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SYSTEMATIC REVIEW AND META-ANALYSIS

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Efficacy of Neo-Adjuvant Chemoradiotherapy for Resectable Pancreatic Adenocarcinoma

A PRISMA-Compliant Meta-Analysis and Systematic Review

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Abstract: We have conducted a meta-analysis and systematic review to determine the overall survival, mortality rate, and complete resection rate of neo-adjuvant chemoradiotherapy (CRT) compared with pancreaticoduodenectomy alone in patients with pancreatic adenocarcinoma. Whether neo-adjuvant CRT is beneficial in the treatment of resectable pancreatic cancer or not, it is still a controversial issue.

Medline and Cochrane were searched with relevant terms. Eight studies with a total of 833 participants were selected. The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

The analysis revealed neo-adjuvant group may have a benefit in the overall survival, as compared with the resection group, although it did not reach statistical significance (pooled hazard ratio = 0.87, 95% confidence interval [CI] = 0.75–1.00, $P = 0.051$). We found no difference in the in-hospital mortality rate (pooled odds ratio [OR] = 1.27, 95% CI = 0.35–4.58, $P = 0.710$). The complete resection rate was significantly higher in the neo-adjuvant group than in the resection group (pooled OR = 2.39, 95% CI = 1.21–4.74, $P = 0.012$).

This meta-analysis found that there was no significant difference in the overall survival between patients treated with neo-adjuvant CRT or pancreaticduodenectomy.

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Abbreviations: CRT = chemoradiotherapy, HR = hazard ratio, OR = odds ratio, RCT = randomized controlled trial, RECIST = Response Evaluation Criteria in Solid Tumors.

INTRODUCTION

Pancreatic cancer is the 6th most common cause of cancer-related death worldwide.[1] The incidence of pancreatic cancer has increased in recent decades, possibly due to increasing prevalence of obesity, aging populations, and unknown factors.[2] The mortality rate of pancreatic cancer remains high. Surgical resection alone is inadequate therapy, with only about a 10% five-year survival rate. In a retrospective study, adjuvant therapy also proved disappointing.[3] Thus, interest has grown in neo-adjuvant (preoperative) therapy for pancreatic cancer. In advanced rectal cancer, neo-adjuvant therapy is considered the standard of care,[4] and neo-adjuvant therapy in patients with resectable pancreatic cancer has yielded some encouraging results.[5–11] The proposed benefits of chemoradiotherapy (CRT) in pancreatic cancer are control of local disease and the improved rate of complete resection. However, whether CRT, especially neo-adjuvant CRT, achieves a significant benefit in resectable pancreatic cancer treatment remains controversial, and well-designed, randomized studies are lacking. Thus, it is not known whether neo-adjuvant therapy improves the survival rate of patients with resectable pancreatic cancer.

In this meta-analysis and systematic review, we examined the overall survival rate, mortality rate, and complete resection rate of neo-adjuvant CRT compared with pancreaticoduodenectomy in patients with resectable pancreatic adenocarcinoma.

PATIENTS AND METHODS

Search Strategy

This systematic review and meta-analysis were conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Medline and Cochrane were searched until November 11, 2014 using the following search terms: the first combination was chemotherapy AND pancreatic adenocarcinoma; the second combination was neo-adjuvant therapy, pancreaticoduodenectomy, pancreatic cancer, with clinical trial as the filter. Reference lists of relevant studies were hand-searched.

Selection Criteria

We used the following inclusion criteria to select studies: patients with resectable or borderline resectable pancreatic adenocarcinoma who had undergone either surgery alone or neo-adjuvant chemoradiation followed by surgery; randomized controlled trials (RCTs), 2-arm prospective studies, and retrospective studies; comparison of quantitative outcomes between the 2 treatment groups.

The exclusion criteria were reviews, protocols, letters, comments, editorials, case reports, proceedings, personal communications, and single-arm studies; unresectable pancreatic adenocarcinoma; studies that compared treatments other than surgery and neo-adjuvant CRT; absence of quantitative outcomes or incomplete data for analysis.

