Adjuvant Therapy for Pancreatic Cancer

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Abstract

Pancreatic cancer is a challenging malignancy to treat, as less than one-fifth of diagnosed cases are resectable, surgery is complex and postoperative recovery slow, treated patients tend to relapse and overall survival rates are low. It is one of the leading causes of cancer-related mortality. Adjuvant therapy has been employed in resectable disease, to target micrometastases and improve prognosis. Chemotherapy, chemoradiotherapy (chemoRT) and chemoradiotherapy (chemoRT) followed on by chemotherapy have been evaluated in randomised controlled trials. The European Study Group for Pancreatic Cancer (ESPAC)-1 and CONKO-001 trials clearly established the survival advantage of adjuvant chemotherapy with 5 fluorouracil (5FU) plus folinic acid and gemcitabine respectively over no chemotherapy. The ESPAC-3 (version 2) trial demonstrated equivalence between 5FU plus folinic acid and gemcitabine in terms of survival parameters, though gemcitabine had a better toxicity profile. The results of these key studies, together with smaller ones have been subjected to meta-analyses, with confirmation of improved survival with adjuvant systemic chemotherapy. The EORTC-40891 and ESPAC-1 trials found no survival advantage with adjuvant chemoRT compared to observation, and this has been reflected in a subsequent meta-analysis. The popularisation of chemoRT, with follow on chemotherapy (versus observation) was based on the small underpowered GITSG trial. The ESPAC-1 trial was unable to find a survival benefit for chemoRT, with follow on chemotherapy compared to

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F. Otto and M. P. Lutz (eds.), *Early Gastrointestinal Cancers*,
Recent Results in Cancer Research 196, DOI: 10.1007/978-3-642-31629-6_5,

observation. The RTOG-9704 trial assessed chemoRT with follow on chemotherapy in both arms and found no difference between survival in the gemcitabine and 5FU arms. There has never been a published head-to-head randomised comparison of adjuvant chemotherapy to chemoRT, with follow on chemotherapy. Ongoing randomised trials are looking into adjuvant combination chemotherapy, chemotherapy with follow on chemoRT, and neoadjuvant therapy. Novel agents continue to be assessed in early phase trials with a major emphasis on predictive and prognostic biomarkers. Based on the available evidence, adjuvant chemotherapy with gemcitabine or 5FU/folinic acid is the current recommended gold standard in the management of resected pancreatic cancer.

Abbreviations

ChemoRT/CRT	Chemoradiotherapy
C.I.	Confidence interval
CT	Chemotherapy
EBRT	External beam radiotherapy
FA	Folinic acid
Gemcap	Gemcitabine + capecitabine
Gy	Gray
h ENT 1	Human equilibrative nucleoside transporter
HR	Hazard ratio
IORT	Intraoperative radiotherapy
IPD	Individual patient data
LNR	Lymph node ratio
PEXG	Cisplatin, epirubicin, capecitabine and gemcitabine
RCT	Randomised controlled trial
RFS	Recurrence-free survival
RT	Radiotherapy

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1 Introduction

Pancreatic cancer is the tenth most common cancer in the UK and USA in terms of incidence (Jemal et al. 2010; Office for National Statistics 2010), but is among the fourth or fifth leading causes of cancer death (Jemal et al. 2010; Office for National Statistics 2010). The only treatment with potential for cure is resection, but even in specialised centres just 10–15 % of diagnosed patients have resectable disease (Stathis and Moore 2010). In this select group, adjuvant chemotherapy has improved overall survival (Neoptolemos et al. 2010) or disease-free survival (Oettle et al. 2007), and more than doubled the 5 years survival rates from 10 % to nearly 25 % (Van Laethem et al. 2011).

Despite improvements, patients continue to succumb to locoregional recurrence and metastatic disease. Elucidation of cancer biology is continuing to evolve (Tuveson and Hanahan 2011; Pérez-Mancera et al. 2012), and recent research has revealed that metastases in pancreatic cancer occur much earlier than expected, providing a window of opportunity to direct treatment strategies sooner rather than later (Tuveson and Neoptolemos 2012). Increasingly efforts are being directed at early diagnosis, better treatment using combinations of existing chemotherapeutic agents (Costello and Neoptolemos 2011), searching for effective novel agents, and assessing individual patient risk and prognosis (Jamieson et al. 2011; Rizzato et al. 2011; Smith et al. 2011).

2 Rationale for Adjuvant Therapy

Pancreatectomy with standard lymphadenectomy is advocated for resectable disease. Meta-analyses of randomised controlled trials (RCT) comparing this against extended lymphadenectomy have failed to reveal any survival advantage for the latter (Michalski et al. 2007). Likewise there were no differences between morbidity, mortality and survival when meta-analyses were undertaken of RCTs examining classic whipple's resection versus pylorus preserving whipple's procedure (Diener et al. 2011).

This inability of radical surgery to improve results is owing to the tendency for the disease to recur either locoregionally or in the liver (Sperti et al. 1997; Abrams et al. 2001; Koshy et al. 2005; Hishinuma et al. 2006). Adjuvant treatment

following curative resection acts by targeting micrometastatic disease (Chua and Cunningham 2005), thereby improving outcomes.

Randomised controlled trials of adjuvant chemotherapy, adjuvant chemoradiotherapy (chemoRT), adjuvant chemoRT with follow on chemotherapy and neoadjuvant therapy will be summarised, as also the results from both aggregate and individual patient data (IPD) meta-analyses.

