Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis

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Summary

Background Major adjuvant treatments for pancreatic adenocarcinoma include fluorouracil, gemcitabine, chemoradiation, and chemoradiation plus fluorouracil or gemcitabine. Since the optimum regimen remains inconclusive, we aimed to compare these treatments in terms of overall survival after tumour resection and in terms of grade 3–4 toxic effects with a systematic review and random-effects Bayesian network meta-analysis.

Methods We searched PubMed, trial registries, and related reviews and abstracts for randomised controlled trials comparing the above five treatments with each other or observation alone before April 30, 2013. We estimated relative hazard ratios (HRs) for death and relative odds ratios (ORs) for toxic effects among different therapies by combining HRs for death and survival durations and ORs for toxic effects of included trials. We assessed the effects of prognostic factors on survival benefits of adjuvant therapies with meta-regression.

Findings Ten eligible articles reporting nine trials were included. Compared with observation, the HRs for death were 0·62 (95% credible interval 0·42–0·88) for fluorouracil, 0·68 (0·44–1·07) for gemcitabine, 0·91 (0·55–1·46) for chemoradiation, 0·54 (0·15–1·80) for chemoradiation plus fluorouracil, and 0·44 (0·10–1·81) for chemoradiation plus gemcitabine. The proportion of patients with positive lymph nodes was inversely associated with the survival benefit of adjuvant treatments. After adjustment for this factor, fluorouracil (HR 0·65, 0·49–0·84) and gemcitabine (0·59, 0·41–0·83) improved survival compared with observation, whereas chemoradiation resulted in worse survival than fluorouracil (1·69, 1·12–2·54) or gemcitabine (1·86, 1·04–3·23). Chemoradiation plus gemcitabine was ranked the most toxic, with significantly higher haematological toxic effects than second-ranked chemoradiation plus fluorouracil (OR 13·33, 1·01–169·36).

Interpretation Chemotherapy with fluorouracil or gemcitabine is the optimum adjuvant treatment for pancreatic adenocarcinoma and reduces mortality after surgery by about a third. Chemoradiation plus chemotherapy is less effective in prolonging survival and is more toxic than chemotherapy.

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Introduction

Pancreatic adenocarcinoma is the most lethal cancer, with a 5-year survival rate of less than 5%.[1] Because relapse occurs in 80–85% of patients after tumour resection,[1–3] adjuvant treatment has been advocated to reduce relapse and prolong survival after surgery. The major adjuvant treatments after resection of pancreatic adenocarcinoma include chemotherapy (fluorouracil or gemcitabine), fluorouracil-based chemoradiation, and chemoradiation plus chemotherapy (fluorouracil or gemcitabine). However, the optimum treatment remains controversial.

The results of previous randomised controlled trials assessing adjuvant fluorouracil and gemcitabine were contradictory, and few issues in oncology have been more divisive than whether chemoradiation should be given after resection of pancreatic adenocarcinoma.[4] Although adjuvant fluorouracil reduced death after resection of pancreatic adenocarcinoma by about 30% in the European Study Group for Pancreatic Cancer (ESPAC) 1 trial,[5] gemcitabine provided only a non-significant[6] or marginal[3] overall survival advantage over observation in previous trials, despite its slight survival advantage over fluorouracil in inoperable pancreatic adenocarcinoma.[7] Chemoradiation is intended to reduce local recurrence by administering radiation to the pancreatic bed with concurrent fluorouracil as a radiosensitiser and is the standard of care in the USA,[8–10] but it did not provide a significant survival benefit over observation in previous trials.[5,11,12] Most notably, in ESPAC-1 it was identified that patients receiving chemoradiation (with or without chemotherapy) seemed to have shorter survival (hazard ratio [HR] for death 1·28, 95% CI 0·99–1·66) than those patients not receiving chemoradiation,[5] therefore chemoradiation is not commonly used in the UK and Europe.[4,5] A previous meta-analysis[13] was attempted to resolve the controversies of this issue, but trials assessing gemcitabine were not available at that time, and the analysis was used to assess different chemotherapeutic drugs as a single treatment and considered only survival benefit but not treatment-related toxic effects.

Synthesis of present evidence on this issue using traditional meta-analysis methods is a challenging task: first, among available treatments, a lack of head-to-head trials makes direct comparisons of certain treatments

See Online for appendix

impossible, and, second, the measures of survival varied among different trials. Bayesian network meta-analysis, also known as mixed treatment comparison, is a potential solution to the above problems. Mixed treatment comparison enables indirect comparison using a common comparator when a head-to-head trial is not available and combines direct and indirect comparisons to simultaneously compare several treatments with preservation of randomisation in individual trials.[14–16] Moreover, different measures of survival can be combined in a single analysis on the HR scale, avoiding potential selection bias and loss of information due to only including studies with the same measure or doing separate analyses for different measures.[17] To establish the optimum adjuvant treatment for pancreatic adenocarcinoma, we did a random-effects network meta-analysis to compare the major adjuvant treatments (fluorouracil, gemcitabine, chemoradiation, chemoradiation plus fluorouracil, and chemoradiation plus gemcitabine) in terms of overall survival and toxic effects.

