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ORIGINAL ARTICLE

Neoadjuvant chemotherapy brings more survival benefits than postoperative chemotherapy for resectable gastric cancer: a Meta-analysis of randomized controlled trials

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Summary

Purpose: *To find out which treatment, neoadjuvant chemotherapy (NAC) or postoperative chemotherapy (PAC), can bring greater survival benefits to gastric cancer patients.*

Methods: *Pubmed, Embase and Cochrane Library databases were searched for randomized controlled trials (RCTs) about multidisciplinary treatment of resectable gastric cancer (NAC vs PAC, NAC + surgery vs surgery alone, and surgery alone vs surgery + PAC). Quality was assessed by collaboration recommendation in Cochrane. All outcomes were evaluated by odds ratio (OR) and 95% confidence interval (CI). Pairwise comparisons were conducted by R3.12 software. Aggregate Data Drug Information System (ADDIS software 1.16.5) was used to perform network meta-analysis.*

Results: *Simple meta-analysis showed NAC could bring more survival benefits than PAC for resectable gastric cancer. NAC was significantly better than PAC in 1-year (I^2=0, p=0.4085, fixed effects model, OR=2.28, 95%CI: 1.27-4.04), 3-year (I^2=0, p=0.6979, fixed effects model, OR=2.10, 95%CI: 1.09-4.03), and 5-year survival (I^2=37.8%, p=0.2048, fixed effects model, OR=2.04, 95%CI: 1.03-4.06). Network meta-analysis showed NAC + surgery was better compared with surgery + PAC and surgery alone. NAC + surgery were significantly better than surgery + PAC and surgery alone in 1-year or 3-year survival. For 5-year survival, NAC + surgery were significantly better than surgery alone, but no significant difference was observed when compared with surgery + PAC. NAC + surgery ranked first in 1-year, 3-year and 5-year probability sequence diagram.*

Conclusion: *NAC brings greater survival benefits than PAC for patients with resectable gastric cancer.*

Key words: *adjuvant chemotherapy, gastric cancer, neoadjuvant chemotherapy, network meta-analysis, survival*

Introduction

According to the International Agency for Research on Cancer, around 951, 000 individuals suffered from gastric cancer and 723, 000 of them died in 2012, accounting for the 5th of morbidity and the 3rd mortality among malignant tumors [1]. Surgery is the major treatment of resectable gastric cancer, but local relapse and metastasis rate after surgery is high. Thus the prognosis of gastric cancer is still poor. Over the last 30 years, many multidisciplinary treatment strategies including neoadjuvant chemotherapy (NAC), intraoperative local chemotherapy, postoperative chemotherapy (PAC), intra-abdominal infusion chemotherapy, and hyperthermic chemotherapy were applied in gastric cancer. NAC and PAC are two important accepted multidisciplinary treatments which could prolong survival and improve the cure rate of resectable gastric cancer [2-4] .

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In order to elucidate which treatment (NAC or PAC) could provide better survival benefit for resectable gastric cancer, we searched important databases about multidisciplinary treatment for gastric cancer and made the present meta-analysis.

Methods

Literature search

We searched Pubmed, Embase and Cochrane Library Databases updated to September 2017 for all the potentially relevant publications. The key search terms were "gastric carcinoma" or "gastric cancer" or "stomach neoplasm" or "cancer of the stomach" and "preoperative chemotherapy" or "neoadjuvant chemotherapy" or "Perioperative chemotherapy" and "post-operation chemotherapy" or "adjuvant chemotherapy" and "surgery" or "Gastrectomy". No language or time restrictions were applied.

Inclusion and exclusion criteria

The inclusion criteria for the present meta-analysis were: (1) the studies were RCTs comparing NAC + surgery vs surgery, surgery + PAC vs surgery, or NAC vs PAC directly; (2) the studies reported at least one of the following outcomes: 1-year, 3-year and 5-year survival data. In addition, RCTs about potentially resectable gastric cancer were included, some of which included potentially resectable stage IV gastric cancer with no distant metastases (staging standard when the articles published). Adenocarcinoma of esophageal–gastric junction was also included.

Non-RCTs, RCTs without followed-up survival, and trials including postoperative recurrence or unresectable gastric cancer were excluded.

Data extraction and quality assessment

Two independent investigators extracted the information from each eligible study, including first author, publication year, study location, therapeutic modality, number of cases in each group, gender, AJCC/UICC stage, follow-up period and 1-year, 3-year and 5-year survival data. Disagreements were resolved by discussion and reexamination. Cochrane collaboration recommendation was applied for RCTs quality evaluation [5]. Egger's test was used to analyze publication bias.