3 Evidence for Adjuvant Chemotherapy

3.1 Systemic Chemotherapy

3.1.1 Published Trials

Bakkevold from Norway conducted the earliest randomised trial to compare chemotherapy to best supportive care (Table 1) following resection (Bakkevold et al. 1993). There was a statistically significant survival advantage for patients in the chemotherapy arm (5FU, doxorubicin and mitomycin C), with a median survival of 23 months compared to 11 months observed in the control group ($p = 0.04$). Limitations of this study are the fact that the regime was toxic, and the study pooled both pancreatic and periampullary tumours.

Takada et al. (Takada et al. 2002) enrolled 508 patients with pancreatic, gall bladder, bile duct and ampulla of Vater cancers, with data available on the subset of the 173 pancreatic cancer patients. Patients were assigned to either chemotherapy with mitomycin C and 5FU, or observation. No difference was seen between the two treatment arms for the endpoints of disease-free survival, time to recurrence and 5 years survival rates. A criticism of this trial was the use of oral 5FU, which has very poor efficacy because of its hepatic metabolism compared to intravenously administered 5FU or specially designed oral fluoropyrimidines (Shore et al. 2003).

The European Study Group for Pancreatic Cancer (ESPAC)-1 trial (Neoptolemos et al. 2001, 2004) was the first adequately powered, randomised study to evaluate adjuvant therapy in pancreatic cancer. This two-by-two factorial design trial accrued 541 patients over 6 years. Besides the two-by-two factorial design allocation (i.e. observation, chemoRT alone, chemotherapy alone and both), randomisation outside of the two-by-two factorial design, into one of the main treatment comparisons (i.e. chemotherapy versus no chemotherapy and chemoRT versus no chemoRT) was permitted.

The final analysis of the ESPAC-1 trial assessed the 289 patients randomised using the two-by-two factorial design, and followed up for a median of 47 months (Neoptolemos et al. 2004). There was significant survival advantage with chemotherapy, with the median survival being 20.1 months in the chemotherapy arm compared to the 15.5 months seen in the no chemotherapy arm ($p = 0.009$) (Fig. 1). Prognostic factors that impacted adversely on survival were the differentiation of tumours ($P < 0.001$), lymph nodal involvement ($P < 0.001$) and a

Table 1 Randomised controlled trials of adjuvant systemic chemotherapy

Series	Period	No of patients	Regimen	Median survival (months)	Actuarial survival (%) 1 year	Actuarial survival (%) 2 year	Actuarial survival (%) 3 year	Actuarial survival (%) 5 years
Bakkevold et al.(1993)	1984– 1987	61 31	5-FU /DOX/ /MMC –	23 11 ($p = 0.02$)	70 45	– –	27 30	4 8
Takada et al.(2002) (pancreas)	1986– 1992	81 77	MMC/5-FU –	– –	– –	– –	– –	11.5 18 (p = ns)
Kosuge et al.(2006)	1992– 2000	45 44	5FU+ Cisplatin –	12.5 15.8 ($p = 0.94$)	– –	– –	– –	26.4 14.9
ESPAC-1 Final (Neoptolemos et al. 2001)	1994– 2000	147 142	5-FU –	20.1 15.5 ($p = 0.009$)	– –	40 30	– –	21 8
Oettle et al.(2007) CONKO-001	1998– 2004	179 175	Gemcitabine –	22.1 20.2 ($p = 0.06$)	– –	– –	34 20.5	22.5 11.5
Ueno et al.(2009)	2002– 2005	58 60	Gemcitabine –	22.3 18.4 ($p = 0.19$)	77.6 75	48.5 40	– –	23.9 10.6
ESPAC-3 (version 2) (Neoptolemos et al. 2010)	2000– 2007	551 537	5FU/FA Gemcitabine	23 23.6 ($p = 0.39$)	78.5 80.1	48.1 49.1	– –	– –

DOX Doxorubicin, *MMC* mitomycin C, *CRT* chemoradiation, *5FU* 5 fluorouracil, *FA* folinic acid

maximum tumour size of >2 cm ($P = 0.003$), while resection margin status did not. In the 481 patients who had undergone either Kausch-Whipple (KW) or Pylorus Preserving KW (PPKW), post-operative complications did not dent the survival benefit seen with adjuvant chemotherapy (Bassi et al. 2005).

A small Japanese RCT by Kosuge et al. evaluated chemotherapy with 5FU and cisplatin versus observation in 89 patients with pancreas cancer, with R0 resection status (Kosuge et al. 2006). There was no survival advantage for chemotherapy (median survival 12.5 months) compared to observation (median survival 15.8 months). The criticisms of this study are the likelihood that it was underpowered, and the suboptimal duration of the chemotherapy as only 2 cycles were administered.

The CONKO-001 trial by Oettle et al. (Oettle et al. 2007) compared gemcitabine to best supportive care in 368 patients, and did not find a difference in overall survival between the 2 groups. Significantly improved disease-free survival was observed in the gemcitabine arm (13.4 versus 6.9 months in control arm; $p < 0.001$). Interestingly, the 5 years survival rate in the gemcitabine arm was nearly double that in the best supportive care group 22.5% versus 11.5 %. Subsequent analyses of their 5 years data (Neuhaus et al. 2008) showed a significantly improved median survival in the gemcitabine arm (22.8 months in the gemcitabine arm versus 20.2 months in the observation arm; $p = 0.005$).

