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Adjuvant Therapy in Pancreatic Cancer

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Abstract

Adjuvant treatment following curative resection for pancreatic cancer is now well established. Historically, the role of adjuvant therapy post resection was uncertain, as was the best form of adjuvant, the choices lying between adjuvant chemotherapy, chemoradiation or a combination of these. The landmark randomized controlled European Study Group for Pancreatic Cancer (ESPAC)-1 trial, provided the strongest evidence for the benefit of adjuvant therapy. ESPAC-1 showed a strong survival advantage for chemotherapy comprising 5-fluorouracil (5-FU) with folinic acid (FA), but no support for the use of chemoradiation. The CONKO-001 trial showed that gemcitabine was also superior to surgery alone. The ESPAC-3 trial showed no superiority for gemcitabine over 5-FU/FA although gemcitabine was less toxic. The effects of adding biological agents or combining agents within regimens are being investigated as well as neo-adjuvant therapies being compared with adjuvant therapy. A network meta-analysis has confirmed reduced survival and increased toxicity with adjuvant chemoradiotherapy. Adjuvant systemic chemotherapy with either gemcitabine or 5-FU/FA following curative resection for pancreatic adenocarcinoma continues as the mainstay of treatment. The five-year survival rates are around 25% with chemotherapy compared to resection alone, with a significant survival benefit also shown for patients with R1 positive resection margins.

Key Words: Adjuvant therapy; Pancreatic cancer; ESPAC

Non Standard Abbreviations: 5-FU: 5-Fluorouracil; FA: Folinic acid; EBRTexternal bean radiotherapy; EORTC: European Organization for Research and Treatment of Cancer; ESPAC: European Study Group for Pancreatic Cancer; HENT1: Human equilibrative nucleoside transporter 1; RTOG: Radiation Therapy Oncology Group

Introduction

Adjuvant treatment following on from curative resection for pancreatic cancer has been in use for nearly thirty years and is still hotly debated. The treatments discussed in this review are centered on adjuvant chemoradiotherapy, combinations of biological agents with chemotherapy and combination chemotherapy with chemoradiotherapy.

Adjuvant Chemoradiotherapy

Clinical studies from the 1970s and 1980s indicated that the survival rates increased in locally advanced pancreatic cancer when treated with external beam radiotherapy (EBRT) with a radiation sensitizer [1, 2]. This led to the Gastrointestinal Tumor Study Group Trial 9173 trial in which patients who had had resection were randomized to either chemoradiotherapy, comprising 40 Gy EBRT with 5-fluorouracil (5-FU) and follow on 5-FU for six months, or no adjuvant treatment [3]. This trial planned to recruit 150 patients, but closed after 8 years, having only recruited 43 patients. The analysis showed an apparent improved survival in the treatment group compared to the control group (**Table 1**). A similar survival was seen in another 30 non-randomized patients registered to the treatment group [4]. Several subsequent studies showed that post-operative chemoradiation was feasible but the true survival benefit remained uncertain because none were randomized [5-7].

An European Organisation for Research and Treatment of Cancer (EORTC) trial randomized patients with various types of pancreatic cancers following resection to either chemoradiotherapy,

Table 1 Summary of the findings from the main studies examining the effect of adjuvant chemo radiotherapy in pancreatic cancer.

		Patient Number	Regime	Median Survival (Months)	Two-year survival (%)	Three-year survival (%)	Five-year survival (%)
GITSG 9173 [3]		21	60 Gy ERBT 5-FU Follow on 5-FU	20	42	-	18*
		22	Surgery/Observation	11	15	-	0*
GITSG (1987) [4]		30	60 Gy ERBT 5-FU Follow on 5-FU	18	46	-	-
EORTC [8,9]	**PDAC** RR 0.7 (0.5-1.1) P=0.099	60	40 Gy ERBT 5-FU	17.1	37	-	20
		54	Surgery/Observation	12.6	23	-	10
	PERI-AMPULLARY RR 0.9 (0.5-1.6) P=0.737	44	40 Gy ERBT 5-FU	39.5	70	-	38
		49	Surgery/Observation	40.1	64	-	36