Study Selection and Data Extraction

Study eligibility was determined by 2 independent reviewers. Where there was uncertainty regarding eligibility, a 3rd reviewer

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was consulted. The following information/data were extracted from studies that met the inclusion criteria: name of the first author, the year of publication, study design, number of participants in each group, participants' age and gender, intervention, mortality rate, overall survival, and complete resection rate.

Quality Assessment

The quality of the included randomized controlled trials was assessed using the Cochrane ''assessing risk of bias'' table (Chichester, West Sussex, UK: The Cochrane Collaboration, 2011).[13] There are 6 domains—random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting risk. We used the Newcastle–Ottawa scale[14] to assess the included retrospective studies. This scale contains 8 items categorized into 3 dimensions: selection, comparability, and outcome. A star system is used for a semi-quantitative assessment of the study quality. The quality of included studies was independently appraised by 2 reviewers. Disagreements were resolved by a 3rd reviewer.

Outcome Measures and Statistical Analysis

The primary outcome was the overall survival rate. The secondary outcomes were in-hospital mortality rate and complete resection rate (R0), which was assessed according to the Response Evaluation Criteria in Solid Tumors. Crude or adjusted hazard ratios (HRs) were extracted for the overall survival and odds ratios (ORs) were determined for the other outcomes. If the available data were presented as the Kaplan–Meier curve, we extracted the survival rates at some specified times in order to reconstruct the HR estimate and its variance, with the assumption that the rate of patients censored was constant during the study follow-up.[15] An $HR < 1$, indicated that the neo-adjuvant CRT group was favored. However, $OR > 1$ for mortality or $OR < 1$ for complete resection rate (R0) indicated that the resection group was favored.

Heterogeneity among the studies was assessed with the Cochran Q and the I^2 statistic. If I^2 statistic indicated heterogeneity ($> 50\%$) between studies, the random-effect model was used (DerSimonian–Laird method). Otherwise, the fixed-effect model (Mantel–Haenszel method) was employed.[16] Pooled estimate (HR or OR) means the risk ratio of neo-adjuvant CRT group to control resection group. Pooled HRs or ORs were calculated, and a 2-sided P value < 0.05 was considered statistical significance. In addition, subgroup analysis of treatment effectiveness was performed according to study type (i.e., RCT and retrospective study). The leave-one-out approach was used to assess sensitivity of the meta-analysis. Publication bias analysis was not performed because the number of studies was too small (<10) to detect an asymmetric funnel.[17] All statistical analyses were performed by use of the statistical software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ).

Ethics

This study did not involve human subjects, so informed consent was not required. In addition, no approval was required from an institutional review board.

RESULTS

Literature Search

A flow diagram of study selection is shown in Figure 1. A total of 171 studies were identified in the database searches, and

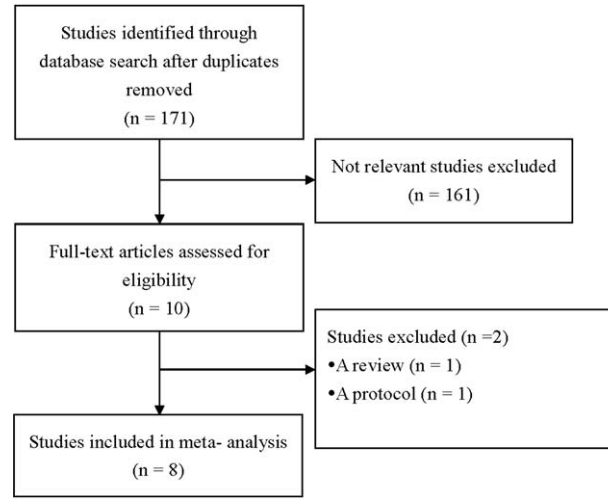

FIGURE 1. Flow chart for study selection.

10 full text articles were reviewed after exclusion of 161 for not meeting the inclusion/exclusion criteria. Two studies were subsequently excluded on the basis of being a review[4] or a protocol.[18] Eight studies were included in the final meta-analysis.

Basic Characteristics

The basic characteristics of the studies included in the meta-analysis[1,3,8–11,19,20] are summarized in Table 1. A total of 833 participants were included in the 8 studies. Among studies in the neo-adjuvant CRT group, the number of participants ranged from 18 to 144; the number in the resection group ranged from 20 to 92. The mean age of patients ranged from 60 to 71.5 years. The percentage of males in the neo-adjuvant CRT group ranged from 37% to 67% and in the resection group from 48% to 70%.