Ueno et al. randomised 119 Japanese patients to receive either 3 cycles of adjuvant chemotherapy with gemcitabine or resection only (Ueno et al. 2009). Median disease-free survival was significantly improved, though not the overall survival, and toxicity profile was acceptable. Limitations of the trial are the suboptimal duration of chemotherapy, the fact that 52 % of patients received intraoperative RT, and its underpowered nature.

Yoshitomi et al. (Yoshitomi et al. 2008) assigned 100 patients in a randomised phase 2 study to receive adjuvant gemcitabine or gemcitabine plus uracil/tegafur. The combination arm did not have an improved disease-free survival, and paradoxically a worse median survival, concluding there was no further role for the combination chemotherapy.

The most recent large RCT in this area, the ESPAC-3v2 trial randomised 1,088 patients over 7 years, with at least 2 years follow up (Neoptolemos et al. 2010). Patients were randomised to receive either 5FU + folinic acid, or gemcitabine, in version 2 of the trial (version 1 included an observation only arm which was closed once the results of ESPAC-1 trial conclusively demonstrated survival benefit for the chemotherapy arm). There was no significant overall survival difference (hazard ratio 0.94; 95 % CI 0.81–1.08) between the 5FU arm (median overall survival 23 months; 95 % CI 21–25 months) compared to the gemcitabine arm (median overall survival 23.6 months; 95 % CI 21.4–26.4 months) (Fig. 2). Likewise, there were no significant differences in progression-free survival and global quality of life scores between the two arms.

Toxicity profile on the other hand was significantly better in the gemcitabine arm compared to the 5FU arm (serious adverse events 7.5 versus 14 %; $p < 0.001$). This is reflected by the fact that median dose intensity was 79 % of the

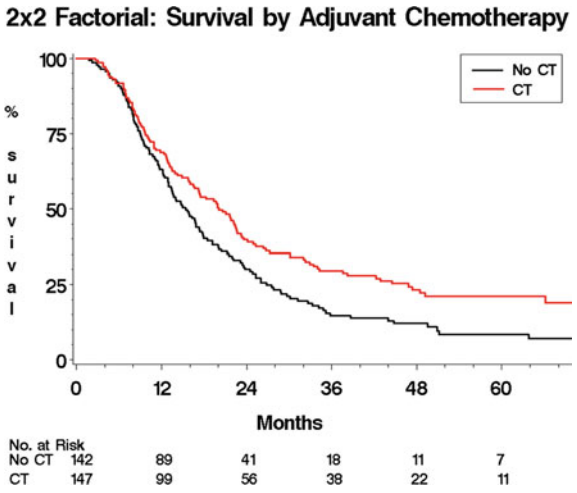

Fig. 1 Kaplan-Meier estimates of survival according to whether or not patients received chemotherapy in the ESPAC-1 trial final results

planned protocol for 5FU arm, compared to the improved 89 % for the gemcitabine arm. Independent prognostic factors of overall survival were tumour size and grade, nodal status, post-operative CA19-9 levels, performance status and smoking. As in ESPAC-1, resection margin status did not impact on overall survival on multivariate analysis.

This trial has credible external validity, as it is adequately powered, has a simple study design (in comparison to the criticism of the 2 × 2 factorial design of the ESPAC-1 trial), and recruited patients across Europe, Australasia, the Far East and North America.

Pooled data from 458 patients enrolled in the ESPAC-1, ESPAC-1 plus and ESPAC-3v1 trials were studied. There was 30 % reduction in risk of death following chemotherapy with 5FU/folinic acid (HR 0.70; 95 % CI 0.55–0.88; $p < 0.003$) compared to the control arm.

Bao et al. (Bao et al. 2011) in a phase 2 trial, studied a novel regime of fixed dose gemcitabine, which theoretically maximises cellular uptake of gemcitabine, plus erlotinib. 25 patients with R0 resection received the combination therapy for 4 months, followed by 8 months of erlotinib. Median recurrence-free survival (RFS) was 14 months in this small select group, similar to the results in ESPAC-3v2. Median overall survival was not reached, but was in excess of 2 years at the time of publication. In addition to the use of fixed-dose gemcitabine bi-weekly, the longer duration of maintenance therapy is a new feature. The authors do point out a potential possibility of overestimating RFS, as this was based on radiological progression with scans done at intervals of 6 months. Molecular analysis of Kras mutation, EGFR protein assessment and EGFR copy number did not influence RFS or recurrence patterns.

3.1.2 Ongoing Trials

The JASPAC-01 phase 3 trial currently recruiting in Japan aims to randomise 360 patients to receive either gemcitabine or S1, an orally active fluoropyrimidine (Maeda et al. 2008).

