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SYSTEMATIC REVIEW

Surgery with adjuvant or neoadjuvant treatment *vs* surgery alone for resectable pancreatic cancer: A network meta-analysis

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Author contributions: Shen P and Zhang T designed and organized the study protocol; Huang KJ and Xiao L reviewed and selected the papers; Shen P and Zhang CZ extracted and analyzed the data and wrote the paper; all authors had access to the data and statistical analyses, approved the final article, and attested to the validity of the results.

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Abstract

BACKGROUND

Pancreatic cancer is one of the most common and lethal malignancies worldwide. The common treatment options for resectable pancreatic cancer include surgery alone, neoadjuvant chemotherapy (CT), neoadjuvant chemoradiotherapy (CRT), adjuvant CT, and adjuvant CRT. However, the optimal treatment is still controversial.

AIM

To identify the most effective approach for pancreatic cancer using network meta-analysis.

METHODS

Eligible studies were searched from PubMed, MEDLINE, EMBASE, Cochrane database, and Google scholar. We searched and included randomized controlled trials reporting on neoadjuvant and adjuvant therapies. For direct comparisons, standard pairwise meta-analysis was performed using the inverse variance DerSimonian-Laird random-effects model. For indirect comparisons, Bayesian network meta-analysis was used to combine direct and indirect evidence. We used relative hazard ratios (HRs) to estimate death difference of different treatments, and relative odds ratios (ORs) for toxic effects. Treatment effects were ranked based on their efficacy for improving survival or reducing toxicity using rankogram. The quality of evidence of estimates from direct comparison and network meta-analysis was evaluated following the GRADE approach.

RESULTS

We included 13 high quality trials with 1591 participants in this network meta-analysis. Compared with surgery alone [pooled HR = 0.7, 95% confidence

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interval (CI): 0.62-0.79] and surgery with adjuvant CRT (pooled HR = 0.6, 95%CI: 0.54-0.72), surgery with adjuvant CT had a higher rate of overall survival. In contrast, standard pairwise meta-analysis showed a statistically significant survival advantage of surgery with adjuvant CT compared with surgery alone (pooled HR = 0.75, 95%CI: 0.63-0.89; $P < 0.001$). Rankogram showed that surgery with adjuvant CT was most likely to rank the best in terms of overall survival (probability: 94.2%), followed by surgery alone (probability: 5.8%). No significant differences in overall toxicity or haematological toxicity were found between all the therapies. High quality evidence supported surgery with adjuvant CT over surgery alone for increasing overall survival. Moderate quality evidence supported surgery with adjuvant CT over surgery with adjuvant CRT for increasing overall survival.

CONCLUSION
Surgery with adjuvant CT prolongs overall survival compared with surgery alone and surgery with adjuvant CRT, suggesting surgery with adjuvant CT is the optimal treatment for resectable pancreatic cancer.

Key words: Pancreatic cancer; Surgery; Network meta-analysis; Adjuvant therapy; Neoadjuvant therapy

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Core tip: No consensus is available in previous studies about the most beneficial treatment option for resectable pancreatic cancer. This is the first network meta-analysis comparing the efficiency of surgery alone, neoadjuvant chemotherapy (CT), neoadjuvant chemoradiotherapy (CRT), adjuvant CT, and adjuvant CRT. We investigated these treatment options in terms of overall survival and toxicity. We found that surgery with adjuvant CT prolonged overall survival compared with surgery alone and surgery with adjuvant CRT. Surgery with adjuvant CT is the optimal treatment for resectable pancreatic cancer.

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INTRODUCTION

Pancreatic cancer is one of the most common and lethal malignancies[1]. Surgical resection is the only potential curative treatment for pancreatic cancer. However, even after radical removal of the tumor (R0), the prognosis remained poor, with the 5-year survival rate being less than 25% and the median survival time being 14-21 mo[2-4]. High incidence of both locoregional and distant recurrences is responsible for the poor prognosis. Thus, a multimodal approach is needed to decrease the high recurrence rate as well as increase overall survival[5,6].

Several neoadjuvant or adjuvant therapies have been shown to be beneficial in selected patients. These therapies are neoadjuvant chemotherapy (CT), neoadjuvant chemoradiotherapy (CRT), adjuvant CT, and adjuvant CRT. However, there are debates over which therapy can benefit patients mostly. Regarding neoadjuvant therapy, recent meta-analysis found no significant difference in the overall survival between neoadjuvant CRT and surgery[7]. With regard to adjuvant therapy, the benefit of adjuvant therapy for resectable pancreatic cancer is still controversial, especially the impact of adjuvant CRT. Adjuvant CRT using fluorouracil is considered standard of care in the United States. However, the EORTC trial demonstrated no benefit of adjuvant CRT over observation in patients with resected pancreatic cancer (median survival: 1.3 year *vs* 1.0 year)[8]. Thus, more powerful and comprehensive evidence is needed to evaluate the best treatment strategy for resectable pancreatic cancer.