Methods

Search strategy and selection criteria

We did our systematic review in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[18] We searched PubMed, the Cochrane Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews, ClinicalTrials.gov, and the American Society of Clinical Oncology database of abstracts for randomised controlled trials of adjuvant treatments of pancreatic adenocarcinoma until the end of April 2013 without language or date restrictions (see appendix for full search terms). We manually searched bibliographies of included trials and related reviews for additional references.

In our meta-analysis we included trials that compared two or more of six treatment strategies (observation alone and the above five adjuvant treatments) after resection of pancreatic adenocarcinoma. We excluded studies if they contained only one or none of the six strategies or did not use randomisation for treatment allocation.

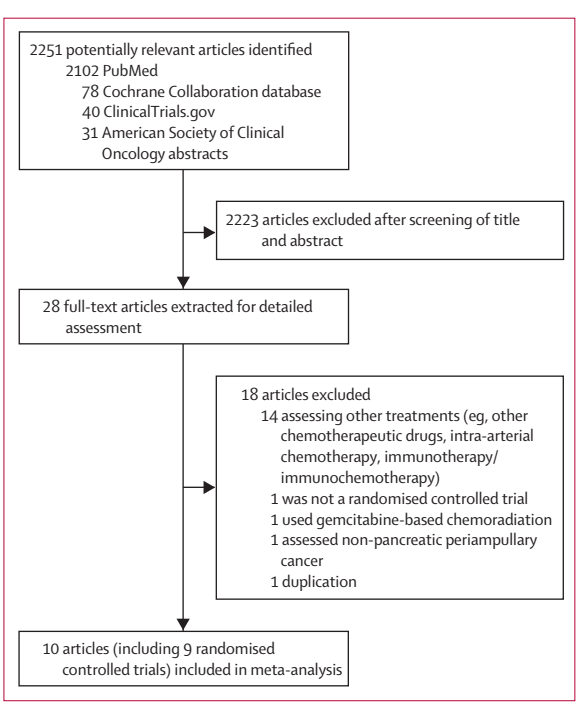

Figure 1: **Literature search and selection**

Data extraction and assessment for risk of bias

Two investigators (W-CL, Y-LL) independently reviewed the full manuscripts of eligible studies and extracted information into an electronic database, including patient characteristics, inclusion and exclusion criteria, treatment protocols, and outcomes (overall survival and grade 3–4 haematological, non-haematological, and overall toxic effects). We focused only on grade 3–4 toxic effects because grade 1–2 had lesser clinical significance and was not consistently reported in the included trials. For reports of the same trial at different follow-up periods, data of the last report were used for analysis. Risk of bias of individual studies was assessed independently by the same reviewers with the Cochrane risk of bias method.[19] Disagreement was resolved by joint review of the manuscript to reach consensus.

Data synthesis and analysis

The outcomes we analysed were overall survival after resection of pancreatic adenocarcinoma, treatment-related grade 3–4 haematological, non-haematological, and overall toxic effects. To account for heterogeneity between studies, we used random-effects models for meta-analysis. For meta-analysis of overall survival, the reported adjusted HRs were our preferred outcome measure because HRs account for censoring, provide time-to-event information, and confounders have been adjusted for.[17] When HRs were not reported we estimated them from summary statistics with the method described by Tierney and colleagues.[20] If the report did not provide enough information for estimating HRs, we used median survival durations. We combined different summary statistics (ie, HRs and survival durations) in a single Bayesian network meta-analysis using the method described by Woods and colleagues.[17] This approach avoids potential selection bias and misleading results caused by selective inclusion of studies and accounts for the correlation among relative treatment effects in trials with more than two treatment groups.[17] To assess whether there was inconsistency between direct and indirect comparisons, we compared the pooled HRs from the network meta-analysis with corresponding HRs from traditional pair-wise random-effects meta-analysis of direct comparisons. To assess whether the effects of

adjuvant treatments on survival were affected by differences in the distribution of prognostic factors between the trials, we did meta-regression by including major prognostic factors as covariates, such as the percentage of patients with positive resection margins, positive lymph nodes, and poorly differentiated or