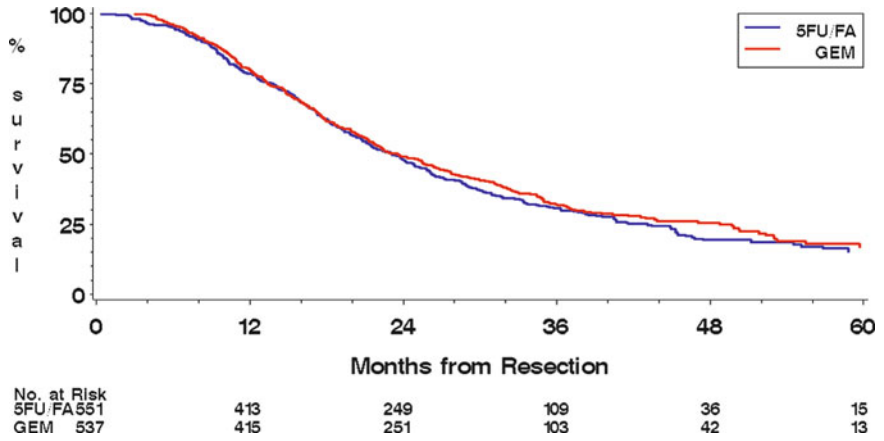

Fig. 2 Kaplan-Meier estimates of survival of the gemcitabine versus 5FU/folinic acid arms in the ESPAC-3v2 trial final results

The currently ongoing ESPAC-4 trial is taking the ESPAC-3v2 results forward, and comparing gemcitabine versus gemcitabine plus capecitabine (gemcap), an orally active fluoropyrimidine. It aims to recruit 1,080 patients, and commenced in 2008. In a recent trial of advanced pancreatic cancer, gemcap had significantly improved progression-free survival and response rate compared to single-agent gemcitabine, and revealed a trend towards improved overall survival (Cunningham et al. 2009). Meta-analyses of gemcap versus gemcitabine in the advanced cancer setting have shown significant overall survival benefit for gemcap over gemcitabine (Sultana et al. 2007). It will be interesting to see if similar results are reflected in the adjuvant situation as well.

The ESPAC-4 trial has a translational element which involves collecting blood, urine and tissue samples with a view to identifying expression profile in tumours that can predict response to treatment with gemcitabine and capecitabine.

3.2 Regional Chemotherapy

The rationale for regional chemotherapy was to direct treatment at the tumour, with the hope of reducing toxicity that accompanies systemically administered chemotherapy. Trials involving regional chemotherapy in the adjuvant setting were developed before results from the ESPAC-1 trial were published.

Based on a small study of 20 patients where a non-significant trend towards reduced liver metastases was seen in the regional chemotherapy arm (Hayashibe et al. 2007), an RCT of regional chemotherapy with 5FU, mitoxantrone and cisplatinum given via celiac axis infusion and 30 × 1.8 Gray (Gy) radiotherapy was conducted by Morak et al. (Morak et al. 2008). The observation arm of this study did not receive any chemotherapy, and once the ESPAC-1 data was in public

domain, it was deemed unethical to continue to recruit to this arm, and the trial closed. In the 120 patients of pancreatic and periampullary tumours randomised, quality of life was improved in the treatment arm compared to the control arm (Morak et al. 2010). The downsides to this trial were that only 21 patients received treatment per protocol, and there was neither overall survival benefit, nor reduction in local/hepatic recurrences in the pancreatic cancer subgroup.

Currently there is insufficient evidence to support the use of regional chemotherapy.

4 Evidence for Adjuvant Chemoradiotherapy

Radiation treatment has been given with the idea of controlling any microscopic residual disease, since most recurrences following pancreaticoduodenectomy occur at the site of resection. Radiation has been given intraoperatively (IORT) or postoperatively and often with concurrent chemotherapy both for radiosensitisation and to address systemic micrometastases.

4.1 Intraoperative Radiotherapy

The irradiation of the upper abdomen by external beam radiotherapy (EBRT) causes considerable toxicity and IORT can reduce this, sparing normal tissues. The surrounding tissues can either be displaced or shielded, thereby allowing the delivery of larger RT doses in a single fraction to volumes harbouring tumour cells.

As most series on IORT are dogged by small numbers, inclusion of all stages of the disease and heterogenous treatment strategies, it is difficult to draw conclusions or make recommendations (Hiraoka et al. 1990; Zerbi et al. 1994; Fossati et al. 1995; Coquard et al. 1997; Reni et al. 2001). The one small randomised trial on IORT (Sindelar and Kinsella 1986) was published in abstract form and found no difference in survival between surgery only and IORT (median survival 12 months in both groups). At the present time there is little to support the use of adjuvant IORT, either alone or in combination with other forms of treatment.

4.2 Postoperative Chemoradiotherapy

Klinkenbijl et al. from Norway (EORTC-40891 trial) (Klinkenbijl et al. 1999) (Table 2) randomised 218 patients with both pancreatic and periampullary tumours to either observation or radiotherapy with split course RT (40 Gy) and concurrent 5FU as continuous infusion. In patients with pancreatic cancer, the trend was in favour of chemoradiation, with the overall survival being 12.6 months in the observation group and 17.1 months in the treatment group ($p = 0.099$). The long-term results of this trial, after a median follow up of 11.3 years maintained no

difference in overall survival between the chemoRT and observation arms (death rate ratio 0.91; 95 % CI 0.68–1.23; $P = 0.54$) (Smeenk et al. 2007). The 10 years survival in the pancreatic head cancer subgroup was 8 %. The limitations of this study were the inclusion of pancreatic head and periampullary tumours, lack of maintenance chemotherapy and a questionable statistical design that limited its ability to detect a benefit for adjuvant chemoradiation (Garofalo et al. 2006).

In the ESPAC-1 trial (Neoptolemos et al. 2001), 70 patients were randomised to the chemoRT arm in the 2 × 2 factorial design, while a further 68 were randomly assigned to either chemoRT or no chemoRT. Radiation was administered as a split course, concurrent with 5FU. There was no difference in the median survival (15.5 months in chemoRT arm and 16.1 months in no chemoradiation arm; $p = 0.24$) and 2 year survival following chemoRT.