Overall median survival time ranged from 15 to 54 months among patients in the neo-adjuvant CRT group and ranged from 13 to 36 months in the resection group. The HR for overall survival ranged from 0.75 to 1.20. The in-hospital mortality rate ranged from 3.0% to 5.6% in the neo-adjuvant CRT group and ranged from 0% to 10% in the resection group. The complete resection rate ranged from 15% to 92% in the neo-adjuvant CRT group and ranged from 12% to 81% in the resection group (Table 2).

Outcome Evaluation: Overall Survival

The forest plot illustrating the results of the meta-analysis for patients' overall survival is shown in Figure 2. Two studies[11,20] were excluded from this analysis because they did not report overall survival. Significant heterogeneity was not observed when data from the remaining 6 studies were pooled (heterogeneity test: $Q = 2.63$, $df = 5$, $P = 0.756$, $I^2 = 0\%$); therefore, a fixed-effect model of analysis was used. The overall analysis revealed that patients in the neo-adjuvant CRT group had better overall survival as compared with those in the resection group, although this did not reach statistical difference (pooled $HR = 0.87$, 95% confidence interval [CI] $= 0.75–1.00$, $P = 0.051$).

We performed subgroup analysis to assess if the study design affected the results. For subgroup analysis of the 2 RCT studies, a fixed-effect model was used for the analysis ($Q = 0.870$, $df = 1$, $P = 0.351$, $I^2 = 0.0\%$). The results of RCT

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TABLE 1. Summary of Basic Characteristics of Studies Included in the Meta-Analysis

Authors (Year)	Study Design	Interventions	CRT Protocol	n	Age, y	Male, %
Casadei (2015)[19]	RCT	Neo-ad CRT	Gemcitabine + 45 Gy	18	71.5 (51–78)*	44
		Resection		20	67.5 (48–79)*	70
Golcher (2015)[8]	RCT	Neo-ad CRT	Gemcitabine mitomycin (or cisplatin) + 55.8 Gy	33	62.5 (33, 76)*	55
		Resection		33	65.1 (46, 73)*	52
Tzeng (2014)[18]	Retrospective	Neo-ad CRT	Gemcitabine + cisplatin + 30 Gy	115	65.5 (38, 79)*	53
		Resection		52	61.9 (25, 79)*	58
Sho (2013)[11]	Retrospective	Neo-ad CRT	Gemcitabine + 50 (or 54) Gy	61	65.1 (36, 78)†	59
		Resection		71	66.3 (33, 82)†	52
Papalezova (2012)[3]	Retrospective	Neo-ad CRT	5-FU-based chemotherapy + 45 Gy	144	64 (12)‡	54
		Resection		92	65 (12)‡	53
Satoi (2009)[10]	Retrospective	Neo-ad CRT	5-FU + cisplatin (or gemcitabine) + 40 Gy	27	64 (47, 74)*	37
		Resection		41	66 (50, 83)*	56
Golcher (2008)[9]	RCT	Neo-ad CRT	Gemcitabine + cisplatin + 50.4 Gy	21	Median: 60	67
		Resection		58	Median: 66	59
Vento (2007)[1]	Retrospective	Neo-ad CRT	Gemcitabine + 50.4 Gy	22	65 (49, 83)*	59
		Resection		25	63 (43, 76)*	48

Data expressed as *median (range), †mean (range), and ‡mean (standard deviation).
5-FU = 5-fluorouracil, CRT = chemoradiotherapy, RCT = randomized controlled trial.

subgroup showed no significant difference in overall survival between the neo-adjuvant CRT group and the resection group (pooled HR: 0.85, 95% CI: 0.58–1.25, $P = 0.412$). Subgroup analysis of the 4 retrospective studies indicated that there was no significant difference in the OS between the neo-adjuvant CRT group and the resection group (pooled HR: 0.87, 95% CI: 0.74–1.02, $P = 0.076$). These findings suggest that the study design did not impact the findings.