	Number of patients	Median overall survival in months (95% CI)	Hazard ratio (95% CI)	Number of patients experiencing toxic effects		
				Overall	Haematological	Non-haematological
GITSG (North America)[25]						
20 Gy and 500 mg/m² daily fluorouracil for 3 days for two courses, then 500 mg/m² weekly fluorouracil for 2 years	22	20	NA	3	3	0*
Observation	21	11	NA	..	..	..
ESPAC-1 (Europe)[5,11]						
Subgroup 1 (reported in 2001) 20 mg/m² daily folinic acid and 425 mg/m² fluorouracil for 5 days every 28 days for six courses	92	NA	0·44 (0·29–0·65)†	NA	NA	NA
Observation	96	NA	1 (Ref)	..	..	..
Subgroup 2 (reported in 2001) 20 Gy and 500 mg/m² daily fluorouracil for 3 days for two courses	33	NA	0·79 (0·43–1·44)†	NA	NA	NA
Observation	35	NA	1 (Ref)	..	..	..
Subgroup 3 (updated in 2004) 20 Gy and 500 mg/m² daily fluorouracil for 3 days for two courses	73	13·9 (12·2–17·3)	1·36 (0·96–1·94)†	2	0	2
20 mg/m² daily folinic acid and 425 mg/m² fluorouracil for 5 days every 28 days for six courses	75	21·6 (13·5–27·3)	0·70 (0·49–1·02)†	11	2	9
20 Gy and 500 mg/m² daily fluorouracil for 3 days for two courses, then 20 mg/m² daily folinic acid and 425 mg/m² fluorouracil for 5 days every 28 days for six courses	72	19·9 (14·2–22·5)	*vs* fluorouracil: 1·31 (0·90–1·90)†, *vs* chemo-radiation: 0·67 (0·47–0·95)†	16	5	11
Observation	69	16·9 (12·3–24·8)	1 (Ref)	..	..	..
CONKO-001 (Europe)[3]						
Weekly gemcitabine 3 weeks on/1 week off for six courses	179	22·1 (18·4–25·8)	0·79 (0·63–1·01)†	5*	NA	NA
Observation	175	20·2 (17·0–23·4)	1 (Ref)	..	..	..
EORTC 40891 (Europe)[12]						
40 Gy and 25 mg/kg fluorouracil, daily with the first 20 Gy and 1–5 days with the remaining 20 Gy	63	21·6 (18·0–28·8)	0·74 (0·49–1·10)	10	0	10
Observation	57	19·2 (14·4–27·6)	1 (Ref)	..	..	..
RTOG 9704 (North America)[9,26]‡						
1000 mg/m² weekly gemcitabine for 3 weeks, then radiation 50·4 Gy with 250 mg/m² daily fluorouracil, then weekly gemcitabine 3 weeks on/1 week off for three courses	221	NA	0·82 (0·65–1·02)	175	129	129
250 mg/m² daily fluorouracil for 3 weeks, then radiation 50·4 Gy with 250 mg/m² daily fluorouracil, then daily fluorouracil 4 weeks on/2 weeks off for two courses	230	NA	1 (Ref)	143	22	137
JSAP-02 (Japan)[6]						
Weekly gemcitabine 3 weeks on/1 week off for 3 courses	58	22·3 (16·1–30·7)	0·77 (0·51–1·14)	51	40	11
Observation	60	18·4 (15·1–25·3)	1 (Ref)			..
ESPAC-1+, ESPAC-3 v1 (Europe)[27]						
20 mg/m² daily folinic acid and 425 mg/m² fluorouracil for 5 days every 28 days for six courses	158	ESPAC-1+ 24·0 (18·8–29·4) ESPAC-3 v1 25·9 (18·3–36·3)	ESPAC-1+ 0·58 (0·42–0·80) ESPAC-3 v1 0·89 (0·59–1·33)	NA	NA	NA
Observation	156	ESPAC-1+ 12·8 (10·2–16·9) ESPAC-3 v1 20·3 (18·1–31·7)	ESPAC-1+ 1 (Ref) ESPAC-3 v1 1 (Ref)	..	..	..
ESPAC-3 v2 (Europe)[28]						
1000 mg/m² weekly gemcitabine for 3 weeks every 4 weeks for six courses	537	23·6 (21·4–26·4)	0·90 (0·78–1·04)	221	119	102
20 mg/m² daily folinic acid and 425 mg/m² fluorouracil for 5 days every 28 days for six courses	551	23·0 (21·1–25·0)	1 (Ref)	379	121	258

NA=not available. Ref=reference group (hence hazard ratio set to 1). *Serious adverse event. †Estimated from summary statistics. ‡Toxic effects reported in 2008, overall survival updated in 2011.

Table: **Summary of randomised controlled trials of adjuvant treatments for pancreatic adenocarcinoma by trial and region**

undifferentiated tumours in individual studies.[21,22] In our meta-regression model we used a single interaction term, product of the difference in effect of all adjuvant treatments relative to observation and centred covariate value, as recommended by UK's National Institute for Health and Care Excellence.[23] For toxic effects, we compared only the five adjuvant treatments and calculated odds ratios (ORs) from the number of total patients and the number of patients with toxic effects in each trial for meta-analysis.

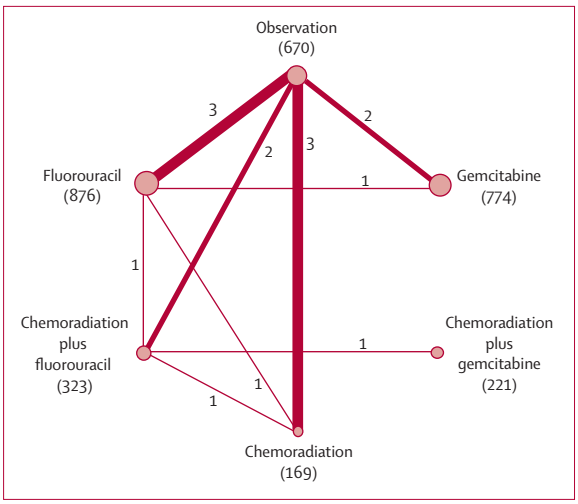

Figure 2: **Network of the comparisons for the Bayesian network meta-analysis**
The size of the nodes is proportional to the number of patients (in parentheses) randomised to receive the treatment. The width of the lines is proportional to the number of trials (beside the line) comparing the connected treatments.