* Estimated
EBRT= External beam Radio-Therapy
5-FU=5-Fluorouracil.
PDAC = Pancreatic Ductal Adenocarcinoma

comprising 40 Gy EBRT and 5-FU (but no follow on 5-FU), or to no adjuvant treatment [8]. The EORTC trial included 114 patients with pancreatic ductal adenocarcinoma of the head of the pancreas and 93 patients with peri-ampullary cancer. There was no survival benefit for chemoradiation (**Table 1**), which was confirmed on longer follow-up [9]. An earlier study from Norway had explored the role of adjuvant combination chemotherapy, completely omitting chemoradiotherapy [10]. In this trial 61 patients with pancreatic cancers (including 14 patients with peri-ampullary cancers) were randomized to adjuvant combination chemotherapy comprising, 5-FU, doxorubicin and mitomycin-C, following resection compared to resection alone. Although the median survival and two-year survival rates were increased in the treatment group, the overall long-term rate was unaffected.

Given these uncertainties, the European Study Group for Pancreatic Cancer (ESPAC) designed a trial that included a two-by-two factorial design plus a simpler pragmatic randomization to answer the basic questions of whether (1) adjuvant therapy provided a survival benefit, and (2) whether this survival benefit required the use of adjuvant chemoradiotherapy, adjuvant chemotherapy or a combination of these. The ESPAC-1 trial two-by-two factorial design randomized each patient twice: (1) to either chemotherapy with 5-FU and folinic acid (FA) for six months or no chemotherapy and (2) to either 5-FU based chemoradiotherapy or no chemoradiotherapy [11]. The ESPAC-1plus pragmatic design randomized patients, by *individual treatment group*, to either (1) chemotherapy with 5-FU/FA for six months or no chemotherapy or (2) to either 5-FU based chemoradiotherapy or no chemoradiotherapy [12]. There were 289 patients randomized into the two-by-two factorial design [11] and a further 252 patients in the single option randomization study giving a total of 541 patients randomized in ESPAC-1 plus [12], from 83 clinicians in 61 cancer centres in 11 countries, thus making it, at the time, the largest adjuvant therapy trial in pancreatic cancer ever to be completed.. The intention to treat analysis showed no survival benefit from chemoradiotherapy but an improvement in five-year survival from around 8% for resection alone to 21% for resection plus adjuvant chemotherapy (**Table 2**).

The Radiation Therapy Oncology Group (RTOG)-9704 study comprised 538 patients with pancreatic cancer all given adjuvant 5-FU-based chemoradiation that were randomized to 3 weeks pre-chemoradiation and 12 weeks post-chemoradiation with either gemcitabine or to continuous infusion 5-FU [13,14]. The design of this study explored two types of add-on chemotherapy (5-FU or gemcitabine) to a 5-FU based chemoradiation backbone. The analysis was not by intention to treat such that only 451 of the 538 patients randomized were analysed, with another analysis on the 388 patients who had adenocarcinoma in the head of the pancreas. Overall, there were no survival differences between the two main treatment arms or subgroups (**Table 3**).

The EORTC 40013/FFCD/GERCOR phase II trial by Van Laethem *et al.* randomised 90 patients with an R0 resection to receive four cycles of gemcitabine chemotherapy, or to combined chemoradiotherapy comprising two courses of gemcitabine followed by 50.4 Gy EBRT with concurrent weekly gemcitabine for 5-6 weeks [15]. Toxicity was comparable between the two arms as well as overall median survival and disease free survival. Local relapse rates were lower in the chemoradiotherapy arm (11% versus 24% respectively), though there was no difference in distant metastases (42% versus 40% respectively).

The additions of interferon-based protocols have been investigated in several studies but are associated with some improvement in survival but at a cost of significant toxicity. Linehan *et al.* undertook a single-centre, single-arm phase II study of 53 patients with resected pancreatic cancer received six weeks of EBRT 50.4 Gy with continuous infusion 5-FU, weekly

Table 2 Summary of the ESPAC-1 data.