There have been several traditional meta-analyses comparing the benefit of neoadjuvant therapy or adjuvant therapy. However, all of the previous meta-analyses

only addressed neoadjuvant therapy[7,9-11] or adjuvant therapy alone[12-14]. Thus, it is interesting and meaningful for us to perform this network meta-analysis, that is, to compare both neoadjuvant and adjuvant therapies with surgery alone. The advantage of network meta-analysis is that it can compare different treatments without direct clinical trials. That is, if we have only clinical trials comparing A to B and B to C, we can estimate A to C using network met-analysis. Besides, treatment options can be ranked based on their efficacy for improving survival or reducing toxicity in network meta-analysis.

The aim of this network meta-analysis was to identify the most effective treatment for resectable pancreatic cancer by comparing overall survival and toxic effects after neoadjuvant or adjuvant CT and CRT.

MATERIALS AND METHODS

The protocol of this network meta-analysis was registered with the prospective register of systematic reviews, PROSPERO (CRD42017057053). This network meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[15] and Cochrane guidelines[16].

Search strategy

Eligible studies were searched from PubMed, Medline, EMBASE, Cochrane database, and Google scholar, using a combination of following terms "pancreatic cancer", "pancreatic neoplasm", "neoadjuvant therapy", and "adjuvant therapy". A manual search through published articles was performed additionally. No publication year was restricted in the search. The search was carried out independently by two authors.

Inclusion and exclusion criteria

The following inclusion criteria were used: (a) Randomized controlled trials; (b) Studies investigating surgery alone, neoadjuvant therapies, or adjuvant therapies for resectable pancreatic cancer; and (c) Studies that had at least one of the following outcomes: Survival and toxicity. Single-arm studies, nonrandomized cohort studies, and studies comparing different ways of adjuvant or neoadjuvant treatment were not included in this network meta-analysis.

Data extraction and quality assessment

The information on study design, methods, patient characteristics, treatment protocols, and outcome (overall survival and toxicity) was extracted independently by two authors. We extracted reported adjusted hazard ratios (HRs) to measure overall survival. When HRs were not reported, we estimated them from summary statistics (Kaplan-Meier curves) in accordance with practical methods for incorporating summary time-to-event data into meta-analysis[17]. If there was no enough information to estimate HRs, median survival durations would be used in this network meta-analysis[18]. Only grade 3 or 4 toxicities (overall toxicities and haematological toxicities) were extracted and analyzed in this network meta-analysis. The quality of randomized control study was assessed by the Cochrane Collaboration's tool[19]. Data collection and study quality assessment were performed following the Quality of Reporting of Meta-Analyses statement.

Data synthesis and analysis

The study outcomes were overall survival and toxicity after neoadjuvant or adjuvant therapies. For network meta-analysis of overall survival, the preferred outcome measure was reported HRs, followed by estimated HRs and median survival durations. Relative treatment effects (HRs) in multi-arm trials were converted to arm-specific outcomes[18]. For network meta-analysis of toxicity (overall toxicity and haematological toxicities), we used odds ratios (ORs) as outcome measures. ORs were calculated from the summary number of reported toxicity events and summary number of exposure patients in each trial. Since the definition and reporting type of toxicity were diverse in the included studies, we only summarize seven toxicity events [nausea/vomiting, infection/fever, asthenia/fatigue, diarrhea, hematological toxicity (leukopenia, thrombopenia, and anemia)] as overall toxicity.

For direct comparisons, standard pairwise meta-analysis was performed using the inverse variance DerSimonian-Laird random-effects model. Heterogeneity was quantified using *I*-squared statistic. Publication bias was evaluated using the funnel plot. Traditional pairwise meta-analysis was performed using REVIEW MANAGER (version 5.0 for Windows; the Cochrane Collaboration, Oxford, United Kingdom).

For indirect comparisons, we conducted random-effects Bayesian network meta-

analysis using Markov chain Monte Carlo methods in The R Programming Language 3.3.2 [R Core Team (2016), R Foundation for Statistical Computing, Vienna, Austria]. Network meta-analysis assumes "consistency" of treatment effects across all included randomized trials, that is, the direct and indirect estimates are the same effects. Network consistency was evaluated by comparing the direct estimates to the indirect estimates using the node splitting model. We used non-informative uniform and normal prior distributions in network meta-analysis. And we used a thinning interval of 500 for each chain and yielded 5000 iterations to obtain the posterior distributions of model parameters. Convergence of iterations was assessed using Gelman-Rubin-Brooks statistic. Trace plot and density plot were used to assess the convergence of the model. The summary effect of each comparison will be presented as point estimate (HR) and the corresponding 95% confidence interval (CI). The probability of each arm achieving the best rank among all the options was calculated and is presented as rankogram. The efficacy of different treatments was ranked using rankogram.

Quality of evidence

We evaluated the quality of evidence of estimates from direct comparison and network meta-analysis following the GRADE approach. The quality of evidence has four levels orderly: High, moderate, low, and very low quality. In this approach, the quality of direct evidence from RCTs is high initially and can be rated down based on risk of bias, indirectness, imprecision, inconsistency, or publication bias. The quality of indirect evidence starts at the lowest level of direct evidence that contributes as the preferred loops to the indirect evidence, and can be rated down based on imprecision or intransitivity. Network meta-analysis combines both direct and indirect evidence to reach a more comprehensive result, thus, the quality of evidence from network meta-analysis is assigned with the higher level of the direct and indirect evidence.