We did the traditional pair-wise meta-analysis with Stata 12 (StataCorp, College Station, TX, USA). Bayesian network meta-analysis was done with WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). We used non-informative uniform and normal prior distributions[14,15] and three different sets of starting values to fit the model, yielding 150 000 iterations (50 000 per chain) to obtain the posterior distributions of model parameters. For overall survival and toxic effects, we used 5000 burn-ins and a thinning interval of 50 for each chain. For non-haematological toxic effects, the thinning interval was increased to 100 to minimise autocorrelation. For haematological toxic effects, chemoradiation could not be reliably compared with other treatments because no event occurred with chemoradiation in included studies, so we only considered comparisons between the other four treatments and increased the burn-in interval to 10 000 and thinning interval to 100. Convergence of iterations was assessed with the Gelman-Rubin-Brooks statistic.[24]

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

A

Observation	0·62 (0·42–0·88) 0·65 (0·49–0·84)	0·68 (0·44–1·07) 0·59 (0·41–0·83)	0·91 (0·55–1·46) 1·10 (0·72–1·63)	0·54 (0·15–1·80) 0·63 (0·25–1·51)	0·44 (0·10–1·81) 0·52 (0·18–1·40)
	Fluorouracil	1·10 (0·70–1·86) 0·91 (0·62–1·36)	1·48 (0·87–2·50) 1·69 (1·12–2·54)	0·87 (0·27–2·69) 0·98 (0·42–2·17)	0·72 (0·18–2·75) 0·80 (0·30–2·04)
		Gemcitabine	1·35 (0·69–2·46) 1·86 (1·04–3·23)	0·79 (0·21–2·71) 1·08 (0·41–2·69)	0·65 (0·14–2·70) 0·88 (0·29–2·52)
			Chemoradiation	0·59 (0·19–1·74) 0·58 (0·26–1·23)	0·48 (0·12–1·79) 0·47 (0·19–1·17)
				Chemoradiation plus fluorouracil	0·82 (0·40–1·71) 0·82 (0·50–1·35)
					Chemoradiation plus gemcitabine

B

Fluorouracil	0·33 (0·03–4·29)	0·13 (0·01–2·12)	1·61 (0·11–19·85)	3·72 (0·09–121·90)
	Gemcitabine	0·39 (0·01–13·60)	4·86 (0·12–135·3)	11·22 (0·12–687·50)
		Chemoradiation	12·01 (0·72–235·60)	27·80 (0·63–1290·0)
			Chemoradiation plus fluorouracil	2·31 (0·18–27·45)
				Chemoradiation plus gemcitabine

Figure 3: **Pooled hazard ratios for death (A) and pooled odds ratios for overall grade 3–4 toxic effects (B)**
The column treatment is compared with the row treatment. In each cell of HR for death (A), the first line is crude HR, and the second line in red is HR adjusted for the percentage of lymph node positivity in each trial. Numbers in parentheses indicate 95% credible intervals. HRs with Bayesian p value less than 0·05 are in blue if crude and green if adjusted.

Results

We identified 2251 studies for review of title and abstract (figure 1). After initial screening, we retrieved the full text of potentially eligible articles for detailed assessment. Ten eligible publications reporting nine randomised controlled trials were included for meta-analysis (table), with a total of 3033 patients randomised to receive one of the six treatment strategies (figure 2). All included studies have been published as full manuscripts and have a low risk of bias (appendix).

All nine trials reported information on overall survival and were included for meta-analysis. HRs were explicitly reported in five studies[6,12,26–28] and could be estimated in three studies,[3,5,11] with one remaining study[25] reporting median survival durations. The ESPAC-1 trial included three subgroups;[11] for the subgroup with two-by-two factorial design we used the overall survival updated in a later report[5] in the analysis. One publication[27] reported composite data of ESPAC-1, ESPAC-1+, and ESPAC-3 v1, thus we included only data from ESPAC-1+ and ESPAC-3 v1 to avoid duplication. We summarise the results of our random-effects network meta-analysis for overall survival in figure 3 and the appendix. Compared with observation, adjuvant chemotherapy with fluorouracil improved overall survival (HR 0·62, 95% credible interval 0·42–0·88). Longer, although not significant, overall survival than observation alone was also noted with gemcitabine