Outcome Evaluation: In-Hospital Mortality Rate

The forest plot of the results of the meta-analysis for the rate of in-hospital mortality is shown in Figure 3A. Four studies[3,8,10,14] were excluded from this analysis because they did not report this outcome. There was no significant heterogeneity when data from the 4 remaining studies were pooled (heterogeneity test: $Q = 1.19$, $df = 3$, $P = 0.755$, $I^2 = 0\%$); therefore, a fixed-effect model of analysis was used. The overall

TABLE 2. Summary of Outcomes of Studies Included in the Meta-Analysis

			Overall Survival			
Authors (Year)	Interventions	n	Median Survival Time, mo	HR (95% CI)	Mortality Rate (in Hospital), n (%)	Complete Resection Rate, n/N (%)
Casadei (2015)[19]	Neo-ad CRT	18	22.4 (10.2–34.6)*	NR	5.6%	38.9%
	Resection	20	19.5 (7.5–31.5)[5]		10%	25%
Golcher (2015)[8]	Neo-ad CRT	33	17.4	0.99 (0.6, 1.64)	NR	5/33 (15%)
	Resection	33	14.4	1	NR	4/33 (12%)
Tzeng (2014)[18]	Neo-ad CRT	115	28.0 (21.7, 34.3)*	0.8 (0.59, 1.07)	NR	85/95 (89.5%)
	Resection	52	25.3 (19.9, 30.7)*	1	NR	39/48 (81.3%)
Sho (2013)[11]	Neo-ad CRT	61	28	NR	2 (3%)	92%
	Resection	71			1 (1%)	52%
Papalezova (2012)[3]	Neo-ad CRT	144	15	0.91 (0.74, 1.13)	NR	59/76 (78%)
	Resection	92	13	1	NR	54/68 (79%)
Satoi (2009)[10]	Neo-ad CRT	27	24.5	0.75 (0.49, 1.16)	NR	52%
	Resection	41	18.5	1	NR	22%
Golcher (2008)[9]	Neo-ad CRT	21	54	0.68 (0.37, 1.25)	1 (4.7%)	90%
	Resection	58	21	1	3 (5.2%)	78%
Vento (2007)[1]	Neo-ad CRT	22	30.2 (25.46, 34.94)*	1.2 (0.6, 2.41)	1 (5%)	NR
	Resection	25	35.9 (10.51, 61.29)*	1	0	NR

Data expressed as *median (95% CI).
CI = confidence interval, CRT = chemoradiotherapy, HR = hazard ratio, NR = not reported.

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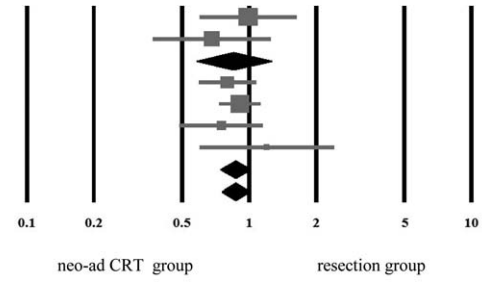
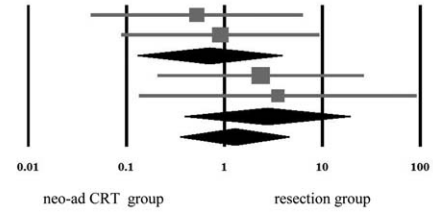
Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Golcher (2015)[8]	0.99	0.60	1.64	-0.04	0.969	59.45
Golcher (2008)[9]	0.68	0.37	1.25	-1.24	0.214	40.55
Subgroup (RCT)	**0.85**	**0.58**	**1.25**	**-0.82**	**0.412**	
Tzeng (2014)[18]	0.80	0.59	1.08	-1.47	0.142	27.49
Papalezova (2012)[3]	0.91	0.74	1.12	-0.87	0.382	54.36
Satoi (2009)[10]	0.75	0.49	1.15	-1.31	0.191	13.12
Vento (2007)[1]	1.20	0.60	2.40	0.51	0.607	5.04
Subgroup (Retrospective)	**0.87**	**0.74**	**1.02**	**-1.77**	**0.076**	
Overall Pooled effect	**0.87**	**0.75**	**1.00**	**-1.95**	**0.051**	



RCT:
Heterogeneity test: Cochran Q=0.870 (df=1), p=0.351; I-square=0.0%.
Retrospective study:
Heterogeneity test: Cochran Q=1.755(df=3), p=0.625; I-square=0.0%.
Total:
Heterogeneity test: Cochran Q=2.63(df=5), p=0.756; I-square=0.0%.