Statistics

Pairwise comparisons were performed by R 3.12 software (R Foundation for Statistical Computing, Beijing, China). OR with their 95% CI were used as a measure of effect size to combine the results. Heterogeneity was determined by Q statistic and I^2 test. If significant heterogeneity was detected ($p<0.05$ or $I^2>50\%$), the random-effects model was used. Otherwise, the fixed-effects model was used [6].

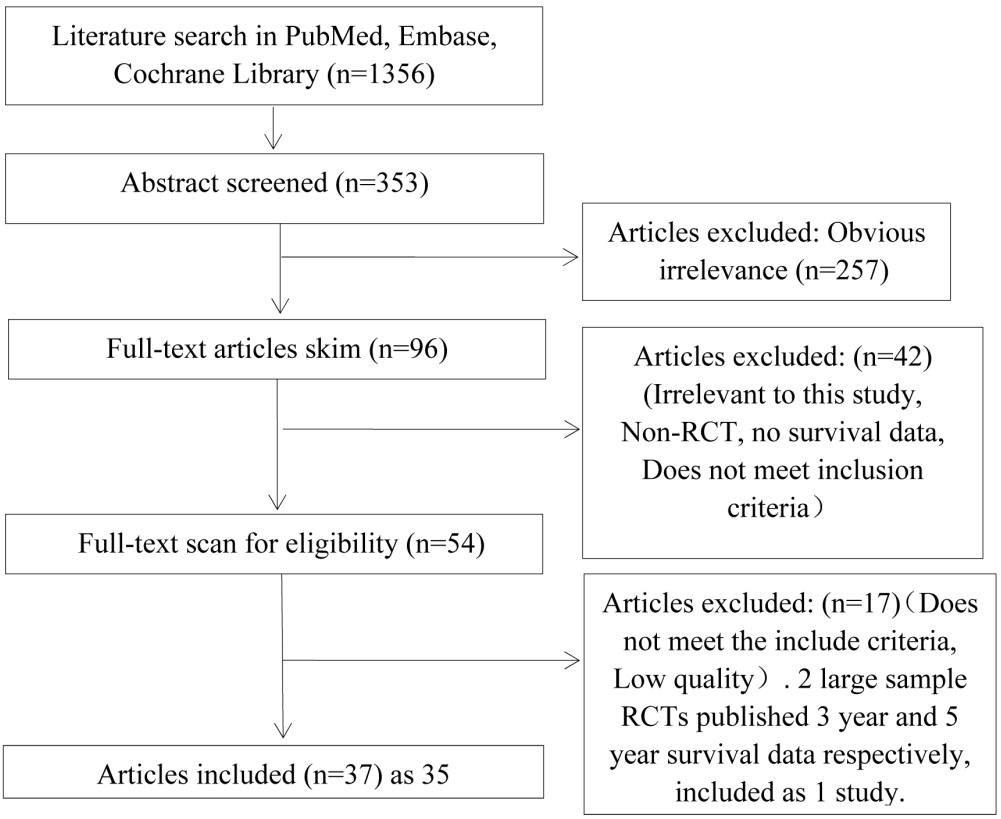

Figure 1. Flow chart of studies. Our systematic literature search identified 1356 citations. We reviewed 96 full texts of 353 abstracts that met the inclusion criteria. Based on the full text reviews, we excluded another 59 studies. Finally, 35 studies were included in our final sample.

