommended as standard therapy. Future adjuvant RCTs will compare approaches using combination therapies to attempt to improve the outlook.

REFERENCES

- 1 **Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ.** Cancer statistics, 2007. *CA Cancer J Clin* 2007; **57**: 43-66 [PMID: 17237035 DOI: 10.3322/canjclin.57.1.43]
- 2 **World Cancer Research Fund International.** Available from: URL: http://www.wcrf.org/cancer_statistics/world_cancer_statistics.php
- 3 **Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW.** Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 2004; **91**: 586-594 [PMID: 15122610 DOI: 10.1002/bjs.4484]
- 4 **Zimmerman SE, Smith FP, Schein PS.** Chemotherapy of pancreatic carcinoma. *Cancer* 1981; **47**: 1724-1728 [PMID: 6456058 DOI: 10.1002/1097-0142(19810315)47:6]
- 5 **Mallinson CN, Rake MO, Cocking JB, Fox CA, Cwynarski MT, Duffey BL, Jackson GA, Hanley J, Wass VJ.** Chemotherapy in pancreatic cancer: results of a controlled, prospective, randomised, multicentre trial. *Br Med J* 1980; **281**: 1589-1591 [PMID: 7004559 DOI: 10.1136/bmj.281.6255.1589]
- 6 **Bakkevold KE, Arnesjø B, Dahl O, Kambestad B.** Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater--results of a controlled, prospective, randomised multicentre study. *Eur J Cancer* 1993; **29A**: 698-703 [PMID: 8471327 DOI: 10.1016/S0959-8049(05)80349-1]
- 7 **Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, Bassi C, Falconi M, Pederzoli P, Dervenis C, Fernandez-Cruz L, Lacaine F, Pap A, Spooner D, Kerr DJ, Friess H, Büchler MW.** Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001; **358**: 1576-1585 [PMID: 11716884 DOI: 10.1016/S0140-6736(01)06651-X]
- 8 **Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW.** A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350**: 1200-1210 [PMID: 15028824 DOI: 10.1056/NEJMoa032295]
- 9 **Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, Nagakawa T, Nakayama T.** Is postoperative ad-

- juvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer* 2002; **95**: 1685-1695 [PMID: 12365016 DOI: 10.1002/cncr.10831]
- 10 **Kosuge T**, Kiuchi T, Mukai K, Kakizoe T. A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. *Jpn J Clin Oncol* 2006; **36**: 159-165 [PMID: 16490736 DOI: 10.1093/jjco/hyi234]
 - 11 **Burris HA**, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**: 2403-2413 [PMID: 9196156]
 - 12 **Oettle H**, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; **297**: 267-277 [PMID: 17227978 DOI: 10.1001/jama.297.3.267]
 - 13 **Neuhaus P**, Riess H, Post S, Gellert K, Ridwelski K, Schramm H, Zuelke C, Fahlke J, Langrehr J, Oettle H. CONKO-001: Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer. *J Clin Oncol ASCO Annual Meeting Proceedings (Post-Meeting Edition)* 2008; **26**(15S): LBA4504
 - 14 **Ueno H**, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, Doi R, Monden M, Hatori T, Tanaka M, Shimada M, Kanemitsu K. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. *Br J Cancer* 2009; **101**: 908-915 [PMID: 19690548 DOI: 10.1038/sj.bjc.6605256]
 - 15 **Neoptolemos JP**, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; **304**: 1073-1081 [PMID: 20823433 DOI: 10.1001/jama.2010.1275]
 - 16 **Neoptolemos JP**, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, Moore M, Padbury R, Doi R, Smith D, Büchler MW. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. *Br J Cancer* 2009; **100**: 246-250 [PMID: 19127260 DOI: 10.1038/sj.bjc.6604838]
 - 17 **Maeda A**, Boku N, Fukutomi A, Kondo S, Kinoshita T, Nagino M, Uesaka K. Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer: Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01). *Jpn J Clin Oncol* 2008; **38**: 227-229 [PMID: 18272475 DOI: 10.1093/jjco/hym178]