RESULTS

Characteristic of included studies

We identified 350 potentially relevant articles without duplicates from database searches and manual searches. After initial screening of these records, we excluded 252 articles because they investigated neither neoadjuvant nor adjuvant therapy of pancreatic cancer. We detailedly assessed the remaining 98 articles by abstracts and excluded 68 not reporting randomized control studies. After assessing full texts of the potential eligible 30 articles, we included 14 articles[8,20-32] (13 trials) in the network meta-analysis (Figure 1). If a single trial was reported in different publications, we combined the data of the different publications. And if a single outcome in a same trial was reported in different publications, the result of the latest publication would be used. The ESPAC-1 trial[29] included three subgroups, as the subgroup with two-by-two factorial design was updated in the following report[28]; this subgroup comparison was recognized as ESPAC-plus trial[28] and the last two subgroups as ESPAC-1 trial[29] in this meta-analysis. Also, we included data from ESPAC-3-v1[25] which was not included in the ESPAC-1 trial to avoid duplication.

The methodological quality of the included 13 trials was high (Supplemental Table 1). Four trials did not report sequence and six trials did not report allocation concealment. Although blinding was not reported in any trial, the primary outcome (overall survival) would not be affected by blinding or not, and a low risk of bias was recognized. Finally, we included 13 high quality trials with 1591 participants in this network meta-analysis (Figure 2). A total of 1591 participants were randomized to receive either neoadjuvant CRT with surgery (n = 51), surgery alone (n = 703), surgery with adjuvant CT (n = 665), or surgery with adjuvant CRT (n = 172).

The characteristics of the 13 included trials are summarized in Table 1 and Supplemental Table 2. All of the included trials were two-arm studies except the ESPAC-1 plus trial[28], which was a four-arm trial using a two-by-two factorial design. The recruitment period ranged from 3 to 8 years. Both pancreatic adenocarcinoma and invasive ductal pancreatic cancer were included in this meta-analysis. For trials including periampullary carcinoma, the data about periampullary cancer were excluded[8]. The median age ranged from 57 to 71.5 years old. Most (> 90%) of included participants had primary tumor stage T1-T3, and most of them had nodal status N0-N1. The schedule of CT or CRT can be recognized briefly in Table 1.

Direct comparison meta-analysis of overall survival

Standard pairwise meta-analysis of direct comparisons was feasible for the following comparisons: neoadjuvant CRT with surgery *vs* surgery alone (2 trials, n = 104), surgery with adjuvant CT *vs* surgery alone (7 trials, n = 1080), and surgery with

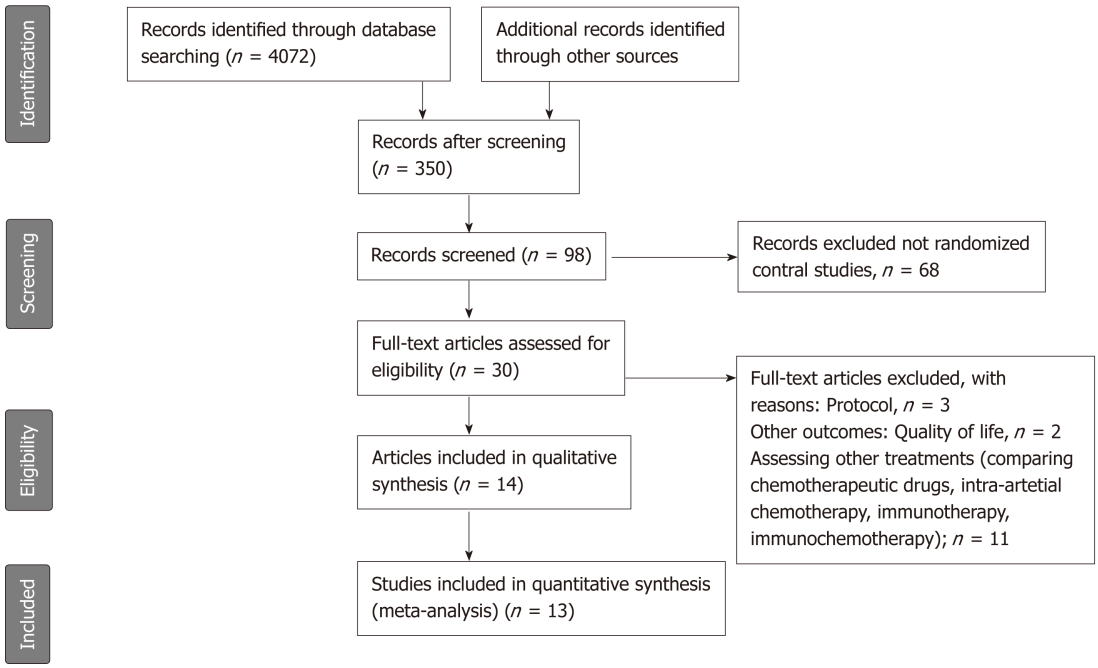

Figure 1 PRISMA flow chart of literature search showing the identification, screening, eligibility, and inclusion phases of the search.

adjuvant CRT *vs* surgery alone (3 trials, n = 254), and surgery with adjuvant CRT *vs* surgery with adjuvant CT (1 trial, n = 90). Only surgery with adjuvant CT showed a statistically significant survival advantage compared with surgery alone (pooled HR = 0.75, 95%CI: 0.63-0.89; P < 0.001) (Figure 3). No statistical difference was found in other direct comparisons. Heterogeneity was found only in the comparison of surgery with adjuvant CRT *vs* surgery alone (I^2 = 72%). No publication bias was found using the funnel plot.