FIGURE 2. Forest plots showing results for the meta-analysis of overall survival. CI = confidence interval.

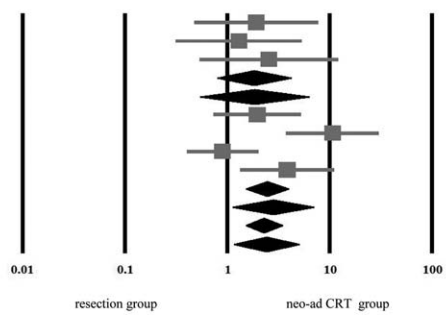
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Golcher (2015)[8]	0.53	0.04	6.39	-0.50	0.617	46.47
Golcher (2008)[9]	0.92	0.09	9.33	-0.07	0.941	53.53
Subgroup (RCT)	**0.71**	**0.13**	**3.88**	**-0.39**	**0.693**	
Sho (2013)[11]	2.37	0.21	26.83	0.70	0.485	64.25
Vento (2007)[1]	3.56	0.14	91.92	0.77	0.444	35.75
Subgroup (Retrospective)	**2.74**	**0.39**	**19.16**	**1.02**	**0.309**	
Overall Pooled effect	**1.27**	**0.35**	**4.58**	**0.37**	**0.710**	



RCT:
Heterogeneity test: Cochran Q=0.100 (df=1), p=0.752; I-square=0.0%.
Retrospective study:
Heterogeneity test: Cochran Q=0.038 (df=1), p=0.845; I-square=0.0%.
Total:
Heterogeneity test: Cochran Q=1.191(df=3), p=0.755; I-square=0.0%.

A

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight (Fixed effect)	Relative weight (Random effects)
Casadei (2015)[19]	1.91	0.48	7.64	0.91	0.360	36.27	34.73
Golcher (2015)[8]	1.29	0.31	5.32	0.36	0.720	34.89	34.13
Golcher (2008)[9]	2.54	0.54	12.02	1.17	0.240	28.83	31.14
Subgroup (RCT)-Fixed effect	**1.81**	**0.79**	**4.17**	**1.39**	**0.164**		
Subgroup (RCT)-Random effects	1.83	0.54	6.21	0.97	0.334		
Tzeng (2014)[18]	1.96	0.74	5.21	1.35	0.177	23.56	24.84
Sho (2013)[11]	10.62	3.77	29.90	4.47	0.000	20.97	24.00
Papalezova (2012)[3]	0.90	0.41	2.00	-0.26	0.795	35.32	27.46
Satoi (2009)[10]	3.84	1.34	11.05	2.50	0.013	20.15	23.70
Subgroup (Retrospective)-Fixed effect	2.43	1.51	3.90	3.67	0.000		
Subgroup (Retrospective)-Random effects	**2.78**	**1.12**	**6.92**	**2.20**	**0.027**		
Overall Pooled effect-Fixed effect	2.26	1.50	3.42	3.88	0.000		
Overall Pooled effect-Random effect	**2.39**	**1.21**	**4.74**	**2.50**	**0.012**		



RCT:
Heterogeneity test: Cochran Q=0.403 (df=2), p=0.817; I-square=0.0%.
Retrospective study:
Heterogeneity test: Cochran Q=14.649 (df=3), p=0.002; I-square=79.52%.
Total:
Heterogeneity test: Cochran Q=14.414 (df=6), p=0.017; I-square=61.07%.

B

FIGURE 3. Forest plots showing results for the meta-analysis of (A) mortality rate and (B) complete resection rate. CI = confidence interval.

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analysis revealed no significant difference between the neo-adjuvant CRT group and the resection group in the in-hospital mortality rate (pooled OR = 1.27, 95% CI = 0.35–4.58, $P = 0.710$).