	Modality	Median Survival (Months)	2 Year Survival (%)	5 Year Survival (%)
ESPAC-1 2x2 Final analysis [12]	Chemo radiotherapy vs	15.9	28.5	10
	No Chemo radiotherapy	17.9	41.4	19.6 (p=0.053)
ESPAC-1 2x2 Final analysis [12]	Chemotherapy vs	20.1	39.7	21.1
	No Chemotherapy	15.5	30	8.4 (p=0.009)
	Observation vs	16.9	38.7	10.7
ESPAC-1 Individual groups [12]	Chemo radiotherapy vs	13.9	21.7	7.3
	Chemotherapy Vs	21.6	44	29 (p=0.0005)
	Chemo radiotherapy plus follow on Chemotherapy	19.9	35	13.2
Composite data ESPAC-1plus and 3 (v1) [35]	5-FU / FA*	23.2	49	24
	Observation	16.8	37	14

5-FU=5-Fluorouracil. FA = Folinic Acid
*HR 0.70, CI (0.55-0.88); p=0.003

Table 3 Summary of randomised trials examining the effect of gemcitabine based chemoradiation.

	Patient Number	Regime	Median Survival (Months)	Two-year survival (%)	Three-year survival (%)
EORTC 40013 [15]	**45**	**4 cycles Gemcitabine**	**24.4**	**50.2**	**-**
	45	**2 cycles Gemcitabine + Gemcitabine and 50.5 Gy EBRT**	**24.3**	**50.6**	**-**
RTOG-9704 [13, 14] Head of pancreas only, eligible = 388	**187**	**Gemcitabine pre-Chemoradiotherapy, 50.4 Gy EBRT + 5-FU, Gemcitabine post-Chemoradiotherapy vs**	**20.5* (p=0.09)**	**-**	**31**
	201	**5-FU pre-Chemoradiotherapy, 50.4 Gy EBRT + 5-FU, 5-FU post-Chemoradiotherapy**	**16.9**	**-**	**22**

*HR=0.82 (0.65-1.03); P=0.09
EBRT – External Beam Radiotherapy
5FU – 5-fluorouracil

intravenous bolus cisplatin and interferon-α subcutaneously 3 times per week followed by two 4-week cycles of gemcitabine [16]. Sixteen patients (30%) failed to complete adjuvant therapy, due to: disease progression (7 patients), toxicity (7 patients), and consent withdrawal (2 patients). No patients completed planned therapy. The median overall survival was 25 months [16]. The American College of Surgeons Oncology Group Z05031 multicentre phase II trial aimed to recruit 93 patients with resected pancreatic head cancer also treated with six weeks of EBRT 50.4 Gy and continuous infusion 5-FU, weekly intravenous bolus cisplatin and interferon−α subcutaneously 3 times per week followed on this occasion by two 6-week courses of continuous infusion 5-FU [17]. The high rates of grades 3 and 4 toxic effects (95%) resulted in closure of the trial after 89 patients had been recruited. The median survival was calculated on only 80 of the patients and this was 25.4 months [18].

The multicentre phase III CapRI trial randomized 132 resected pancreatic cancer patients to receive either adjuvant chemo radiotherapy with six weeks of EBRT 50.4 Gy with a continuous infusion 5-FU, weekly intravenous bolus cisplatin and interferon-α subcutaneously 3 times per week followed by two 6-week courses of continuous infusion 5-FU (n=64) or bolus injections of 5-FU/FA for six cycles (n=68) [18]. Eighty-five percent of patients in the chemoradiotherapy arm and 16% of patients in the 5-FU/FA arm had grade 3 or 4 toxicity. The median survival was 26.5 months and 28.5 months respectively (**Table 4**).