Network meta-analysis of overall survival

All 12 trials reported information on survival and were included for Bayesian network meta-analysis. Density plot, trace plot, and Brooks-Gelman-Rubin diagnosis plot in Bayesian network meta-analysis of overall survival showed satisfied convergence of network plot model (Supplemental Figure 1). We summarize the result of network meta-analysis of overall survival in Figure 4. Surgery with adjuvant CT showed statistically better overall survival compared with surgery alone (pooled HR = 0.7, 95%CI: 0.62-0.79), which is similar to the results in direct comparison. Surgery with adjuvant CT also statistically improved survival compared with surgery with adjuvant CRT (pooled HR = 0.6, 95%CI: 0.54-0.72). No significant results were found between other comparisons (neoadjuvant CRT with surgery *vs* surgery alone, surgery with adjuvant CRT *vs* surgery alone, surgery with adjuvant CT *vs* neoadjuvant CRT with surgery, and surgery with adjuvant CRT *vs* surgery with adjuvant CT) (Figure 4).

Network meta-analysis results are consistent with the results from traditional pairwise meta-analysis, suggesting no inconsistency between direct and indirect evidence. We also compared the results of direct and corresponding indirect comparison using node-splitting model. No inconsistency was found (surgery with adjuvant CT *vs* surgery alone, P = 0.789; surgery with adjuvant CRT *vs* surgery alone, P = 0.562; and surgery with adjuvant CT *vs* surgery with adjuvant CRT P = 0.205). Heterogeneity between studies was found using the random-effects model (I^2_{pair} = 59.9; I^2_{cons} = 67.6).

Rankogram (Figure 5) summarizes the ranking probability of the four treatment strategies in terms of overall survival. Surgery with adjuvant CT had the highest probability (94.2%) to rank the best in terms of improving overall survival, followed by surgery alone (5.8%), neoadjuvant CRT with surgery (0%), and surgery with adjuvant CRT (0%).

The results of grading the quality of evidence for overall survival are summarized in Table 2. Based on network meta-analysis, high quality evidence supported surgery with adjuvant CT over surgery alone for increasing overall survival. Moderate quality evidence supported surgery with adjuvant CT over surgery with adjuvant CRT for increasing overall survival.

Table 1 Study characteristics of included studies

Study	Arms	Number	Period	Country	Schedule
Casadei *et al*[20], 2015	NCRT + S	18	2007-2014	Italy	2 cycles of gemcitabine 1000 mg/m^2 on days 1 and 8 every 21 d, then 45 Gy radiation with gemcitabine 50 mg/m^2 twice weekly for 6 wk
	Surgery	20			
Golcher *et al*[21], 2015	NCRT + S	33	2003-2009	Germany, Switzerland	8 Gy to 55.8 Gy (tumor) or 50.4 Gy (regional lymph nodes) radiation with gemcitabine 300 mg/m^2 and cisplatin 30 mg/m^2 on days 1, 8, 22, and 29
	Surgery	33			
Oettle *et al*[22,26], 2007, 2013	S + ACT	179	1998-2004	Germany, Austria	3 cycles of gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 wk
	Surgery	175			
Kosuge *et al*[27], 2006	S + ACT	45	1992-2000	Japan	2 courses of cisplatin 80 mg/m^2 on the first day; 5-fluorouracil 500 mg/m^2 daily for the first 5 d
	Surgery	44			
Ueno *et al*[24], 2009	S + ACT	58	2002-2005	Japan	3 cycles of gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 wk
	Surgery	60			
Bakkevold *et al*[31], 1993	S + ACT	30	1984-1987	Norway	6 cycles of 5-fluorouracil 500 mg/m^2, doxorubicin 40 mg/m^2, and mitomycin C 6 mg/m^2 once every 3 wk
	Surgery	31			
Smeenk *et al*[8], 2007 Klinkenbijl *et al*[30], 1999	S + ACDT	110	1987-1995	Europe	2 courses of 20 Gy radiotherapy (2 Gy/d, 5 d/wk at weeks 1-2 and 5-6) and 25 mg/kg 5-fluorouracil daily for 5 d
	Surgery	108			
Kalser *et al*[32], 1985	S + ACDT	21	1974-1982	USA	2 courses of 20 Gy (5 d a week) radiotherapy and 500 mg/m^2 fluorouracil daily for 3 d
	Surgery	22			
Van Laethem *et al*[23], 2010	S + ACDT	45	2004-2007	France	2 cycles of gemcitabine 1000 mg/m^2 weekly for 3 wk; followed by 50.4 Gy radiotherapy and 300 mg/m^2 gemcitabine weekly for two weeks
	S + ACT	45			4 cycles of gemcitabine 1000 mg/m^2 weekly for 3 wk
Neoptolemos *et al*[25,28,29], 2001, 2004, 2009 (ESPAC-1)	S + ACDT	73	1994-2000	Europe	2 courses of 20 Gy radiotherapy and 500 mg/m^2 fluorouracil on days 1-3
	S + ACT	75			6 courses of fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 d