In the final results of the ESPAC-1 trial (Neoptolemos et al. 2004) the median survival was 15.9 months in the chemoRT arm and 17.9 months in the group who were not assigned to receive chemoRT ($p = 0.05$) (Fig. 3). The estimated 5-year survival was 10 % in the chemoRT arm compared to 20 % in those who did not receive chemoRT ($p = 0.05$). The lack of a survival advantage following chemoRT could be due to delays in administering radiation in patients who suffered post-operative complications. This reduces the potential benefit of chemotherapy that is derived by administering it as soon as possible after resection.

The EORTC 40013/FFCD/GERCOR phase 2 trial by Van Laethem et al. randomised 90 patients with R0 resection to either chemotherapy alone arm employing 4 cycles of gemcitabine, or chemoradiation arm, using 2 courses of gemcitabine followed by 50.4 Gy radiation concurrent with gemcitabine (Van Laethem et al. 2010). The primary endpoint was toxicity, and this was comparable in both arms (grade 4 toxicity 0 % in chemotherapy and 4.7 % in chemoRT arm). The good toxicity profile was felt to be due to the sequential concept used in the chemoRT arm, with initial chemotherapy followed on by chemoRT. There were no differences between the 2 groups for the secondary end points of overall survival (24 months in both arms), and disease-free survival (12 months in chemoRT arm and 11 months in chemotherapy alone arm).

4.3 Chemoradiotherapy, and Follow on Chemotherapy

4.3.1 Published Trials

The Gastrointestinal Tumour Study Group (GITSG) trial 9173 (Table 3) set the trend for the use of chemoRT followed by chemotherapy in resectable disease (Kalser and Ellenberg 1985). This trial randomised 43 patients to receive either chemotherapy or combined treatment (chemoRT followed by chemotherapy) in the form of split course EBRT (40 Gy) and concurrent 5FU, followed by 5FU for 2 year. The study was terminated prematurely both because of a low rate of accrual and because of an increasingly large difference in survival between the study arms. The median survival for the adjuvant treatment group was 20 months,

Table 2 Randomised controlled trials of adjuvant chemoradiotherapy

Series	Period	Number of patients	Regimen	Median survival (months)	Actuarial survival (%) 1 year	Actuarial survival (%) 2 year	Actuarial survival (%) 3 year	Actuarial survival (%) 5 years
(Klinkenbijl et al. 1999)	1987–1995	110	40 Gy + 5FU	24.5	41	–	–	10
		108	–	19 ($p = 0.208$)	51	–	–	20
ESPAC-1 final—2 × 2 factorial (Neoptolemos et al. 2004)	1994–2000	145	40 Gy + 5FU, with 5FU/FA maintenance	15.9	–	29	–	10
		144	–	17.9 ($p = 0.05$)	–	41	–	20
ESPAC-1 final—individual treatment groups (Neoptolemos et al. 2004)	1994–2000	69	Observation	16.9	–	–	–	11
		73	40 Gy + 5FU	13.9	–	–	–	7
Van Laethem et al. (phase 2)(2010)	2000–2007	45	Gem 4 cycles	24.4	–	50.2	–	–
		45	Gem 2 cycles, followed by Gem + 50.4 Gy	24.3	–	50.6	–	–

5FU 5- fluorouracil, *FA* folinic acid, *Gy* grey, *Gem* gemcitabine

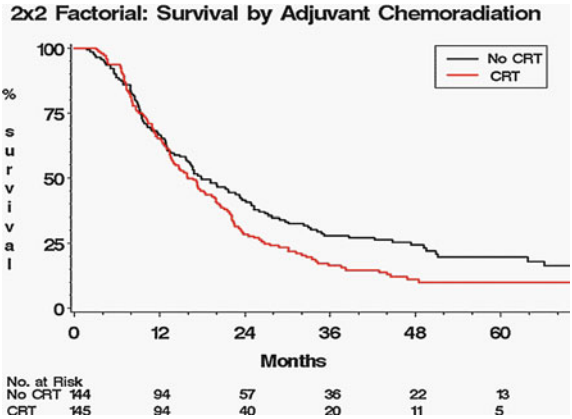

Fig. 3 Kaplan-Meier estimates of survival according to whether or not patients received chemoradiotherapy (*chemoRT*) in the ESPAC-1 trial final results

significantly longer than the 11 months in the no adjuvant treatment arm. Because there were so few cases, a further 30 patients were registered (not randomised) to the treatment arm and the median survival in this group was 18 months, with a 2 year survival rate of 46 % (Doughlass 1987). Owing to the small number of patients, the 95 % confidence intervals of the survival curves were so large as to overlap with survival curves in patients receiving no additional treatment. Thus, no convincing conclusion could be derived from this study, though it must be noted that the benefit from treatment could be due to the maintenance chemotherapy used in this study.

The Radiation Therapy Oncology Group Study 9704 (Regine et al. 2008) RCT compared gemcitabine versus 5FU administered pre- and post-5FU-based chemoradiation. Chemotherapy was given for 3 weeks before and 12 weeks after 50.4 Gy chemoRT. In the 451 patients randomised and eligible, there was no difference in overall survival between the 2 arms ($p = 0.34$). On subgroup analysis of the pancreatic head tumours, there was a trend towards improved survival in the gemcitabine arm (median survival 20.2 months) compared to the 5FU arm (median survival 16.9 months) but this was not statistically significant (HR 0.82; 95 % CI 0.65–1.03). Analysis of their 5 years data showed no changes to the original inferences drawn (Regine et al. 2011).