 - 18 **Fukutomi A**, Uesaka K, Boku N, Kanemoto H, Konishi M, Matsumoto I, Kaneoka Y, Shimizu Y, Nakamori S, Sakamoto H, Morinaga S, Kainuma O, Imai K, Sata N, Hishinuma S, Nakamura S, Kanai M, Hirano S, Yoshikawa Y, Ohashi Y. JASPAC 01: Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 for patients with resected pancreatic cancer. *J Clin Oncol Gastrointestinal Cancers Symposium* 2013; **31**(4S): 145
 - 19 **Antoniou G**, Kountourakis P, Papadimitriou K, Vassiliou V, Papamichael D. Adjuvant therapy for resectable pancreatic adenocarcinoma: review of the current treatment approaches and future directions. *Cancer Treat Rev* 2014; **40**: 78-85 [PMID: 23810287 DOI: 10.1016/j.ctrv.2013.05.008]
 - 20 **Stocken DD**, Büchler MW, Dervenis C, Bassi C, Jeekel H, Klinkenbijn JH, Bakkevold KE, Takada T, Amano H, Neoptolemos JP. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. *Br J Cancer* 2005; **92**: 1372-1381 [PMID: 15812554 DOI: 10.1038/sj.bjc.6602513]
 - 21 **Klinkenbijn JH**, Jeekel J, Sahnoud T, van Pel R, Couvreur ML, Veenhof CH, Arnaud JP, Gonzalez DG, de Wit LT, Hennipman A, Wils J. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg* 1999; **230**: 776-82; discussion 782-4 [PMID: 10615932]
 - 22 **Kalser MH**, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985; **120**: 899-903 [PMID: 4015380 DOI: 10.1001/archsurg.1985.01390320023003]
 - 23 Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. *Cancer* 1987; **59**: 2006-2010 [PMID: 3567862]
 - 24 **Boeck S**, Ankerst DP, Heinemann V. The role of adjuvant chemotherapy for patients with resected pancreatic cancer: systematic review of randomized controlled trials and meta-analysis. *Oncology* 2007; **72**: 314-321 [PMID: 18187951 DOI: 10.1159/000113054]
 - 25 **Butturini G**, Stocken DD, Wente MN, Jeekel H, Klinkenbijn JH, Bakkevold KE, Takada T, Amano H, Dervenis C, Bassi C, Büchler MW, Neoptolemos JP. Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. *Arch Surg* 2008; **143**: 75-83; discussion 83 [PMID: 18209156 DOI: 10.1001/archsurg.2007.17]
 - 26 **Liao WC**, Chien KL, Lin YL, Wu MS, Lin JT, Wang HP, Tu YK. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. *Lancet Oncol* 2013; **14**: 1095-1103 [PMID: 24035532 DOI: 10.1016/S1470-2045(13)70388-7]
 - 27 **Haslam JB**, Cavanaugh PJ, Stroup SL. Radiation therapy in the treatment of irresectable adenocarcinoma of the pancreas. *Cancer* 1973; **32**: 1341-1345 [PMID: 4127980]
 - 28 **Moertel CG**, Childs DS, Reitemeier RJ, Colby MY, Holbrook MA. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet* 1969; **2**: 865-867 [PMID: 4186452]
 - 29 **Wang F**, Kumar P. The role of radiotherapy in management of pancreatic cancer. *J Gastrointest Oncol* 2011; **2**: 157-167 [PMID: 22811846 DOI: 10.3978/j.issn.2078-6891.2011.032]
 - 30 **Yeo CJ**, Abrams RA, Grochow LB, Sohn TA, Ord SE, Hruban RH, Zahurak ML, Dooley WC, Coleman J, Sauter PK, Pitt HA, Lillemoe KD, Cameron JL. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. *Ann Surg* 1997; **225**: 621-633; discussion 633-636 [PMID: 9193189 DOI: 10.1097/00000658-199705000-00018]
 - 31 **Thomas A**, Dajani K, Neoptolemos JP, Ghaneh P. Adjuvant therapy in pancreatic cancer. *Dig Dis* 2010; **28**: 684-692 [PMID: 21088421 DOI: 10.1159/000320099]
 - 32 **Regine WF**, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, Benson AB, Macdonald JS, Kudrimoti MR, Fromm ML, Haddock MG, Schaefer P, Willett CG, Rich TA. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA* 2008; **299**: 1019-1026 [PMID: 18319412 DOI: 10.1001/jama.299.9.1019]

- 33 **Regine WF**, Winter KA, Abrams R, Safran H, Hoffman JP, Kanski A, Benson AB, Macdonald JS, Rich TA, Willett CG. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol* 2011; **18**: 1319-1326 [PMID: 21499862 DOI: 10.1245/s10434-011-1630-6]
- 34 **Schmidt J**, Abel U, Debus J, Harig S, Hoffmann K, Herrmann T, Bartsch D, Klein J, Mansmann U, Jäger D, Capussotti L, Kunz R, Büchler MW. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. *J Clin Oncol* 2012; **30**: 4077-4083 [PMID: 23008325 DOI: 10.1200/JCO.2011.38.2960]