	S + ACT + ACDT	72			2 courses of 20 Gy radiotherapy and 500 mg/m^2 fluorouracil on days 1-3; then 6 courses of fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 d
	Surgery	69			
ESPAC-1 plus	S + ACDT	33	1994-2000	Europe	2 courses of 20 Gy radiotherapy and 500 mg/m^2 fluorouracil on days 1–3
	Surgery	36			
	S + ACT	97			6 courses of fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 d
	Surgery	95			
ESPAC-3 (V1)	S + ACT	61	1994-2000	Europe	6 courses of fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 d
	Surgery	61			

NCRT + S: Neoadjuvant chemoradiotherapy with surgery; S + ACT: Surgery with adjuvant chemotherapy; S + ACRT: Surgery with adjuvant chemoradiotherapy.

Network meta-analysis of toxicity

Data on toxicity were available in seven trials. We summarize all the reported toxicity events [nausea/vomiting, infection/Fever, asthenia/Fatigue, diarrhea, and hematological toxicity (leukopenia, thrombopenia, and anemia)] in Supplemental Table 3. Neoadjuvant or adjuvant CT and CRT were well tolerated, and grade 3 or 4 toxicities occurred infrequently. We summarize the result of network meta-analysis on overall toxicity and haematological toxicity in Figure 4. Density plot, trace plot, and Brooks-Gelman-Rubin diagnosis plot showed satisfied convergence of network plot model (Supplemental Figure 2). No significant differences in overall toxicity or haematological toxicity were found between all the comparisons (neoadjuvant CRT with surgery, surgery with adjuvant CRT, and surgery with adjuvant CT) (Figure 4).

DISCUSSION

This study is the first analysis to compare efficacy of neoadjuvant therapies, adjuvant therapies, and surgery alone for resectable pancreatic cancer together in a single analysis. In our network meta-analysis, we included 13 high quality trials with 1591 participants. We demonstrated three principal findings in our analysis: surgery with adjuvant CT has better survival compared with surgery alone and surgery with adjuvant CRT; neoadjuvant CRT with surgery shows no significant difference in survival compared with surgery alone and adjuvant therapies; and toxicities after CT or CRT are well tolerated and show no significant difference among the treatment strategies included in this meta-analysis.

In our network meta-analysis, high quality evidence confirmed the survival advantage of adjuvant CT over surgery alone. Although overall survival associated with adjuvant CT had been evaluated in several head-to-head comparisons[22,24,25,27,31], the absence of statistical significance led to equivocal conclusions[24,31]. Previous meta-analysis also demonstrated a survival difference when comparing surgery alone and surgery with adjuvant CT[12-14]. However, the most recent meta-analysis[13] was performed in 2007 and only included five randomized control studies. Moreover, it used only median survival time and 5-year survival rate instead of HRs to estimate survival difference, which was less precise. In our study, we estimated the survival difference by combining direct and indirect comparisons of different treatments. Moreover, we used both reported HRs and estimated HRs from all the included studies to minimize the selection bias. Thus, we provided the most powerful and reliable evidence that adjuvant CT is better than surgery alone in increasing overall survival for resectable pancreatic cancer.

The survival difference between adjuvant CT and adjuvant CRT for resectable pancreatic cancer remains controversial. Only a few studies demonstrated the

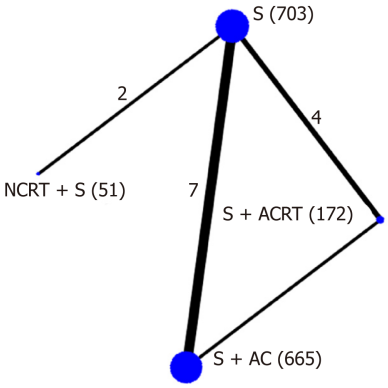

Figure 2 Network plot. Network plot showing the following different treatment strategies for resectable pancreatic cancer: neoadjuvant chemoradiotherapy with surgery (NCRT + S) (*n* = 51), surgery alone (S) (*n* = 703), surgery with adjuvant chemotherapy (S + ACT) (*n* = 665), or surgery with adjuvant chemoradiotherapy (S + ACRT) (*n* = 172).

survival difference between adjuvant CT and adjuvant CRT[23,29]. A phase II randomized controlled study involving 90 participants compared the toxicity and survival between adjuvant gemcitabine alone and gemcitabine-based CRT, and no significant difference was found in survival due to small sample size[23]. The ESPAC-1 trial compared the survival using a two-by-two factorial design (observation, CRT alone, CT alone, or both)[29]. However, the trial was not powered to compare these four groups directly, and only found a potential benefit of adjuvant CT but not adjuvant CRT. In our study, moderate quality evidence supported surgery with adjuvant CT over surgery with adjuvant CRT for increasing overall survival. We confirmed the survival benefit of adjuvant CT over surgery with adjuvant CRT for the first time. Pancreatic cancer is a systemic disease and micrometastasis after surgery may be responsible for high recurrence and low survival. Thus, adjuvant CT but not CRT can benefit the survival of pancreatic cancer patients after surgery. However, CRT in the included studies was performed mainly using external beam, and more highly targeted radiotherapy is now available. The survival benefit between highly targeted radiotherapy and adjuvant CT should be reevaluated in the future study.