Table 1. Characteristics of included studies

Author	*Public. year*	*Study location*	*Study year*	*Item*	*N*	*Age, yr*	*M/F*	*AJCC/UICC*	*Tumour stage (T1/T2/T3/T4)*	*Nodal stage (N0/N1/N2/N3)*	*1 OS*	*3 OS*	*5 OS*
Schuhmacher	2010	France, Germany	1999.07-2004.02	S	72	58(26-69)	50/22	III, IV	NA/NA/62/8	4/48/6/1	58	34	11
				NAC	72	56(38-70)	50/22		NA/NA/64/7	6/44/5/1	61	41	15
Shchepotin	1995	NA	1988.02- 1991.04	S	50	NA	NA	NA	0/3/33/14	17/33(N1+N2)	18	15	NA
				NAC	47	NA	NA		0/0/35/14	15/32(N1+N2)	42	37	NA
Wang	1999	China	1987-1988	S	30	55(33-67)	27/3	I, II, IIIB	NA	NA	NA	NA	7
				NAC	30	54(37-65)	23/7		NA	NA	NA	NA	12
Hartgrink	2004	Netherlands	1993.09-1996.01	S	29	NA	NA	I, II, III,	NA	NA	18	14	10
				NAC	27	NA	NA		NA	NA	17	9	6
Nio	2004	Japan	1991-1999	S	193	65.3±11.5	141/52	I, II, III, IV	NA	NA	175	143	137
				NAC	102	63.5±11.9	70/32		NA	NA	96	78	73
Imano	2010	Japan	1992-2002	S	16	59.5±7.7	9/7	NA	NA/11/5/NA	NA/14/2/0	13	8	6
				NAC	47	59.3±11.0	32/15		NA/22/25/NA	NA/40/6/1	40	26	20
Ychou	2011	France	1995.11-2003.12	NAC	113	63(36-75)	96/17	I, II, III	0/38/57(T3+T4)	32/66(N1+N2+N3)	93	53	27
				S	111	63(38-75)	91/10		0/27/58(T3+T4)	17/68(N1+N2+N3)	79	38	16
Cunningham	2006	United Kingdom	1994.7- 2002.4	NAC	250	NA	205/45	II, III	0/16/106/16	42/72/19/2	168	79	38
				S	253	NA	191/62		1/128/225/14	42/68/34/12	155	50	18
Bang	2012	South Korea, China, et al	2006.06-2009.06	S	515	55.8±11.6	358/157	IB, II, IIIA, IIIB, IV	3/282/229/1	56/308/151/0	443	344	137
				PAC	520	56.1±11.1	373/147		8/282/227/3	47/313/160/0	452	376	169
Miyagaki	2011	Japan	1993.01-1998.03	S	133	57(23-73)	88/45	NA	2/39/88/4	32/51/38/5	121	88	81
				PAC	135	59(33-75)	94/41		3/48/77/7	41/49/35/4	124	100	84
Kulig	2009	Poland	1995.01-1999.02	S	154	64(61-66)	111/43	IB, II, III	3/40/69/42	51/43/46/14	128	75	62
				PAC	141	61(58-67)	100/41		3/27/71/40	40/37/39/25	113	73	63
Bajetta	2002	Italy	1992.12-1997.12	PAC	135	57(23-70)	81/54	NA	65(T1+T2)/70(T3+T4)	15/120(N1+N2+N3)	124	50	27
				S	136	57(31-70)	93/43		63(T1+T2)//73(T3+T4)	12/124(N1+N2+N3)	122	62	29
Bonfanti	1988	Italy	1977.3-1981.6	PAC	69	58(26-69)	49/20	NA	12/21/36(T3+T4)	26/43(N1+N2+N3)	60	40	29
				S	69	56(38-70)	44/25		17/23/29(T3+T4)	33/36(N1+N2+N3)	59	35	30
Bouche	2005	France	1989.4-1997.12	PAC	127	60(32-82)	93/34	II, III, IV	28(T1+T2)/94/5	20/69/18/15)	114	73	59
				S	133	62(31-83)	93/40		31(T1+T2)/97/5	23/69/30/6)	111	73	56
Chipponi	2004	France	1989.10-1997.9	PAC	93	Mean:59	58/35	II, III, IV	NA	19/74(N1+N2+N3)	81	45	34
				S	103	Mean:63	71/32		NA	14/89(N1+N2+N3)	82	50	38