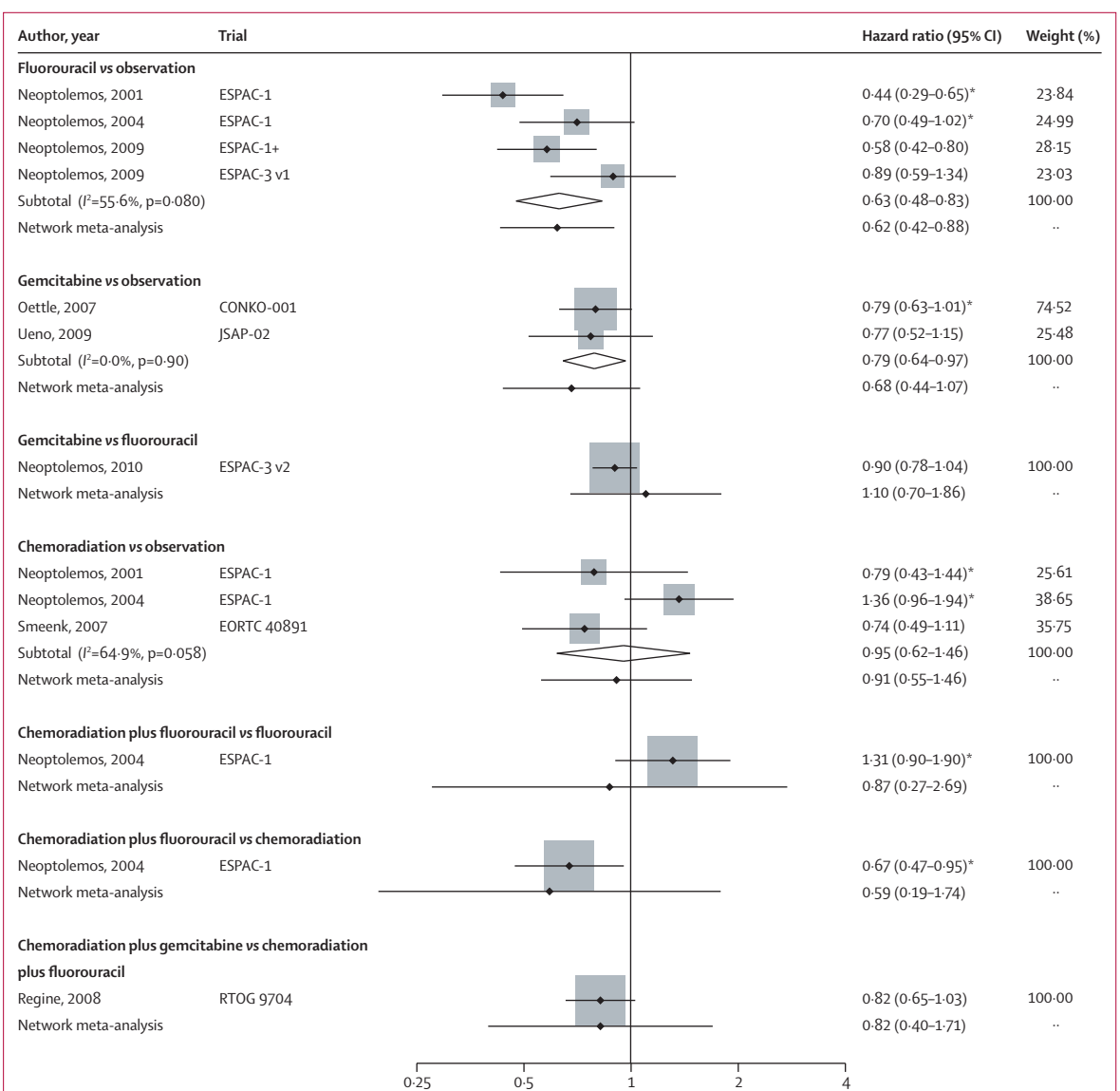

Figure 4: **Pooled hazard ratios for death by Bayesian network meta-analysis and traditional meta-analysis**
CI=confidence interval for traditional meta-analysis and credible interval for Bayesian network meta-analysis. *Hazard ratios (HRs) estimated from reported summary statistics. Chemoradiation plus fluorouracil versus observation not plotted since it was assessed in only one trial[25] and the HR was not reported and could not be estimated.

(HR 0·68, 95% credible interval 0·44–1·07). Comparing results from traditional pairwise meta-analysis and network meta-analysis did not suggest inconsistency between direct and indirect evidence (figure 4).

Meta-regression showed that the proportion of patients with positive lymph nodes, but not that of positive resection margins and poorly differentiated or undifferentiated tumours, was inversely associated with the overall survival benefit of adjuvant treatments over observation. The HRs for death for adjuvant treatments versus observation increased by 2·5% (95% credible interval 0–5·3) per 1% increase in the proportion of patients with positive lymph nodes. After adjustment for this factor, fluorouracil (HR 0·65, 0·49–0·84) and gemcitabine (HR 0·59, 0·41–0·83) provided an overall survival benefit over observation alone, whereas chemoradiation was associated with poorer overall survival compared with fluorouracil (HR 1·69, 1·12–2·54) and gemcitabine (HR 1·86, 1·04–3·23; figure 3). Chemoradiation plus fluorouracil or gemcitabine did not provide a survival advantage over fluorouracil or gemcitabine (figure 3).