CT agents for adjuvant CT are diverse. It is still controversial regarding the best CT agents for adjuvant CT. The ESPAC-3 trial demonstrated that fluorouracil plus folinic acid resulted in similar overall survival to gemcitabine in patients after complete resection of pancreatic cancer[33]. A recent network meta-analysis showed that adjuvant CT with fluorouracil or gemcitabine provided better overall survival than observation[34]. S-1 is another new CT agent for pancreatic cancer. Recent randomized control trials showed that S-1 was superior to gemcitabine, suggesting that S-1 is a new standard care for resected pancreatic cancer[35-37]. In our study, CT agents for adjuvant therapy included gemcitabine[22,24], cisplatin[27], 5-fluorouracil plus doxorubicin plus mitomycin C[31], and fluorouracil plus folinic acid[31]. We combined all of the adjuvant CT with different CT agents in a single arm in this network meta-analysis, because we assumed that the effect of different CT agents for adjuvant CT was consistent. Besides, we tried to compare the effect difference of adjuvant CT with adjuvant CRT and neoadjuvant CRT, and the effect difference was not affected by different CT agents.

The necessity and survival benefit of neoadjuvant therapy for pancreatic cancer is controversial. Borderline pancreatic cancer recently emerged as a category clinically distinct from resectable or locally advanced disease. Neoadjuvant therapy is currently recommended for borderline resectable disease in the National Comprehensive Cancer Network guidelines[38,39]. However, only two reported RCTs access neoadjuvant CRT for resectable pancreatic cancer so far, and both two RCTs found no survival benefit of neoadjuvant CRT. One of the included RCTs involving 38 participants chose R0 resection as the primary endpoint[20], and another RCT involving 66 patients was terminated early due to slow recruiting[21]. Neoadjuvant therapy is also assessed in our network meta-analysis. Only neoadjuvant CRT with surgery was assessed, as no RCTs about neoadjuvant CT can be found. We found no significant result when comparing neoadjuvant CRT with surgery alone, adjuvant CT, and adjuvant CRT. Now, several randomized controlled trials are ongoing to investigate the survival benefit of neoadjuvant CRT for the treatment of borderline and resectable pancreatic cancer[40-43]. Our result showed no survival benefit of neoadjuvant CRT. Thus, we should be cautious with using neoadjuvant CRT for resectable pancreatic cancer until other powerful evidence exists.

Table 2 Pooled hazard ratio of overall survival from direct and network meta-analysis

Intervention	Direct meta-analysis		Network meta-analysis	
	HR	Evidence	HR	Evidence
Compared to surgery alone				
Neoadjuvant CRT + S	0.96 (0.68, 1.37)	Low[1,2]	1.10 (0.64, 1.90)	Low
S + adjuvant CT	0.75 (0.63, 0.89)	High	0.70 (0.62, 0.79)	High
S + adjuvant CRT	0.88 (0.51, 1.54)	Moderate[3]	1.10 (0.97, 1.30)	Moderate
Compared to neoadjuvant CRT + S				
S + adjuvant CT	-	-	0.63 (0.36, 1.10)	Low
S + adjuvant CRT	-	-	1.00 (0.57, 1.80)	Low
Compared to S + adjuvant CT				
S + adjuvant CRT	0.98(0.59, 1.64)	Low[4]	1.6 (1.40, 1.80)	Moderate

[1]Risk of bias: one of included trial did not report allocation concealment and random sequence generation.
[2]Imprecision: small sample size.
[3]Inconsistency: heterogeneity was found in this comparison (I^2 = 72%).
[4]Imprecision: wide confidence interval. HR: Hazard ratio; CRT: Chemoradiotherapy; S: Surgery; CT: Chemotherapy.

Our network meta-analysis has several strengths. It is the first comprehensive analysis of all the major treatment strategies for resectable pancreatic cancer including neoadjuvant therapy, surgery, and adjuvant therapy. We combined both direct and indirect evidence to reach more precise conclusions, which also allowed us to compare therapies indirectly and rank different therapies clearly. Furthermore, we assessed both overall survival and toxicity of all the therapies. Our meta-analysis provides comprehensive and clear evidence for the treatment of resectable pancreatic cancer, which is great important and meaningful in clinical care.