The ECOG 2204 phase II trial randomised 137 (129 eligible) patients with resected pancreatic cancer to receive either cetuximab plus gemcitabine before chemo radiotherapy of 50.4Gy with capecitabine follwed by cetuximab plus gemcitabine (n=67) or bevacuzimab plus gemcitabine before chemo radiotherapy of 50.4Gy with capecitabine follwed by bevacuzimab plus gemcitabine (n=62) [19]. The two-year survival was 35% and 37% resepctively and over 10% of patients suffered disease reoccurance during adjuvant treatment [19] (**Table 4**).

The PACT-7 phase II trial randomized 102 patients with resected pancreatic cancer to either cisplatin, epirubicin, 5-FU, gemcitabine (PEFG) or gemcitabine every 4 weeks for 3 months and followed by followed by chemoradiation with continuous infusion of 5-FU. The combination chemotherapy group had a non-significant survival improvement and more haematological toxicity [20] (**Table 4**).

The RTOG 0848 phase III factorial-designed trial commenced recruitment in 2009 aiming to randomize 950 patients with resected pancreatic head cancer to adjuvant gemcitabine versus gemcitabine with erlotinib. After 5 cycles of gemcitabine those patients with no progression would then be randomised to concurrent fluoropyrimidine treatment and radiotherapy or continue with adjuvant gemcitabine based chemotherapy. In February 2014 after 378 patients had been recruited the erlotinib arm was closed to further recruitment because there was no evidence of benefit. The EORTC protocol 40084-22084 follows the RTOG 0848 protocol [21].

The CapRI-2 trial (phase II) was launched in 2008 with a view to randomise 135 patients to one of three arms [22]. The first arm involves radiotherapy (3-D conformal or intensity modulated) with cisplatin and interferon-α-2b, and 3 cycles of 5-FU chemotherapy, the second arm excludes cisplatin from the treatment schedule and the third arm excludes cisplatin and radiotherapy. It hypothesises that de-escalation of the CapRI regime is likely to reduce toxicity, with minimal impact on clinical response.

Algenpantucel-L is an immunotherapy comprising irradiated live allogenic human pancreatic cancer HAPa-1 and HAPa-2cell lines 2 genetically modified to express cell surface alpha-gal carbohydrates. In a phase II trial of 70 patients the median disease free survival was 14.1 months when used in combination with gemcitabine plus 5-FU based chemo radiotherapy [23,24]. A phase III trial which commenced in May 2010 which plans to recruit 722 patients and passed its first safety meeting in March 2014 after 222 patients had been randomised [25].

Aduvant Chemotherapy

ESPAC-1 provided evidence that adjuvant chemotherapy improves survival compared to resection without chemotherapy (**Table 2**). The survival benefit of chemotherapy was evident in resection margin positive (R1) as well as resection margin negative (R0) patients. A meta-analysis of all adjuvant chemotherapy trials showed a death reduction in patients with resected pancreatic cancers of 25% [26] with a survival advantage of post-resectional chemotherapy in those patients with an R0 margin over those with an R1 margin [27]. Adjuvant chemotherapy has been shown not to affect the improved quality of life following resection alone [28].

The CONKO-001 randomized phase III trial compared gemcitabine, which had been shown to have some advantages over 5-FU in the advanced setting [29], to observation alone following resection of pancreatic cancer [30]. Median disease free survival for the gemcitabine group was 13.4 months, significantly longer when compared to 6.9 months for the observation arm. The estimated disease free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group vs. 7.5% and 5.5% in the observation group, respectively. With longer term follow-up a significantly improved overall median survival in the gemcitabine arm of 22.8 months was also shown, versus 20.2 months in the observation arm [31] . Studies from Japan have also supported a role for gemcitabine in the adjuvant setting [32,33] (**Table 5**).

The ESPAC-3 trial initially compared resection alone with adjuvant 5-FU/FA as in ESPAC-1plus [11, 12] and also with gemcitabine based on results from the advanced cancer setting [29]. With the subsequent final results of the two-by-two factorial trial of ESPAC-1 [12] this was modified to ESPAC3 (v2) with only two arms randomizing 1088 patients to either 5-FU/FA or gemcitabine. Gemcitabine did not have an improved survival advantage of over 5-FU/FA but had a better toxicity profile [34]. By combining the data form ESPAC-1plus and the data from the initial three-armed ESPAC-3 trial it was also possible to comfirm the survival advantage of 5-FU/FA compared to resection alone (Table 5) [35].