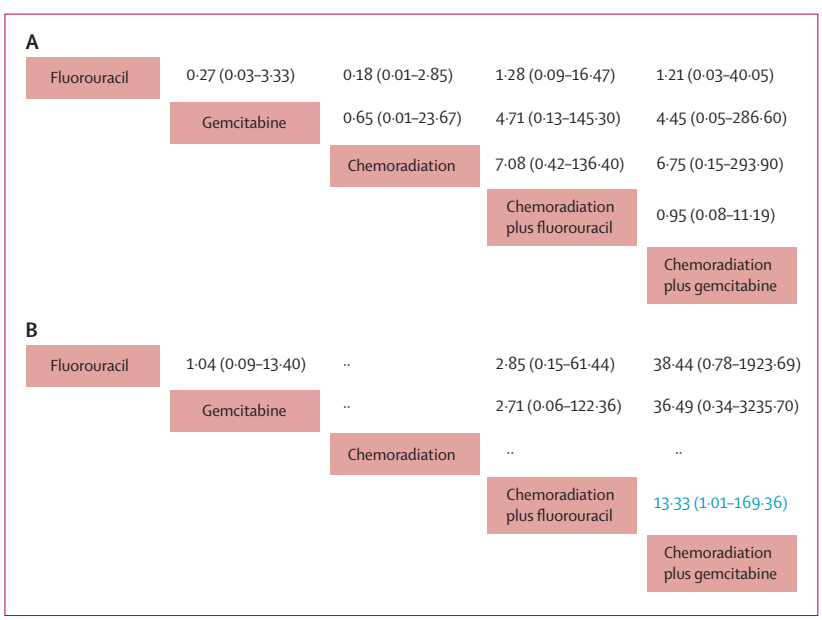

Figure 5: **Pooled odds ratios for grade 3–4 non-haematological (A) and haematological toxic effects (B)**
The column treatment is compared with the row treatment. Numbers in parentheses are the 95% credible intervals. ORs with a Bayesian p value of less than 0·05 are in blue. ··=not compared.

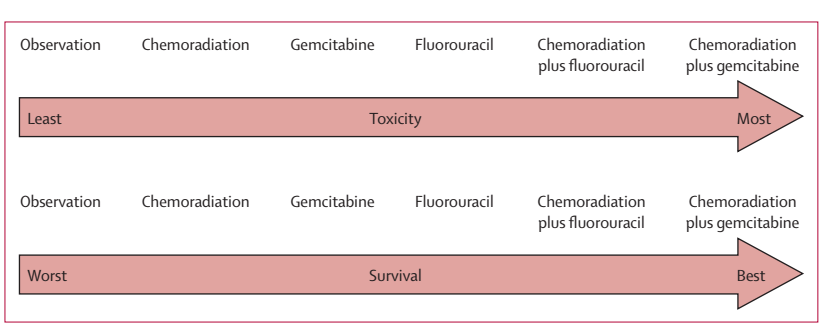

Figure 6: **Ranking of treatments in terms of overall survival benefit and overall grade 3–4 toxic effects**
Each treatment was ranked by the percentage of 150,000 iterations (see appendix).

Data on overall toxic effects were available in seven studies and haematological and non-haematological toxic effects were available in six studies (table). When the number of patients with overall toxic effects was not reported, we calculated the study-specific ORs for overall toxic effects with the sum of patients with haematological and non-haematological toxic effects in three studies[6,12,28] and the number of patients with treatment-related serious adverse events in two studies.[3,25] Two studies[6,28] did not report the overall number of haematological toxic effects, but reported the number of grade 3–4 leukopenia, thrombocytopenia, and anaemia separately, and we used the largest of the three numbers to calculate the study-specific ORs for haematological toxic effects. Three studies[6,12,28] did not report the overall number of non-haematological toxic effects, but reported the number of individual non-haematological toxic reactions separately, and we used their sum to calculate the study-specific ORs for non-haematological toxic effects. We summarise comparisons of toxic effects of the five adjuvant treatments in figures 3 and 5, and the appendix. Chemoradiation plus gemcitabine was more likely to cause grade 3–4 haematological toxic effects than chemoradiation plus fluorouracil (figure 5).

In figure 6 we summarise the rankings of the six competing treatment strategies in terms of overall survival and toxic effects—with details provided in the appendix. Gemcitabine and fluorouracil had similar ranking and were more favourable in terms of the balance between treatment benefit and harm. By comparison, chemoradiation plus gemcitabine or fluorouracil was most likely to be ranked the best or second best in terms of overall survival, but also most likely to be the worst or second worst in terms of overall toxic effects. Chemoradiation was ranked as the least effective and toxic treatment. The rankings with respect to haematological and non-haematological toxic effects were similar to that of overall toxic effects (appendix).

Discussion

Our network meta-analysis compares all major adjuvant treatments for pancreatic adenocarcinoma, and also includes both benefits and toxic effects when comparing those treatments (panel). Our results suggest that adjuvant chemotherapy with fluorouracil or gemcitabine provides an overall survival advantage over observation or chemoradiation, whereas adding chemoradiation to chemotherapy provides little further survival benefit, but increases toxic effects.