For subgroup analysis of the 2 RCT studies, a fixed-effect model was used as the data were heterogeneous ($Q = 0.100$, $df = 1$, $P = 0.752$, $I^2 = 0.0\%$). The results showed no significant difference in the in-hospital mortality rate between the neo-adjuvant CRT group and the resection group (pooled OR: 0.71, 95% CI: 0.13–3.88, $P = 0.693$). Similarly, the results of 2 retrospective studies indicated that there was no significant difference in the in-hospital mortality between the 2 treatment groups (pooled OR: 2.74, 95% CI: 0.39–19.16, $P = 0.309$). These findings indicate that the findings were similar, independent of the study design.

Outcome Evaluation: Complete Resection Rate (R0)

The forest plot illustrating the results of the meta-analysis for patients' complete resection rate (R0) of pancreaticoduodenectomy is shown in Figure 3B. One study[1] was excluded from this analysis because it did not report the complete resection rate (R0). There was significant heterogeneity when data from the remaining 7 studies were pooled (heterogeneity test: $Q = 14.414$, $df = 6$, $P = 0.017$, $I^2 = 61.1\%$); therefore, a random-effect model of analysis was used. The complete resection rate (R0) was significantly higher in the neo-adjuvant CRT group than in the resection group (pooled OR = 2.39, 95% CI = 1.21–4.74, $P = 0.012$).

For the subgroup analysis of the 3 RCT studies, a fixed-effect model was used for the analysis ($Q = 0.403$, $df = 2$, $P = 0.817$, $I^2 = 0.0\%$). In contrast to the overall findings, the results of RCT subgroup showed no significant difference in the complete resection rate (R0) between the neo-adjuvant CRT group and the resection group (pooled OR: 1.81, 95% CI: 0.79–4.17, $P = 0.164$). For the subgroup analysis of the 4 retrospective studies, a random-effect model was used ($Q = 14.649$, $df = 3$, $P = 0.002$, $I^2 = 79.52\%$). Similar to the overall findings, the results of the retrospective subgroup indicated that the complete resection rate (R0) was significantly higher in the neo-adjuvant CRT group than in the resection group (pooled OR: 2.78, 95% CI: 1.12–6.92, $P = 0.027$). The subgroup analysis indicated that the findings were dependent upon the study design.

Sensitivity Analysis

Sensitivity of the findings was performed using the leave-one-out approach (Figure 4). The removal of 2 studies[1,8] for the overall survival analysis (Figure 4A) resulted in the pooled HR becoming significant ($P = 0.043$ when Golcher et al[8] was removed; and $P = 0.035$ when Vento et al[1] was removed), suggesting that these studies overly influenced the overall survival findings. The direction and magnitude of the pooled estimates for in-hospital mortality rate and complete resection did not differ when each study was removed in turn (Figure 4B), indicating that the meta-analysis of these outcomes are robust.

Quality Assessment

Assessment of the quality of the included randomized trials indicated that there was a low risk of bias for the different evaluated criteria (Table 3). However, information with regard to the performance bias or detection bias was unclear. The data suggest that the included randomized trials were of good quality. The quality assessment of the 5 retrospective studies according to the Newcastle–Ottawa scale[14] indicated that the studies were of good quality (score of 7 for each; Table 4).

DISCUSSION

The aim of this meta-analysis and systematic review was to investigate the effect of neo-adjuvant CRT plus pancreaticoduodenectomy for patients with resectable pancreatic adenocarcinoma. The major findings were that the overall survival rates and in-hospital mortality rates for the patients who received neo-adjuvant CRT were similar to those who received only pancreaticoduodenectomy. However, there was a trend for better overall survival in the neo-adjuvant group. These findings indicate that neo-adjuvant therapy is not superior to resection. Subgroup analysis that evaluated overall survival and in-hospital mortality rate in the randomized controlled trials or the retrospective studies found similar results as the overall analysis, suggesting that the study design did not impact these results. The complete resection rate was significantly higher in patients who received neo-adjuvant therapy. However, when only randomized controlled trials were used in the analysis, there was no difference between treatments ($P = 0.164$). Analysis with only retrospective studies found a higher complete resection rate in the neo-adjuvant CRT groups compared with the resection group ($P = 0.027$), suggesting that the study design did impact findings. Thus, these results, which corroborate the results of several studies not included in this analysis,[5–7,21,22] indicate that neo-adjuvant therapy for resectable pancreatic adenocarcinoma may not show a survival benefit. However, it must be appreciated that our study, as well as others, did not have large numbers of participants, so study of larger populations may yet reveal significant advantages of the neo-adjuvant therapy. Moreover, more effective chemotherapeutic agents may be developed that will be worth exploring in future trials. It is also possible that the higher rate of complete resection associated with neo-adjuvant therapy may eventually yield an improved patient survival.