ESPAC-3 data have been evaluated to determine the optimal duration and time to initiate chemotherapy [36]. They concluded that completion of all 6 cycles of chemotherapy was an independent prognostic factor after resection for pancreatic adenocarcinoma and there was no survival disadvantage identified from delaying initiation of chemotherapy for up to 12 weeks, thus allowing adequate time for postoperative recovery [36]. Using blinded analysis of tissue microarrays from 434 patients randomized to chemotherapy in the ESPAC-3 trial plus true controls from ESPAC-1 and ESPAC-3, it was shown that hENT1 (human equilibrative nucleoside transporter 1) expression using the 10D7G2 anti-hENT1 antibody for immunohistochemistry has the potential for greatly increased survival when using adjuvant gemcitabine in patients with a low hENT-1 levels and 5-FU/FA in those with high levels [37].

The JASPAC-01 phase III trial randomized 385 patients in Japan to receive either gemcitabine or S-1 an orally active fluoropyrimidine [38] . S-1 contains a prodrug of 5-FU (tegafur) along with two other agents designed to minimize gastrointestinal and systemic toxicity (gimerecil and oteracil) effectively increasing the tolerable tumor dose of 5-FU. The two-year survival for S-1 was 70%, significantly greater when compared to 53% for gemcitabine. Adjuvant S-1 therapy will need to be investigated in western patients with pancreatic

Table 4 Summary of the findings from randomized studies examining the effect of combination biological adjuvant chemo radiotherapy .

	Patient Number	Regime	Median Survival (Months)	Two-year survival (%)
ECOG-2204 [19]	67	Cetuximab+ Gemcitabine pre-Chemoradiotherapy, 50.4Gy +Capecitabine Chemoradiotherapy Cetuximab+Gemcitabine post-Chemoradiotherapy vs	-	35
	62	Bevacuzimab+ Gemcitabine pre- Chemoradiotherapy, 50.4Gy + capecitabine Chemoradiotherapy Bevacuzimab+ Gemcitabine post- Chemoradiotherapy	-	37
CapRI [18]	53	5-FU+CP+iFNα2b Chemoradiotherapy + 2 cycles of 5-FU post- Chemoradiotherapy vs	32.1*	-
	57	6 cycles of 5-FU/FA	28.5	-
PACT-7 [20]	51	Gemcitabine 3 months + 5-FU or capecitabine Chemoradiotherapy vs	24.8	-
	49	PEFG 3 months + 5-FU or capecitabine Chemoradiotherapy	28.9	-

HR=1.2 (0.49-2.95); p=0.49
5-FU=5-Fluorouracil.
PEFG = cisplatin, epirubicin, 5-FU, gemcitabine

cancer as their toxicity profile is quite different to patients from Japan and other parts of Asia (**Table 5**).

A recent network meta-analysis has shown that the best survival results are achieved with either adjuvant 5-FU or gemcitabine chemotherapy reducing mortality after surgery by about a third whilst chemoradiation plus chemotherapy is less effective in prolonging survival and is more toxic than chemotherapy [39]. The evidence now suggests that older and relatively ineffective chemotherapy combinations should be discarded [10,40,41] (Table 6), whereas regimens using 5-FU/FA, gemcitabine or S-1 will be the platforms for future development of adjuvant therapies [42]. In a multicentre, non-randomized phase II study, 76 patients with resected pancreatic cancer received gemcitabine and cetuximab with a median disease free survival of 10 months and a median overall survival of 22.4 months. It was concluded that the addition of cetuximab to adjuvant gemcitabine did not appear to improve survival [43]. Another phase II trial used fixed dose gemcitabine plus erlotinib in 25 patients with R0 resection for 4 months, followed by 8 months of erlotinib with a median recurrence free survival of 14 months [44].