The limitations of this meta-analysis also need to be acknowledged. First of all, the RCTs included in this analysis were conducted over four decades, and changes in CRT schedule, CT agents, schedules, and surgery techniques may affect the results. However, transitivity assumption was met and there was no evidence of statistically significant inconsistency in this network. This may have less effect on the result. Second, we included both neoadjuvant and adjuvant therapies to offer a comprehensive overview. However, we included only a limited number of trials (n = 13), and only two trials evaluated neoadjuvant therapies. Thus, although no sig-nificant result about overall survival was found when comparing neoadjuvant therapies with other treatments, this conclusion about neoadjuvant therapies should be interpreted with some caution. Finally, since the definition and reporting type of toxicity were diverse in the included studies, we only summarized seven typical toxicity events as overall toxicity. Although some toxicity events may be neglected in this analysis, the results should still provide effective estimates.

In conclusion, our network meta-analysis show that surgery with adjuvant CT prolongs overall survival compared with surgery alone and surgery with adjuvant CRT. Therefore, we recommend surgery with adjuvant CT as the optimal care for resectable pancreatic cancer. Later research should be focused on the best agents for adjuvant CT.

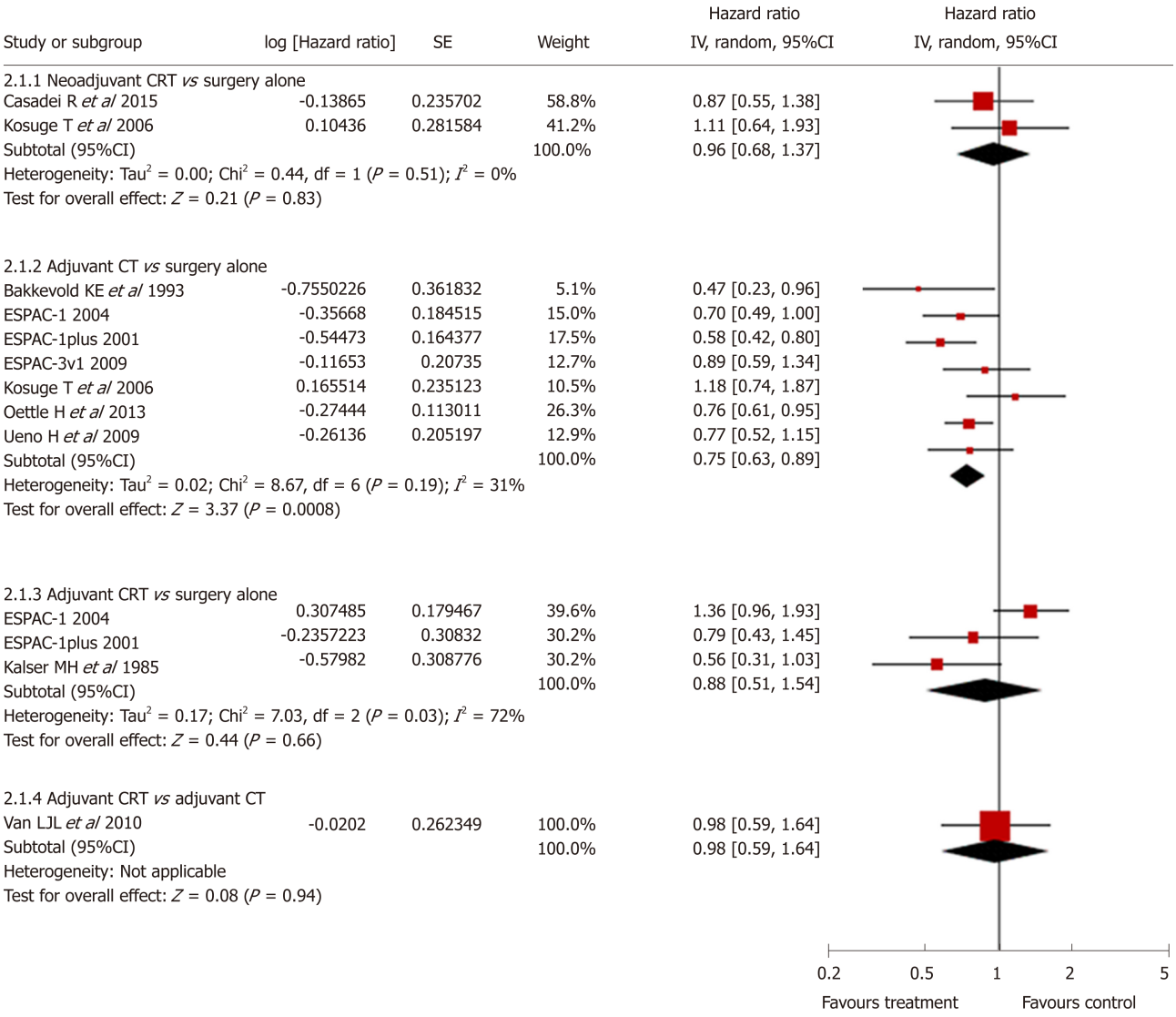

Figure 3 Forest plot of direct comparison meta-analysis of overall survival. Squares and horizontal lines correspond to the study-specific HRs and 95% CIs, respectively. The area of the squares correlates with the weight of each enrolled study, and the diamonds represent the summary HRs and 95% CIs. HRs: Hazard ratios; CI: Confidence interval.