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Author	*Public. year*	*Study location*	*Study year*	*Item*	*N*	*Age, yr*	*M/F*	*AJCC/UICC*	*Tumour stage (T1/T2/T3/T4)*	*Nodal stage (N0/N1/N2/N3)*	*1 OS*	*3 OS*	*5 OS*
Chou	1994	Taiwan	1986.1-1992.12	PAC	44	60.4±11.8	21/23	II, III	NA	NA	36	21	16
				S	37	60±12.7	25/12		NA	NA	28	8	4
De Vita	2007	Italy	1996.6-2001.6	PAC	112	63(39-70)	66/46	IB, II, III	3/19/69/21	32/38/42/NA	102	77	52
				S	113	62(41-70)	65/48		5/18/73/17	30/39/44/NA	100	78	49
Di Costanzo	2008	Italy	1995.1-2000.9	PAC	130	NA	79/51	IB, II, IIIA	NA/NA/64/6	20/104/(N1+N2+N3	114	75	43
				S	128	NA	78/50		NA/NA/60/8	22/109(N1+N2+N3	109	72	49
Hallissey	1994	UK	1981.6-1986.7	PAC	138	63(58-68)	98/40	II, III	NA	NA	88	35	26
				S	145	63(57-69)	106/39		NA	NA	81	40	29
Krook	1991	USA	NA	PAC	61	63(33-77)	47/14	I, II, III	NA	12/49(N1+N2+N3	45	20	20
				S	64	62(38-78)	51/13		NA	18/46(N1+N2+N3	51	22	21
Macdonald	1995	USA	1978.3-1991.8	PAC	93	59(27-75)	59/34	IB, IC, II, III	NA	NA	76	45	34
				S	100	60(18-75)	64/36		NA	NA	82	42	31
Nakajima	1999	Japan	1988-1992	PAC	288	NA	174/114	I, II, III	91/167/30/0	107/157/21/3	282	266	204
				S	285	NA	189/96		97/156/32/0	130/129/25/1	279	252	158
Nakajima	2007	Japan	1997.6-2001.3	PAC	93	Mean:63	70/23	II, III	0/93/0/0	0/69/24/0	91	84	71
				S	95	Mean:64	73/22		0/95/0/0	0/72/23/0	93	72	65
Nashimoto	2003	Japan	1993.1-1994.12	PAC	127	58.4(33-75)	93/34	I, II, III	53/67/7/0	75/38/14(N2+N3)	124	119	116
				S	123	57.5(25-75)	76/47		53/61/9/0	64/42/9(N2+N3)	120	110	106
Nitti	2006	NA	1990.7-1998.3	PAC	194	55(20-70)	123/71	Ib, II, III II IIIB, IV	9/65/108/12	36/79/77/0	166	103	65
				S	203	57(27-71)	129/74		14/64/113/12	37/84/82/0	162	111	65
Ochiai	1983	Japan	1976.1-1978.12	PAC	40	NA	28/21	I, II, III, IV	NA	NA	21	18	13
				S	49	NA	29/11		NA	NA	22	17	15
Engstrom	1985	USA	1975.9-1980.6	PAC	91	NA	57/34	NA	NA	NA	66	33	9
				S	89	NA	63/26		NA	NA	57	32	8
Popiela	2004	Poland	NA	PAC	53	59.6±10.6	31/21	III, IV	38(T2+T3)/15(T4)	0/27/26/0	49	39	36
				S	52	58.4±11.6	43/10		42(T2+T3)/10(T4)	0/35/17/0	40	22	14
Sakuramoto	2007	Japan	2001.10-2004.12	PAC	529	63(27-80)	367/162	II, IIIA IIIB, IV	1/289/225/14	51/296/182/0	515	416	316
				S	530	63(33-80)	369/161		0/286/232/12	64/281/185/0	504	365	268

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Author	*Public. year*	*Study location*	*Study year*	*Item*	*N*	*Age, yr*	*M/F*	*AJCC/UICC*	*Tumour stage (T1/T2/T3/T4)*	*Nodal stage (N0/N1/N2/N3)*	*1 OS*	*3 OS*	*5 OS*
Stablein	1982	USA	1975.1-1980.9	PAC	71	NA	50/21	NA	NA	22/38/11(N2+N3)	64	43	32
				S	71	NA	50/21		NA	23/36/12(N2+N3)	61	32	23
Yonemura	1993	Japan	1988.05-1991.12	NAC	29	64.1±8.34	21/8	IV	NA	NA	16	6	NA
				PAC	26	56.4±9.6	20/6		NA	NA	8	2	NA
Sun	2011	China	2008.07-2010.07	NAC	29	52.6(33-72)	37/18	IV	NA	NA	16	NA	NA
				PAC	26				NA	NA	12	NA	NA
Fazio	2016	Italy	1999-2005	NAC	34	57(25-75)	47	II, IIB	NA	NA	30	22	16
				PAC	35	59(39-76)	22				28	19	14
Li	2012	china	2001-2005	NAC	33	65(41-75)	53	I, II, III	6/4/20/3	12/11/9/1	31	26	25
				PAC	37	61(27-78)	17		0/3/34/0/	4/17/16/0	35	22	18
Qu	2010	china	2005-2008	NAC	39	NA	48	II, IIIB	NA	NA	38	NA	NA
				PAC	39	NA	30		NA	NA	30	NA	NA

S: only surgery, NAC: neoadjuvant chemotherapy, PAC: postoperative adjuvant chemotherapy, OS: overall survival, AJCC/UICC stage: American Joint Cancer Committee/Union Internationale Contre le Cancer, SD: standard deviation, age: years; M: male, F: female, Age: Mean ±standard deviation or median (range), NA: Not available