- 35 **Picozzi VJ**, Kozarek RA, Traverso LW. Interferon-based adjuvant chemoradiation therapy after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am J Surg* 2003; **185**: 476-480 [PMID: 12727570 DOI: 10.1016/S0002-9610(03)00051-5]
- 36 **Picozzi VJ**, Abrams RA, Decker PA, Traverso W, O'Reilly EM, Greeno E, Martin RC, Wilfong LS, Rothenberg ML, Posner MC, Pisters PW. Multicenter phase II trial of adjuvant therapy for resected pancreatic cancer using cisplatin, 5-fluorouracil, and interferon-alfa-2b-based chemoradiation: ACOSOG Trial Z05031. *Ann Oncol* 2011; **22**: 348-354 [PMID: 20670978 DOI: 10.1093/annonc/mdq384]
- 37 **Herman JM**, Swartz MJ, Hsu CC, Winter J, Pawlik TM, Sugar E, Robinson R, Laheru DA, Jaffee E, Hruban RH, Campbell KA, Wolfgang CL, Asrari F, Donehower R, Hidalgo M, Diaz LA, Yeo C, Cameron JL, Schulick RD, Abrams R. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol* 2008; **26**: 3503-3510 [PMID: 18640931 DOI: 10.1200/JCO.2007.15.8469]
- 38 **Corsini MM**, Miller RC, Haddock MG, Donohue JH, Farnell MB, Nagorney DM, Jatoi A, McWilliams RR, Kim GP, Bhatia S, Iott MJ, Gunderson LL. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). *J Clin Oncol* 2008; **26**: 3511-3516 [PMID: 18640932 DOI: 10.1200/JCO.2007.15.8782]
- 39 **Artinyan A**, Hellan M, Mojica-Manosa P, Chen YJ, Pezner R, Ellenhorn JD, Kim J. Improved survival with adjuvant external-beam radiation therapy in lymph node-negative pancreatic cancer: a United States population-based assessment. *Cancer* 2008; **112**: 34-42 [PMID: 18000805 DOI: 10.1002/cncr.23134]
- 40 **Greco JA**, Castaldo ET, Feurer ID, Pinson CW, Chakravarthy AB, Merchant NB, Parikh AA. Survival benefit with adjuvant radiation therapy in surgically resected pancreatic cancer. 2007 Jan 19-21; Orlando, US: ASCO Gastrointestinal Cancers Symposium Proceedings, 2007: Abstract 109
- 41 **Moody JS**, Sawrie SM, Kozak KR, Plastaras JP, Howard G, Bonner JA. Adjuvant radiotherapy for pancreatic cancer is associated with a survival benefit primarily in stage IIB patients. *J Gastroenterol* 2009; **44**: 84-91 [PMID: 19159077 DOI: 10.1007/s00535-008-2280-8]
- 42 **Hazard L**, Tward JD, Szabo A, Shrieve DC. Radiation therapy is associated with improved survival in patients with pancreatic adenocarcinoma: results of a study from the Surveillance, Epidemiology, and End Results (SEER) registry data. *Cancer* 2007; **110**: 2191-2201 [PMID: 17918259 DOI: 10.1002/cncr.23047]
- 43 **Sawada N**, Fujimoto-Ouchi K, Ishikawa T. Anti tumour activity of combination therapy with capecitabine plus vinorelbine, and capecitabine plus gemcitabine in human tumor xenograft models. *Proc Am Assoc Cancer Res* 2002; **43**: 1088 (Abstract 5388)
- 44 **Cunningham D**, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Crellin A, Adab F, Thompson J, Leonard P, Ostrowski J, Eatock M, Scheithauer W, Herrmann R, Neoptolemos JP. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009; **27**: 5513-5518 [PMID: 19858379 DOI: 10.1200/JCO.2009.24.2446]
- 45 **European Study Group for Pancreatic Cancer - Trial 4**. Combination versus single agent chemotherapy in resectable pancreatic ductal and peri-ampullary cancers. Available from: URL: <http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=4307>
- 46 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécauarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachtet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]
- 47 **Gourgou-Bourgade S**, Bascoul-Molleivi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécauarn Y, Adenis A, Raoul JL, Boige V, Bérille J, Conroy T. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013; **31**: 23-29 [PMID: 23213101 DOI: 10.1200/JCO.2012.44.4869]
- 48 Trial comparing adjuvant chemotherapy with gemcitabine versus mFolfinrox to treat resected pancreatic adenocarcinoma. Available from: URL: <http://clinicaltrials.gov/show/NCT01526135>
- 49 **Moore MJ**, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966 [PMID: 17452677 DOI: 10.1200/JCO.2006.07.9525]