Our meta-analysis shows that both adjuvant fluorouracil and gemcitabine reduce mortality after resection of pancreatic adenocarcinoma by about a third, more than suggested in previous studies. ESPAC-1 first reported a significant survival benefit with adjuvant fluorouracil

(HR for death 0·71, 95% CI 0·55–0·92),[5] and a subsequent meta-analysis in 2005 concluded that adjuvant chemotherapy reduces mortality by 25% (HR 0·75, 0·64–0·90).[13] However, the complex factorial design of ESPAC-1 rendered the results difficult to interpret and compare with other studies.[3,4] The HR of adjuvant fluorouracil in ESPAC-1 was derived by comparing patients receiving fluorouracil (fluorouracil alone and chemoradiation plus fluorouracil) with those not receiving fluorouracil (observation alone and chemoradiation), rather than directly comparing fluorouracil with observation.[5] The previous meta-analysis did not include trials assessing gemcitabine, relying heavily on data from ESPAC-1,[29] and various chemotherapeutic drugs and regimens were indiscriminately pooled as adjuvant chemotherapy. By contrast, our meta-analysis assessed fluorouracil and gemcitabine separately and incorporated ESPAC-1 using four pairwise HRs (including those for fluorouracil *vs* observation, chemoradiation *vs* observation, chemoradiation plus fluorouracil *vs* fluorouracil, and chemoradiation plus fluorouracil *vs* chemoradiation)[20] derived from results published in the original study. The potential correlations between those four HRs were accounted for in our network meta-analysis, and joint modelling of direct and indirect comparisons should provide greater statistical power and more precise estimates.[14–16] Our results suggest that adjuvant chemotherapy with fluorouracil or gemcitabine prolongs overall survival with a balanced benefit–toxicity ratio and is the optimum treatment after resection of pancreatic adenocarcinoma.

This meta-analysis is the first to assess chemoradiation, chemoradiation plus fluorouracil, and chemoradiation plus gemcitabine separately and fills a crucial knowledge gap regarding chemoradiation. Our results show that adding chemoradiation to chemotherapy provides little survival benefit, but increases toxic effects, and therefore future trials with chemoradiation are probably unwarranted. We did not identify a survival advantage over observation or chemotherapy for chemoradiation plus chemotherapy. The adjusted HRs for death of chemoradiation plus fluorouracil versus fluorouracil or gemcitabine were close to 1 (figure 3), suggesting that adding chemoradiation to fluorouracil is not necessary. Although the finding that chemoradiation plus gemcitabine had the highest probability of being ranked the best in prolonging survival seems to suggest that it might provide a survival advantage over fluorouracil or gemcitabine in certain patients, the potential benefit is slight at best as judged by the relative HRs. The failure of chemoradiation plus gemcitabine to provide an unequivocal survival benefit might be due to the negative survival effect of its high level of haematological toxic effects, which had a 92·8% probability of being ranked the highest and was significantly greater than that of the second-ranked chemoradiation plus fluorouracil. Furthermore, patients with pancreatic adenocarcinoma are usually elderly,[1] and elderly patients are under-represented in oncology trials,[30,31] but at higher risk of complications from haematological toxic effects,[32,33] suggesting that routine administration of chemoradiation plus gemcitabine could cause greater toxic effects than our results suggest. Since even after adjuvant treatment about 80% of patients relapse and median survival remains less than 2 years,[3,9,28] highly toxic treatments such as chemoradiation plus gemcitabine might not be ideal because of the unfavourable risk–benefit ratio.

Another possible reason why chemoradiation provides little survival benefit is that occult systemic tumour dissemination happens early in pancreatic adenocarcinoma.[3,9] Therefore, distant metastasis occurs in about 60% of patients despite a seemingly curative resection and is the main determinant of overall survival,[3,9,21,22] but chemoradiation as a local treatment reduces local recurrence but not distant metastasis.[4,9] Indeed, in the RTOG 9704 trial it was noted that chemoradiation plus chemotherapy achieved a lower local recurrence rate

***Panel:* Research in context**

Systematic review

Major adjuvant treatments for pancreatic adenocarcinoma include fluorouracil, gemcitabine, chemoradiation, chemoradiation plus fluorouracil, and chemoradiation plus gemcitabine. To establish the optimum treatment, we did a Bayesian network meta-analysis to compare these treatments in terms of overall survival after surgery and grade 3–4 toxic effects. We searched PubMed, the Cochrane Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews, ClinicalTrials.gov, and the American Society of Clinical Oncology database of abstracts to identify randomised controlled trials of adjuvant treatments for pancreatic adenocarcinoma before April 30, 2013 with MeSH terms including "pancreatic neoplasms" and "adjuvants, pharmaceutic" (see appendix for detailed terms). No language or date restrictions were applied. Studies were included if they were randomised controlled trials and compared two or more of the six possible treatment strategies (observation and the five adjuvant treatments).