Our findings are consistent with other nonrandomized studies that indicate neo-adjuvant therapy may improve surgical outcomes. Thus, Laurence et al[6] and Kang et al[7] have stated that CRT may increase the chances of having margin-negative tumors at operation. Also other authors[21,22] have stated that CRT may lead to a higher proportion of RO resections. In contrast to our results, the meta-analysis of Festa et al[5] showed that down-staging of lesions after neo-adjuvant therapies was uncommon for patients with borderline resectable pancreatic cancer. Some studies[9–11] have reported a lower rate of lymph node metastases after neo-adjuvant treatment of resectable pancreatic cancers. Vento et al[1] suggested that a clear benefit of neo-adjuvant therapy may be the sparing of surgery in patients with progressive disease, during the time that CRT is being delivered. It is noteworthy that all the included studies in the present meta-analysis had patients undergoing neo-adjuvant chemoradiation and none with neo-adjuvant chemotherapy.

The failure of the studies in our meta-analysis to find improved overall survival with neo-adjuvant CRT of pancreatic adenocarcinoma is similar to the prior meta-analyses.[5–7,22] Three meta-analyses[23–25] failed to support a benefit of neo-adjuvant therapies. Xu et al[26] in their systematic review and meta-analysis found no significant effect on overall survival and progression-free survival for neo-adjuvant CRT compared with non-CRT in the treatment of resectable pancreatic cancer. They

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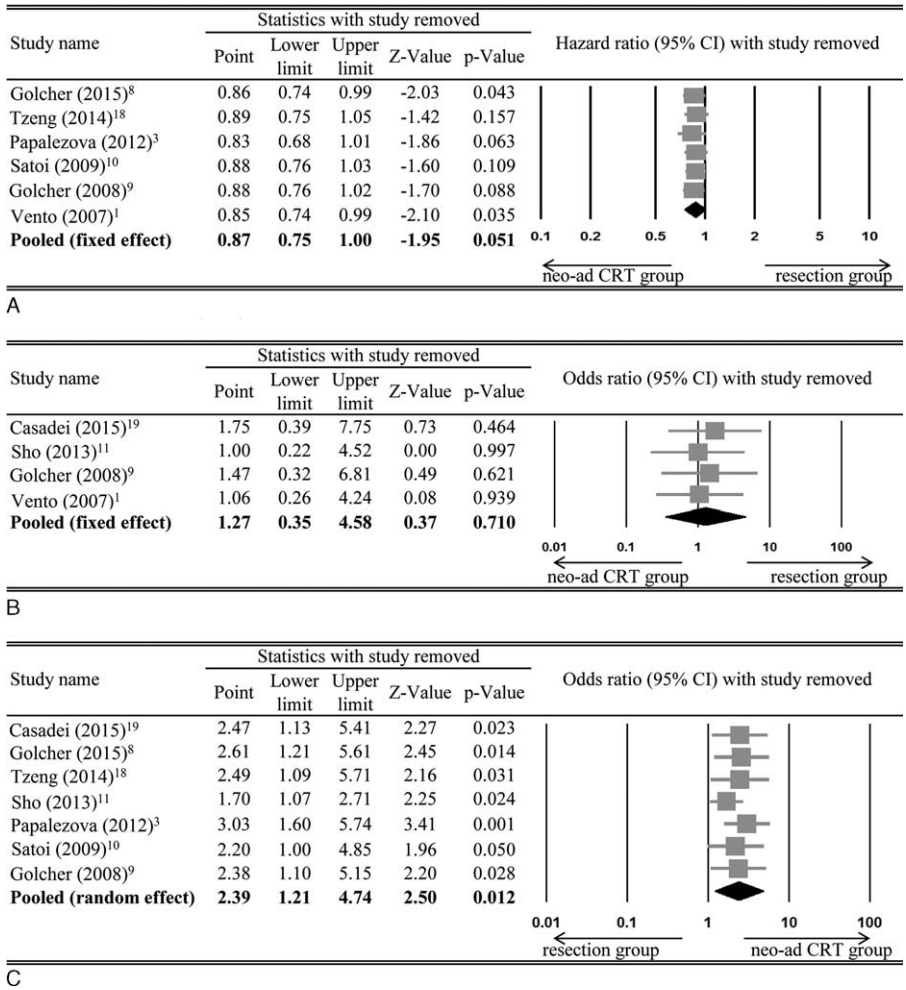