This was the first phase 3 trial to prospectively evaluate post-resectional CA19-9 levels (Berger et al. 2008). In Lewis antigen positive patients, post-resectional CA19-9 values of both >90 kU/L (HR 3.4; $p < 0.001$) and >180 kU/L (HR 3.53; $p < 0.001$) adversely impacted on survival. The prognostic value of nodal involvement is known, and the RTOG dataset was used to assess the influence of total examined nodes, number of positive nodes and lymph node ratio (LNR) on survival (Showalter et al. 2011). Total lymph nodes examined cut off of 15 was suggested to improve disease staging. Number of positive lymph nodes of >3 and LNR of 33 % were associated with worse overall and disease-free survival.

Immunohistochemistry for human equilibrative nucleoside transporter 1 (hENT1) protein, which transports gemcitabine into cells, was performed on tissue

microarrays of 229 patients from the RTOG 9704 trial (Farrell et al. 2009). In both univariate and multivariate analyses, hENT1 expression was associated with improved overall and disease-free survival in the gemcitabine arm, but not the 5FU arm. Another secondary analysis in 141 patients suggested the RecQ1 A159C genotype had prognostic relevance in the chemoradiation arm (Li et al. 2011).

Review of the RT quality assurance in RTOG 9704 (Abrams et al. 2012) found that RT administration was nearly evenly split by per protocol versus less than per protocol (52 % versus 48%) administration. On post hoc analysis of overall survival, those patients who had received per protocol RT had significantly improved survival compared to the less than per protocol group (HR 0.75; 95 % CI 0.60–0.93). This is an interesting observation, but it must be interpreted against the backdrop that the RT quality assessment's impact on survival was not one of the a priori outcomes of the trial.

The ASOCOG Z05031 phase 2 trial evaluated cisplatin, 5FU and interferon-alfa-2b-based 3 dimensional conformal RT, followed on by 5FU chemotherapy (Picozzi et al. 2011). This study was closed to accrual before its target recruitment number of 93 was reached due to 95 % (80/89 patients) grade 3 or more all cause toxicity. Forty four percent of patients did not complete all phases of the treatment per protocol, and only 17 % were able to complete the chemoRT component without interruption. A previous phase 2 trial of interferon-based chemoRT, which differed from the ASOCOG Z05031 trial in using gemcitabine for follow on chemotherapy, also reported significant dose and treatment-limiting toxicities (Linehan et al. 2008).

The CAPRI trial evaluated chemotherapy with 5FU versus chemoradiation using cisplatin, interferon alpha-2b and 5FU, with follow on 5FU chemotherapy (Knaebel et al. 2005; Marten et al. 2009). The chemoradiation protocol was based on a phase II trial conducted by Picozzi et al. who reported an impressive 5 year survival of 55 % in 43 patients (Picozzi et al. 2003). In the 110 patients randomised, there was significantly reduced local recurrence in the chemoRT arm (29.3% versus 55.6 %; $p = 0.014$). This however did not translate into a survival benefit, as there was no significant difference in overall survival between the adjuvant 5FU/folinic acid arm (median overall survival 28.5 months) and the chemoRT arm (median overall survival 32.1 months) (Marten et al. 2010). There was greater grade 3/4 toxicity in the chemoRT arm (68 %) compared to the adjuvant chemotherapy group (16 %).

A phase 2 trial ECOG 2204 randomised 137 patients to receive one of 2 novel agents viz., cetuximab or bevacuzimab against a backdrop of capecitabine-based radiotherapy, with gemcitabine administered pre- and post-chemoRT (Berlin et al. 2010). The safety and toxicity profiles were acceptable, but as over 10 % of patients experienced recurrence, further development of this regime was felt to be futile.

4.3.2 Ongoing Trials

Algenpantucel-L (irradiated live allogenic human pancreatic cancer cells) in combination with gemcitabine chemotherapy plus 5FU-based radiotherapy (as in RTOG 9704) has been subjected to a phase 2 trial (NLG0205) (Hardacre et al. 2011).

Table 3 Randomised controlled trials of adjuvant chemoradiotherapy, followed on by chemotherapy

Series	Period	Number of patients	Regimen	Median survival (months)	Actuarial survival (%) 1 year	Actuarial Survival (%) 2 year	Actuarial Survival (%) 3 year	Actuarial Survival (%) 5 years
GITSG 9173(Kalser and Ellenberg 1985)	1987–1995	21	40 Gy + 5FU, with 5FU maintenance	21	–	43	–	19
		22	Observation	10.9 ($p = 0.03$)	–	18	–	5
ESPAC-1 final—individual treatment groups(Neoptolemos et al. 2004)	1994–2000	69	Observation	16.9	–	38.7	–	29
		72	40 Gy + 5FU, with 5FU/FA maintenance	19.9	–	35.5	–	13
RTOG-9704(Regine et al. 2008) All patients head of pancreas only eligible = 381	1998–2002	221	Gem preCRT, 50.4 Gy + 5FU, gem post CRT	–	–	–	–	–
		230	5FU preCRT, 50.4 Gy + 5FU, 5FU post CRT	– ($p = 0.34$)	–	–	–	–
		187	Gem preCRT, 50.4 Gy + 5FU, gem post CRT	20.5	–	–	31	–
		194	5FU preCRT, 50.4 Gy + 5FU, 5FU post CRT	16.9 ($p = 0.09$)	–	–	22	–

5FU 5- fluorouracil, *FA* folinic acid, *Gem* gemcitabine, *Gy* gray, *CRT* chemoradiation

In the 73 patients enrolled, toxicity was low, the median disease-free survival was 16 months (improved compared to the 11 months observed in the RTOG trial) and median overall survival had not been reached. These outcomes prompted the investigators to launch a phase 3 trial which commenced enrolment May 2010.