- 50 **Bao PQ**, Ramanathan RK, Krasinkas A, Bahary N, Lembersky BC, Bartlett DL, Hughes SJ, Lee KK, Moser AJ, Zeh HJ. Phase II study of gemcitabine and erlotinib as adjuvant therapy for patients with resected pancreatic cancer. *Ann Surg Oncol* 2011; **18**: 1122-1129 [PMID: 21104328 DOI: 10.1245/s10434-010-1401-9]
- 51 **Herman JM**, Fan KY, Wild AT, Hacker-Prietz A, Wood LD, Blackford AL, Ellsworth S, Zheng L, Le DT, De Jesus-Acosta A, Hidalgo M, Donehower RC, Schulick RD, Edil BH, Choti MA, Hruban RH, Pawlik TM, Cameron JL, Laheru DA, Wolfgang CL. Phase 2 study of erlotinib combined with adjuvant chemoradiation and chemotherapy in patients with resectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2013; **86**: 678-685 [PMID: 23773391 DOI: 10.1016/j.ijrobp.2013.03.032]
- 52 CONKO-005: Adjuvant Therapy in R0-resected Pancreatic Cancer Patients with Gemcitabine plus Erlotinib vs. Gemcitabine over 24 Weeks - a Prospective, Randomized Phase III Study. Available from: URL: <http://apps.who.int/trialsearch/trial.aspx?trialid=DRKS00000247>
- 53 Gemcitabine hydrochloride with or without erlotinib hydrochloride followed by the same chemotherapy regimen with or without radiation therapy and capecitabine or fluorouracil in treating patients with pancreatic cancer that has been removed by surgery. Available from: URL: <http://clinicaltrials.gov/show/NCT01013649>
- 54 **Heinrich S**, Schäfer M, Weber A, Hany TF, Bhure U, Pestalozzi BC, Clavien PA. Neoadjuvant chemotherapy generates a significant tumor response in resectable pancreatic cancer without increasing morbidity: results of a prospective phase II trial. *Ann Surg* 2008; **248**: 1014-1022 [PMID: 19092346 DOI: 10.1097/SLA.0b013e318190a6da]

- 55 **Sahora K**, Kuehrer I, Eisenhut A, Akan B, Koellblinger C, Goetzinger P, Teleky B, Jakesz R, Peck-Radosavljevic M, Ba'ssalamah A, Zielinski C, Gnant M. NeoGemOx: Gemcitabine and oxaliplatin as neoadjuvant treatment for locally advanced, nonmetastasized pancreatic cancer. *Surgery* 2011; **149**: 311-320 [PMID: 20817204 DOI: 10.1016/j.surg.2010.07.048]
- 56 Hyperthermia European Adjuvant Trial (HEAT). Available from: URL: <http://clinicaltrials.gov/show/NCT01077427>
- 57 **Issels RD**. Hyperthermia adds to chemotherapy. *Eur J Cancer* 2008; **44**: 2546-2554 [PMID: 18789678 DOI: 10.1016/j.ejca.2008.07.038]
- 58 **Adachi S**, Kokura S, Okayama T, Ishikawa T, Takagi T, Handa O, Naito Y, Yoshikawa T. Effect of hyperthermia combined with gemcitabine on apoptotic cell death in cultured human pancreatic cancer cell lines. *Int J Hyperthermia* 2009; **25**: 210-219 [PMID: 19437237 DOI: 10.1080/02656730802657036]
- 59 **Ishikawa T**, Kokura S, Sakamoto N, Ando T, Imamoto E, Hattori T, Oyamada H, Yoshinami N, Sakamoto M, Kitagawa K, Okumura Y, Yoshida N, Kamada K, Katada K, Uchiyama K, Handa O, Takagi T, Yasuda H, Sakagami J, Konishi H, Yagi N, Naito Y, Yoshikawa T. Phase II trial of combined regional hyperthermia and gemcitabine for locally advanced or metastatic pancreatic cancer. *Int J Hyperthermia* 2012; **28**: 597-604 [PMID: 22838644 DOI: 10.3109/02656736.2012.695428]
- 60 **Tschoep-Lechner KE**, Milani V, Berger F, Dieterle N, Abdel-Rahman S, Salat C, Issels RD. Gemcitabine and cisplatin combined with regional hyperthermia as second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer. *Int J Hyperthermia* 2013; **29**: 8-16 [PMID: 23245336 DOI: 10.3109/02656736.2012.740764]
- 61 Study to Compare Disease-free Survival of Subjects with Surgically Resected Pancreatic Cancer in the Adjuvant Setting Who Are Taking Nab-paclitaxel in Combination with Gemcitabine vs Gemcitabine Alone. Available from: URL: http://www.cancer.gov/clinicaltrials/search/view?cdrid=753839&version=HealthProfessional&protocolsearchid=12450288#Objectives_CDR0000753839
- 62 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]

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