CRD summary
This review assessed the effects of adjuvant chemoradiation and adjuvant chemotherapy on survival in patients with potentially curative resected pancreatic cancer, using individual patient data. The authors concluded that chemotherapy prolongs survival but chemoradiation does not. The lack of reporting of the review methods means that the reliability of the authors’ conclusions cannot be verified.

Authors’ objectives
To assess the effects of adjuvant chemoradiation and adjuvant chemotherapy on survival in patients with potentially curative resected pancreatic cancer, using individual patient data (IPD) from randomised controlled trials (RCTs).

Searching
The authors searched ISI Web of Knowledge, MEDLINE and EMBASE for studies published worldwide; the search terms and dates searched were not reported. Members of the European Study Group for Pancreatic Cancer (ESPAC) were contacted for details of ongoing trials in 11 European countries.

Study selection
Study designs of evaluations included in the review
The review included IPD from RCTs that were closed to recruitment.

Specific interventions included in the review
Studies of adjuvant treatments were eligible for inclusion. The included studies compared chemoradiation or chemotherapy with surgery alone, or no chemoradiation or chemotherapy. The patients must have started adjuvant treatment within 8 weeks of surgery.

Participants included in the review
Studies of adults (aged over 18 years) with resected histologically proven ductal adenocarcinoma of the pancreas were eligible for inclusion. The patients were predominantly male (58%), aged over 60 years (55%), most had negative resection margins (68%, range: 17 to 100% across trials) and about half had regional lymph node involvement (53%, range: 33 to 60% across trials).

Outcomes assessed in the review
The primary review outcome was overall survival, measured from the date of the operation to the date of death (from any cause) or censor date. Median follow-up within the individual included trials was at least 24 months.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state what procedures were used to check the data. The authors did not state how judgments of validity were made, in terms of who made the decisions or the criteria used.

Data extraction
The trial investigators provided IPD for their trials. The categories of data requested included prognostic information, additional follow-up data for survival, patient characteristics, tumour characteristics, resection margin status, nodal status, smoking, pre-operative diabetes status, and survival information. The reviewers reinstated any ineligible patients.
who had been deleted from published data where data were available. Intention-to-treat data were reanalysed for each trial and median survival with 95% confidence interval (CI), 2- and 5-year survival rates, and hazard ratios (HRs) with 95% CI were calculated.

Methods of synthesis
How were the studies combined?
The studies were grouped according to adjuvant treatment (chemoradiation or chemotherapy) and combined using a meta-analysis of IPD. Intention-to-treat data were used to estimate the pooled HR (with 95% CI) and 2- and 5-year survival rates for each treatment group.

How were differences between studies investigated?
Statistical heterogeneity across trials was tested using the chi-squared test. Where significant heterogeneity was found, the trials responsible were identified and potential reasons for heterogeneity were discussed. The influence of the following pre-specified prognostic factors on survival was examined: age (60 or younger or older than 60 years), resected margin status (positive or negative), differentiation of tumour (moderate or poor), lymph node status (positive or negative) and tumour size (2 cm or less or more than 2 cm). The data were reanalysed with the inclusion of summary data from the one relevant RCT that provided no IPD (this analysis is not reported here).

Results of the review
IPD from four RCTs were included (n=875). One other RCT was also identified, but was not included in the meta-analysis because IPD were not available on account of the age of the trial.

Adjuvant chemoradiation (3 trials, 478 patients).
There was no statistically significant difference in the risk of death with chemoradiation compared with no chemoradiation (HR 1.09, 95% CI: 0.89, 1.32, P=0.43). There was borderline statistically significant heterogeneity (P=0.05). Median survival was 15.8 months with chemoradiation and 15.2 months without. The 2- and 5-year survival rates were 30% and 12%, respectively, with chemoradiation and 34% and 17% without. The subgroup analysis showed no significant heterogeneity, except for a significant difference in the effect of chemoradiation on resection margin status (P=0.04), where chemoradiation was estimated to be effective in patients with positive resection margins. This treatment effect was not significant.

Adjuvant chemotherapy (4 RCTs, 686 patients).
The meta-analysis of all 4 RCTs showed that chemotherapy significantly reduced the risk of death compared with no chemotherapy (HR 0.75, 95% CI: 0.64, 0.90, P=0.001), but statistically significant heterogeneity was found (P=0.009). After removing one RCT with an unusually high proportion of patients with positive resection margins, significant heterogeneity was no longer present (P=0.29) and the reduction in risk of death with chemotherapy was still statistically significant (HR 0.65, 95% CI: 0.54, 0.80, P<0.001).
Median survival was 19 months with chemotherapy and 13.5 months without. The 2- and 5-year survival rates were 38% and 19%, respectively, with chemotherapy and 28% and 12% without.

The subgroup analysis showed no significant heterogeneity, except for a significant difference in the effect of chemotherapy on resection margin status (P=0.007), where chemotherapy was estimated to be less effective in patients with positive resection margins. This treatment effect was not significant.

The results for all subgroup analyses were reported.

Authors’ conclusions
Adjuvant chemotherapy prolongs survival in patients with resected pancreatic cancer, but chemoradiation does not. Further research into the effects of chemoradiation in patients with positive resection margins is required.
CRD commentary
The review addressed a clear question in terms of the participants, intervention, outcomes and study design. The search of two databases and an internet site, plus contact with European researchers, might have resulted in the omission of studies conducted by non-European researchers. Attempts were made to locate unpublished studies, thus minimising publication bias. Studies conducted worldwide were eligible but it was not reported whether there were any restrictions on the language of publication. The authors stated the number of identified trials with unavailable IPD. The methods used to select studies and retrieve and check IPD were not reported. The data were analysed using appropriate methods for IPD and heterogeneity was assessed. Predefined subgroup analyses were used to explore the influence of various prognostic factors. The lack of reporting of review methods means that the reliability of the authors’ conclusions cannot be verified.

Implications of the review for practice and research
Practice: The authors stated that standard care of patients with resectable pancreatic cancer should be based on curative surgery followed by adjuvant systemic chemotherapy. Adjuvant chemoradiation is not warranted as standard treatment.

Research: The authors stated that further research is needed to identify the best chemotherapy regimen and to investigate the effects of chemoradiation in patients with positive resection margins.

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the reliability of the review and the conclusions drawn.