Based on successes in the advanced pancreatic cancer setting current ongoing adjuvant trials are comparing gemcitabine with gemcitabine and capecitabine [45,46] in ESPAC-4, and adjuvant gemcitabine / capecitabine / hypothermia in the phase III Hypothermia European Adjuvant Trial (HEAT Trial) [47]. The phase II/III trial PACT 15 is evaluating adjuvant cisplatin, epirubicin, capecitabine and gemcitabine (PEXG) versus adjuvant gemcitabine versus neoadjuvant plus adjuvant PEXG [48]. The study opened in 2010 and an estimated 370 patients are planned to be recruited. CONKO-005 will investigate the effect of adjuvant erlotinib plus gemcitabine versus gemcitabine alone [49]. A combination of FA, 5-FU, irinotecan and oxaliplatin (FOLFIRINOX) [50] is being tested in both the adjuvant and neoadjuvant settings [51] and the APACT study which opened in March 2014 is testing adjuvant albumin bound paclitaxel (Abraxane) [52] plus gemcitabine against gemcitabine alone [53].

Conclusions

The understanding of pancreatic cancer biology progresses [54,55], providing earlier opportunities for treatment [56]. The current data interpretation strongly supports the continued use of adjuvant systemic chemotherapy with either 5-FU and FA or gemcitabine following curative resection for pancreatic adenocarcinoma. Gemcitabine has the added advantage of lesser

Table 5 Gemcitabine based adjuvant chemotherapy in pancreatic cancer.

	Patient Number	Regime	Median Survival (Months)	One-year Survival (%)	Two-year survival (%)	Three-year survival (%)	Five-year survival (%)
CONKO-001 [30, 31]	179	Gemcitabine	22.1	72.5	47.5	34	22.5
	175	Surgery / Observation	20.2	72.5	42	20.5	11.5
Yoshitomi et al [33]	50	Gemcitabine	29.8	85.7	-	46.9	-
	50	Gemcitabine + Uracil/tegafur	21.2 (p=0.28)	80	-	30.4	-
JSAP02 [32]	58	Gemcitabine	22.3	77.6	48.5	-	23.9
	60	Surgery alone	18.4*	75	40	-	10.6
ESPAC-3(v2) [34]	537	Gemcitabine	23.6 (p=0.39)	80.1	49.1	-	-
	551	5-FU / FA	23	78.5	48.1	-	-
JASPAC 01 [38]	191	Gemcitabine	25.5	-	53	-	-
	187	S-1	46.3**	-	70***	-	-

*HR=0.77 (0.51-1.14); p=0.19
**P<0.0001 vs gemcitabine
***HR=0.56 (042-0.74); P<0.0001
5-FU=5-Fluorouracil
FA = Folinic Acid

Table 6 Comparison of randomised trials using combination chemotherapy for resected pancreatic cancer.

	Patient Number	Regime	Median Survival (Months)	Two-year survival (%)	Three-year survival (%)	Five-year survival (%)
Bakkevold et al [10]	30	5-FU Doxorubicin Mitomycin-C	23 (p=0.02)	70	27	4
	31	Observation	11	45	30	8
Takada et al [40]	81	5-FU Mitomycin-C	-	-	-	11.5
	77	Observation	-	-	-	18
Kosuge et al [41]	45	5-FU Cisplatin	12.5	-	-	26.4
	44	Observation	15.8	-	-	14.9 (p=0.94)

5-FU=5-Fluorouracil
FA=Folinic Acid.
*Disease free survival, p<0.001
** HR 0.70, CI (0.55-0.88); p=0.003

toxicity than 5-FU, and is therefore recommended as the first line adjuvant chemotherapy agent. Adjuvant S-1 looks promising, whilst stratified medicine using predictive biomarkers such as hENT1 also need further evaluation. To date there are no studies which provide sufficient evidence to support the use of adjuvant chemoradiation, however its role in neoadjuvant therapies, is currently under investigation [57].

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