The CapRI-2 trial has been launched, with a view to randomise 135 patients to one of 3 arms (Marten et al. 2009). Two arms involve radiotherapy (3D conformal or intensity modulated), though the CapRI protocol has been de-escalated, while the third arm has adjuvant chemotherapy plus interferon alpha-2-b. It hypothesises that removal of the cisplatin and radiotherapy components are likely to reduce toxicity, with minimal impact on clinical response.

Another recently opened RCT, the EORTC/US Intergroup/RTOG 0848 trial aims to assess gemcitabine versus gemcitabine plus erlotinib given for 6 cycles, followed on by either 1 cycle of chemotherapy or 1 cycle of chemoRT (with 5FU or capecitabine, and employing intensity-modulated RT plus prospective central quality assurance of RT) in selected patients who do not progress on the initial chemotherapy (Regine et al. 2011). It remains to be seen if this trial will be adequately powered to assess the second part i.e. chemotherapy versus chemoRT in those with non-progressive disease, and if there really is any role for chemoRT so far down the line.

5 Evidence for Neoadjuvant Therapy

5.1 Published Studies

The attractiveness of neoadjuvant therapy lies in the fact that nearly 20–30 % of resected patients fail to receive adjuvant therapy on the grounds of delayed recovery from major surgery, co-morbidities, patient choice and early recurrence. The advantages with neoadjuvant treatment are a relatively fitter patient, earlier treatment of systemic micrometastases, the ability to in vivo assess tumour response, avoidance of unnecessary surgery in those with occult metastases, reducing risk of tumour spillage at surgery and potential for down staging disease from unresectable/borderline resectable to resectable. The disadvantages are difficulty in differentiating between pancreatic head and periampullary tumours, risk of exposure to chemotherapy in the absence of malignancy, the necessity for histology with the potential for attendant delays, loss of window of opportunity to pursue curative resection and risk of increased postoperative complications.

Drawing from the experience of neoadjuvant therapy in the advanced disease, Palmer et al. randomised 50 patients with resectable disease in a randomised phase 2 study to either receive neoadjuvant gemcitabine or gemcitabine plus cisplatin (Palmer et al. 2007). During the course of the trial, the gemcitabine cisplatin administration schedule was altered to reduce toxicity. The primary end point of resection rate was significantly higher in the combination arm (70% versus 38 %), without increased postoperative morbidity. Twelve month survival rate was also

higher in the combination arm (62 % versus 42 %), suggesting further study of the combination arm in a phase 3 trial. An American phase 2 prospective study using the same combination obtained similar results (Heinrich et al. 2008a; Heinrich et al. 2008b).

Gemcitabine-based chemoRT (Evans et al. 2008), gemcitabine cisplatin-based chemoRT (Le Scodan et al. 2009) and docetaxel-based chemoRT (Turrini et al. 2010) were promising in phase 2 trials, though upfront gemcitabine plus cisplatin (4 cycles) followed by gemcitabine chemoRT did not confer any added advantage (Varadhachary et al. 2008). Comparison of gemcitabine chemoRT to gemcitabine, cisplatin, 5FU chemo followed by 5FU chemoRT in a randomised phase 2 trial revealed significantly greater toxicity in the combination arm (Landry et al. 2010). Moreover, this trial closed prematurely due to poor accrual.

5.2 Ongoing Studies

Despite the multitude of phase I/II trials, and observational studies in this area, there is only one phase 3 randomised study comparing resection followed by adjuvant chemotherapy to neoadjuvant chemoRT (gemcitabine + cisplatinum; 3 dimensional conformal RT at dose of 55.8 Gy to tumour and 50.4 to regional lymph nodes), followed by resection and adjuvant chemotherapy (Brunner et al. 2007). Disappointingly this trial has recruited less than a third of its planned 254 patients over 7 years, and will be closed before target accrual is reached (Gillen et al. 2010).

An Italian Co-operative group (Reni 2010) have launched a phase 2 randomised study, with one arm allocated to adjuvant therapy with gemcitabine for 6 months, a second arm to receive adjuvant treatment with cisplatin, epirubicin, capecitabine and gemcitabine (PEXG) for 6 months and a third arm assigned to 3 months PEXG neoadjuvant therapy followed by surgery and adjuvant 3 months of PEXG.

6 Evidence from Meta-Analyses

6.1 Adjuvant Therapy

An IPD meta-analyses (Stocken et al. 2005) evaluated the roles of adjuvant chemotherapy, and chemoradiation in patients with pancreatic ductal adenocarcinoma. Of the 5 eligible RCTs (939 patients), IPD were available in 4 studies (875 patients). Adjuvant chemotherapy resulted in 25 % reduction in the risk of death (hazard ratio = 0.75, 95 % CI: 0.64, 0.90, $P_{strat} = 0.001$) compared to no chemotherapy. In contrast, there was no significant difference between chemoradiation versus no chemoradiation (hazard ratio = 1.09, 95 % CI: 0.89, 1.32, $P_{strat} = 0.43$). Subgroup analyses based on age, tumour size, differentiation, resection margin status and nodal status revealed that chemotherapy was less effective ($\chi^2 = 7.3$; $p = 0.007$) in the

subgroup with positive resection margin, in comparison to chemoradiation which was more effective here ($\chi^2 = 4.2$; $p = 0.04$).