A			
S	1.1 (0.64, 1.9)	0.7 (0.62, 0.79)	1.1 (0.97, 1.3)
	Neoadjuvant CRT + S	0.63 (0.36, 1.1)	1.0 (0.57, 1.8)
		S + adjuvant CT	1.6 (1.4, 1.8)
			S + adjuvant CRT
B			
	Neoadjuvant CRT + S	0.68 (0.21, 22)	0.33 (0.0064, 13)
		S + adjuvant CT	0.50 (0.042, 3.8)
			S + adjuvant CRT
C			
	Neoadjuvant CRT + S	0.67 (0.019, 20)	0.33 (0.0053, 12)
		S + adjuvant CT	0.49 (0.040, 3.9)
			S + adjuvant CRT

Figure 4 Network meta-analysis of overall survival (A), overall toxicity (B), and haematological toxicity (C). The column treatment is compared with the row treatment. Overall survival was estimated using pooled hazard ratios and 95% confidence intervals. Toxicity was estimated using pooled odds ratios and 95% confidence intervals.

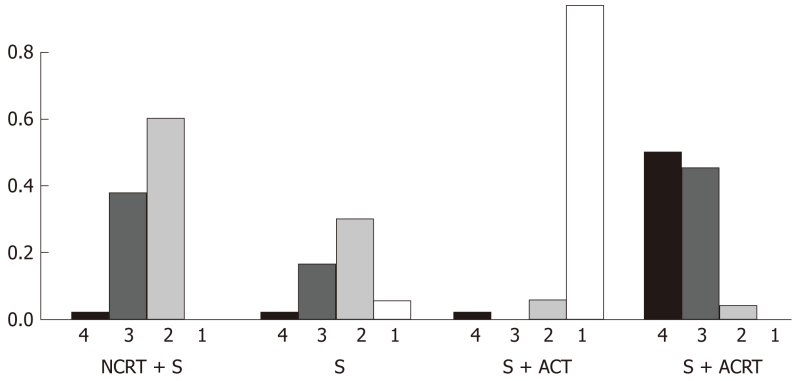

Figure 5 Rankogram of overall survival. The height of column represents the probability of ranking the first (1) second (2), third (3), and fourth (4). NCRT + S: Neoadjuvant chemoradiotherapy with surgery; S: Surgery alone; S + ACT: Surgery with adjuvant chemotherapy; S + ACRT: Surgery with adjuvant chemoradiotherapy.

ARTICLE HIGHLIGHTS

Research background

Pancreatic cancer is one of the most common and lethal malignancies worldwide. The common treatment options for resectable pancreatic cancer include surgery alone, neoadjuvant chemotherapy (CT), neoadjuvant chemoradiotherapy (CRT), adjuvant CT, and adjuvant CRT. However, the optimal treatment is still controversial.

Research motivation

The optimal treatment for resectable pancreatic cancer is still controversial.

Research objectives

This study aimed to identify the most effective approach for resectable pancreatic cancer using network meta-analysis.

Research methods

Eligible studies were searched from PubMed, Medline, EMBASE, Cochrane database, and Google scholar. We searched and included randomized controlled trials reporting on neoadjuvant and adjuvant therapies. For direct comparisons, standard pairwise meta-analysis was performed using the inverse variance DerSimonian-Laird random-effects model. For indirect comparisons, Bayesian network meta-analysis was used to combine direct and indirect evidence. We used relative hazard ratios (HRs) to estimate survival difference between different treatments, and relative odds ratios (ORs) for toxic effects. Treatment effects were ranked based on their efficacy for improving survival or reducing toxicity using rankogram. The quality of evidence of estimates from direct comparison and network meta-analysis were evaluated following the GRADE approach.

Research results

We included 13 high quality trials with 1591 participants in this network meta-analysis. Compared with surgery alone (pooled HR = 0.7, 95%CI: 0.62-0.79) and surgery with adjuvant CRT (pooled HR = 0.6, 95%CI: 0.54-0.72), surgery with adjuvant CT had a higher rate of overall survival. In contrast, standard pairwise meta-analysis only showed a statistically significant survival advantage of surgery with adjuvant CT compared with surgery alone (pooled HR = 0.75, 95%CI: 0.63-0.89; $P < 0.001$). Rankogram showed that surgery with adjuvant CT was most likely to rank the best in terms of overall survival (probability: 94.2%), followed by surgery alone (probability: 5.8%). No significant differences in overall toxicity or haematological toxicity were found between all the therapies. High quality evidence supported surgery with adjuvant CT over surgery alone for increasing overall survival. Moderate quality evidence supported surgery with adjuvant CT over surgery with adjuvant CRT for increasing overall survival.

Research conclusions

Our network meta-analysis show that surgery with adjuvant CT prolongs overall survival compared with surgery alone and surgery with adjuvant CRT.

Research perspectives

We recommend surgery with adjuvant CT as the optimal care for resectable pancreatic cancer. Later research should be focused on the best agents for adjuvant CT.

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