Interpretation

Results of previous trials assessing adjuvant fluorouracil and gemcitabine were contradictory. Whether adjuvant chemoradiation should be given is controversial. Adjuvant chemoradiation is the standard of care in the USA, but is not commonly used in Europe and the UK. In our network meta-analysis we considered different treatments individually and synthesised direct and indirect evidence to compare all major adjuvant treatments simultaneously. Our results show that chemotherapy with fluorouracil or gemcitabine is the optimum adjuvant treatment and reduces mortality after resection by about a third, whereas adding chemoradiation to chemotherapy provides little further survival benefit, but increases toxic effects.

(28%) than in studies using chemotherapy alone, but the distant metastasis rate (73%) remained similarly high.[4,26] By contrast, the significant survival benefit of chemotherapy accords with the notion that pancreatic adenocarcinoma is a systemic disease early on,[3,9] and sustained delivery of chemotherapy might be vital to improve survival.[34] Furthermore, chemoradiation might also induce resistance to treatment, with surviving tumour cells expressing an aggressive phenotype of faster growth and greater angiogenesis.[35] New therapies which can achieve greater reduction of systemic tumour burden might be the key to further improve the prognosis after tumour resection, and future trials should assess whether combining fluorouracil or gemcitabine with other chemotherapeutic drugs or targeted treatments can further prolong overall survival.

Although lymph node-positive patients also benefit from adjuvant chemotherapy,[5] a notable finding was that lymph node positivity negatively affects the survival benefit of adjuvant treatments and caused significant confounding, suggesting adjustment of this factor is needed when assessing existing evidence. Lymph node positivity also predicts distant metastasis and shorter survival after curative resection of pancreatic adenocarcinoma,[22] supporting that it might correlate with more widespread tumour dissemination and adversely affects adjuvant treatments. Lymph-node status should be considered when assessing the risk–benefit ratio of adjuvant treatment, as well as in designing future trials and comparing different studies.

Our study has several strengths. Rather than only grouping various treatments into chemotherapy or chemoradiation, this meta-analysis assesses every treatment individually and compares all major treatments simultaneously. Assessment of both overall survival and toxic effects provide new insights into the benefit–risk ratio of different adjuvant treatments. We overcame the difficulty of different measures of survival across studies and synthesised all available studies within a single meta-analysis, avoiding potential selection bias.[17] Bayesian network meta-analysis also allowed us to compare therapies indirectly when no head-to-head trial existed and obtain more precise effect estimates by jointly assessing direct and indirect comparisons.[14–16] Furthermore, we also analysed the effects of major prognostic factors on the benefit of adjuvant treatments and adjusted for associated confounding in comparing different treatments. Our updated synthesis of existing evidence provides new insights into controversies on this issue with important implications in clinical care and future research.

Our study also has limitations. We decided not to do meta-analysis on disease-free survival because this outcome was not reported in four studies. Disease-free survival has less significance than overall survival or toxic effects for treatment selection; measurement of disease-free survival is less precise than that of overall survival, and might be affected by heterogeneity in follow-up across studies. The reporting of toxic effects was incomplete and inconsistent in the included studies, and thus we had to use imputed data as described in our methods. Although our meta-analysis on toxic effects should be interpreted with some caution, the results should still provide effective estimates. Bayesian network meta-analysis pools the ratios rather than differences between treatments in each study, and therefore the study-specific ratios calculated from the imputed number of patients should be similar to real ratios as long as the same imputation method is used for every treatment in the study. For example, in ESPAC-3[28] the real ratio of overall toxic effects for fluorouracil versus gemcitabine was 1·71, similar to 1·93 if serious adverse events were used to impute the data. Additionally, because included studies used different survival measures (HR and survival duration) we could not do formal statistical testing for consistency between direct and indirect comparisons. However, the credible intervals of all pooled HRs from network meta-analysis included CIs of corresponding HRs from direct comparisons by pairwise meta-analysis and the point estimates of HRs were also similar between the two meta-analyses, supporting that there was no significant inconsistency between direct and indirect comparisons. Finally, our meta-analysis was done with summary statistics rather than individual patient data. There might be some covariates at the individual patient level that might affect the treatment outcomes, but were not reported; therefore they could not be adjusted for in our network meta-analysis. Access to and examination of data from individual patients could resolve the problem of missing information on certain prognostic factors and increase the power of the meta-analysis.

In conclusion, our network meta-analysis suggested that chemotherapy with fluorouracil or gemcitabine is the optimum adjuvant treatment for pancreatic adenocarcinoma and reduces mortality after tumour resection by about a third. Chemoradiation alone has little benefit, and chemoradiation plus chemotherapy is less effective in prolonging survival and more toxic than chemotherapy, especially with chemoradiation plus gemcitabine.

Contributors

W-CL, Y-KT, Y-LL, and K-LC contributed to study concept and design, data analysis and interpretation, and writing of the report. M-SW, J-TL, and H-PW contributed to data interpretation and provided expert insight into the writing of the report. All authors approved the final version of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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