FIGURE 4. Results of sensitivity analysis to examine the influence of individual studies on pooled estimates, as determined by the leave-one-out approach. (A) Overall survival, (B) mortality rate, and (C) complete resection rate. CI = confidence interval.

also found that neo-adjuvant CRT was not superior to post-operative adjuvant CRT.

Examination of toxicities associated with neo-adjuvant CRT was not an objective of this study. However, grade ≥ 3 toxicities were common in the studies included in our analysis: grade ≥ 3 toxicities were experienced by 20% or more of patients in the study by Golcher et al,[8] whereas Sho et al[11] reported that 60% of the patients experienced grade ≥ 3 toxicities in their study. Despite the observed toxicities, the authors stated that their regimen of neo-adjuvant CRT was well tolerated and feasible as an outpatient treatment. Vento et al[1] reported similar complication rates in patients treated with and without neo-adjuvant CRT, but raised the possibility that neo-adjuvant CRT increases the susceptibility to serious infection

TABLE 3. Quality Assessment for Randomized Clinical Trial

Authors (Year)	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Did the Analysis Include an Intention-to-Treat Analysis?
Casadei (2015)[19]	Y	Y	UN	UN	Y	Y	Y
Golcher (2015)[8]	Y	UN	UN	UN	Y	Y	Y
Golcher (2008)[9]	Y	UN	UN	UN	Y	Y	UN

Y = low risk of bias, UN = unclear risk of bias.

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TABLE 4. Quality Assessment for Retrospective Studies

Authors (Year)	Selectivity	Comparability	Outcome
Tzeng (2014)[18]	****	–	***
Sho (2013)[11]	****	–	***
Papalezova (2012)[3]	****	–	***
Satoi (2009)[10]	****	–	***
Vento (2007)[1]	****	–	***

such as abdominal sepsis. Adverse effects of neo-adjuvant CRT on patients' nutritional status also have been described.[11] Lower rates of toxicity have been reported with newer neo-adjuvant regimens.[27]

Guidelines of the National Comprehensive Cancer Network for the treatment of pancreatic adenocarcinoma recommend laparoscopic resection for patients with resectable tumor and neo-adjuvant therapy for patients with borderline resectable tumor. However, the efficacy and safety of neo-adjuvant therapy remains unproven. The marginal differences between CRT and no CRT in the treatment of resectable pancreatic adenocarcinoma make it evident that large populations of patients will have to be studied to assess this issue. However, large clinical trials may be difficult due to recruitment problems, as has been encountered in some studies.[1,8]

This study has several limitations. One was that practices and protocols in the use of chemotherapy and chemoradiation vary, so likely there were differences in the therapeutic regimens applied. Another is that the review included only 1 randomized controlled study.[8]

In addition, while some studies excluded patients with borderline resectable pancreatic cancer,[3,19] others recruited both borderline resectable and resectable pancreatic cancer patients.[10,11] We did not perform a subgroup analysis on the resectability status, hence its influence on the present results is unknown.

We conclude that this meta-analysis and systematic review found no improved overall survival or in-hospital mortality rates from neo-adjuvant CRT in patients with resectable pancreatic adenocarcinoma; improved complete resection rates, however, were found. The efficacy and safety of neo-adjuvant CRT in resectable pancreatic adenocarcinoma remains to be established and likely will require large, well-designed studies for resolution.

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