The influence of resection margin on survival was explored further by the Pancreatic Meta-analyses Group (Butturini et al. 2008) using the same IPD (Stocken et al. 2005). Resection margin status did not impact on overall survival (HR 1.10; 95 % CI 0.94–1.29), though there was a trend towards reduced survival in the R1 group (median survival 14.1 months; 95 % CI 11.9–16.4 months) compared to the R0 group (median survival 15.9 months; 95 % CI 14.6–17.4 months). Adjuvant chemotherapy resulted in a significant (35 %) reduction in risk of death (HR 0.65; 95 % CI 0.53–0.80) in the R0 group, with a 7 months survival advantage compared to the no chemotherapy arm. On the other hand, chemoradiation did not significantly reduce the risk of death in the R1 group (HR 0.72; 95 % CI 0.47–1.10).

A subsequent aggregate data meta-analyses (Boeck et al. 2007) of 5 RCTs (951 patients) of adjuvant treatment concluded that chemotherapy improved median survival by 3 months (95 % CI 0.3–5.7 months; $p = 0.03$), but did not impact on 5 years survival rates, possibly due to the low numbers at risk at this time point. It included two further RCTs on chemotherapy versus best supportive care (Kosuge et al. 2006; Oettle et al. 2007), compared to the previously published IPD meta-analyses, but did not include the 5 years results from the CONKO-001 trial. Chemotherapy with either 5FU and folinic acid, or gemcitabine was advocated, though significant inter-trial heterogeneity was noted. A criticism of this study was that the methodology of the meta-analyses, utilising median survival and rates at different time points. These have been shown to not be the ideal surrogate measures for meta-analyses of survival data (Michiels et al. 2005).

6.2 Neoadjuvant Therapy

In the absence of published randomised phase 3 trials of neoadjuvant therapy to date, a comprehensive systematic review by Gillen et al. of 111 prospective ($n = 78$), including phase I/II studies and retrospective ($n = 33$) studies has been carried out (Gillen et al. 2010). There was significant inter-trial heterogeneity, and potential for bias owing to the non-randomised nature of the studies. The majority (>90 %) of neoadjuvant treatment was in the form of chemoRT. In hospital mortality (5.3 %; 95 % CI 4.1–6.8 %) in resectable patients who received upfront treatment was at the upper limits of figures quoted for high volume centres.

The median survival for resectable patients who received neoadjuvant chemotherapy and went on to have a resection was 23.3 months (95 % CI 12–54 months), comparable with survival following resection and adjuvant treatment in the ESPAC-3v2 trial. Paradoxically in resectable patients who progressed on neoadjuvant therapy and did not undergo resection, the median survival was an abysmal 8.4 months (95 % CI 6–14 months). It appears likely that these patients lost their window of opportunity to undergo curative resection.

Two other meta-analyses on neoadjuvant therapy, one looking at 14 phase 2 clinical trials (536 patients) (Assifi et al. 2011) and another evaluating 20 prospective studies of preoperative/neoadjuvant gemcitabine (707 patients) (Andriulli et al. 2011) echoed the results of Gillen et al's exhaustive meta-analyses. The conclusion from all 3 meta-analyses was that currently neoadjuvant therapy appears to only benefit patients with borderline resectable/locally advanced disease.

7 Conclusions

Currently, there is strong level 1a evidence to support the continued use of adjuvant systemic chemotherapy with either 5FU/folinic acid or gemcitabine following curative resection. There is level 1b evidence to support adjuvant gemcitabine over 5FU/folinic acid on the grounds of reduced toxicity.

Despite advances in radiotherapy delivery techniques and quality assurance, there is still neither level 1a nor level 1b evidence to support the use of adjuvant chemoRT alone or with a follow on chemotherapy, over adjuvant chemotherapy. Based on available literature, there is insufficient evidence to support neoadjuvant therapy, intraoperative radiotherapy and regional chemotherapy.

8 Future Directions

Personalised chemotherapy using predictive biomarkers may enable us to utilise existing resources more effectively. Higher levels of hENT1 and human concentrative nucleoside transporter (h CNT) 1 and 3 expression may be associated with improved overall and disease-free survival in patients who received gemcitabine, but this notion has yet to be properly evaluated (Farrell et al. 2009; Marechal et al. 2009). Expanding this to assess the roles of other enzymes involved in gemcitabine metabolism such as cytidine deaminase, cytidine deoxy kinase and ribonucleoside reductase subunits 1 and 2, may predict sensitivity to gemcitabine (Tempero et al. 2003). Likewise in colorectal cancer, thymidylate synthase can predict sensitivity for fluorinated pyrimidines and this could be extended to the pancreatic cancer setting.

In addition to evaluating combinations of chemotherapy, translational research into prognostic and predictive biomarkers and new biological agents merit attention. Assessing neoadjuvant therapy in patients with borderline resectable disease, with clear cut definition of what constitutes this, would also be an area for future studies.

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