Table 2. Meta analysis on Egger's test of literature publication bias

Variable	*Group*	*Sample size*			*Test of association*			*Model*	*Test of heterogeneity[a, b]*			*Egger's test[c]*	
		K	*Group 1*	*Group 2*	*OR (95%CI)*	*Z*	*P*		*Q*	*P*	*I2 (%)*	*t*	*P*
1 OS	NAC vs PAC	5	164	163	2.2783 [1.2726; 4.0787]	2.7714	0.0056	Fixed	3.98	0.4085	0	0.3224	0.7683
	NAC vs S	7	658	724	1.8818 [1.0921; 3.2426]	2.2771	0.0228	Random	18.54	0.005	67.6	0.5692	0.5938
	PAC vs S	22	3284	3327	1.2779 [1.0980; 1.4873]	3.1681	0.0015	Fixed	12.27	0.9322	0	0.4983	0.6237
3 OS	NAC vs PAC	3	96	98	2.0961 [1.0902; 4.0303]	2.2188	0.0265	Fixed	0.72	0.6979	0	0.8936	0.5357
	NAC vs S	7	658	724	1.6577 [1.0496;2.6181]	2.1675	0.0302	Random	18.92	0.043	68.3	0.2711	0.7972
	PAC vs S	22	3284	3327	1.2771 [1.1014; 1.4809]	3.2392	0.0012	Random	34.5	0.0321	39.1	0.765	0.4532
5 OS	NAC vs PAC	2	67	72	2.0414 [1.0256; 4.0634]	2.0320	0.0422	Fixed	1.61	0.2048	37.8	-*	-*
	NAC vs S	7	641	704	1.4702 [1.0442; 2.0701]	2.2079	0.0273	Random	7.86	0.2486	23.7	0.5634	0.5975
	PAC vs S	22	3284	3327	1.2843 [1.1099; 1.4859]	3.3616	0.0008	Random	34.27	0.0339	38.7	0.1531	0.8798

[a] Random-effects model was used when the P for heterogeneity test was <0.05, otherwise the fixed-effect model was used. [b] P <0.05 is considered statistically significant for Q statistics. [c] Egger's test to evaluate publication bias, P <0.05 is considered statistically significant; CI: confidence interval.

ADDIS is a decision support system developed to store data from clinical trials in a structured way and create meta-analyses (as well as benefit-risk assessments), based on Bayesian framework and Markov Chain Monte Carlo (MCMC) theory [7, 8]. ADDIS software (1.16.5) was applied in this network meta-analysis. The parameters were set as: Number of chains: 4, Tuning iterations: 20000, Simulation iterations: 50000, Thinning interval: 10, Inference samples: 10000, Variance scaling factor: 2.5. All outcomes were evaluated by OR and 95% CI under a random-effects model. Consistency was evaluated by Inconsistency Factors. If 95% CI of log (OR) included 0, consistency was proposed and the consistency model was applied; otherwise, inconsistency model was used. Convergence of the model was assessed by the Brooks-Gelman-Rubin method, and expressed by Potential Scale Reduction Factor (PSRF). The closer to 1 of the PSRF value, the better convergence of the model was. PSRF less than 1.20 was acceptable [9].

Results

Eligible studies and their characteristics

The flow chart of literature search and study selection is shown in Figure 1. A total of 1356 articles were obtained in Cochrane Database, Pubmed, and Embase. Among them, 1003 articles which did not meet the criteria were excluded by title skim. Then, 257 were excluded from the 353 studied after abstract skimmed. Full-text skim for eligibility of the 96 articles excluded 42 studies which did not meet inclusion criteria (researches irrelevant to this study, Non-RCT, without survival data, or the survival data does not meet inclusion criteria). Full-text scan of 54 articles excluded 17 articles which did not meet the inclusion criteria or with low quality. Finally, 37 RCT articles [3, 10-45] with eligible survival data were included. ACTS-GC and CLASIC research published 3-year and 5-year survival data separately, so they were each included as one article. Finally, 35 RCTs were included in our study (NAC plus surgery vs surgery alone: 8 RCTs, surgery plus PAC vs surgery alone: 22 RCTs, NAC vs PAC: 5 RCTs). All the articles were RCTs published between 1982 to September 2017. The cases were mainly distributed in European countries, Japan, China, Korea, and USA. There was no difference among each treatment groups in terms of demographic characteristics such as age and gender (Table 1).

RCTs quality evaluation of the included studies showed high risk in both performance bias and detection bias (Figure 2). No significant publication bias was detected (Table 2).

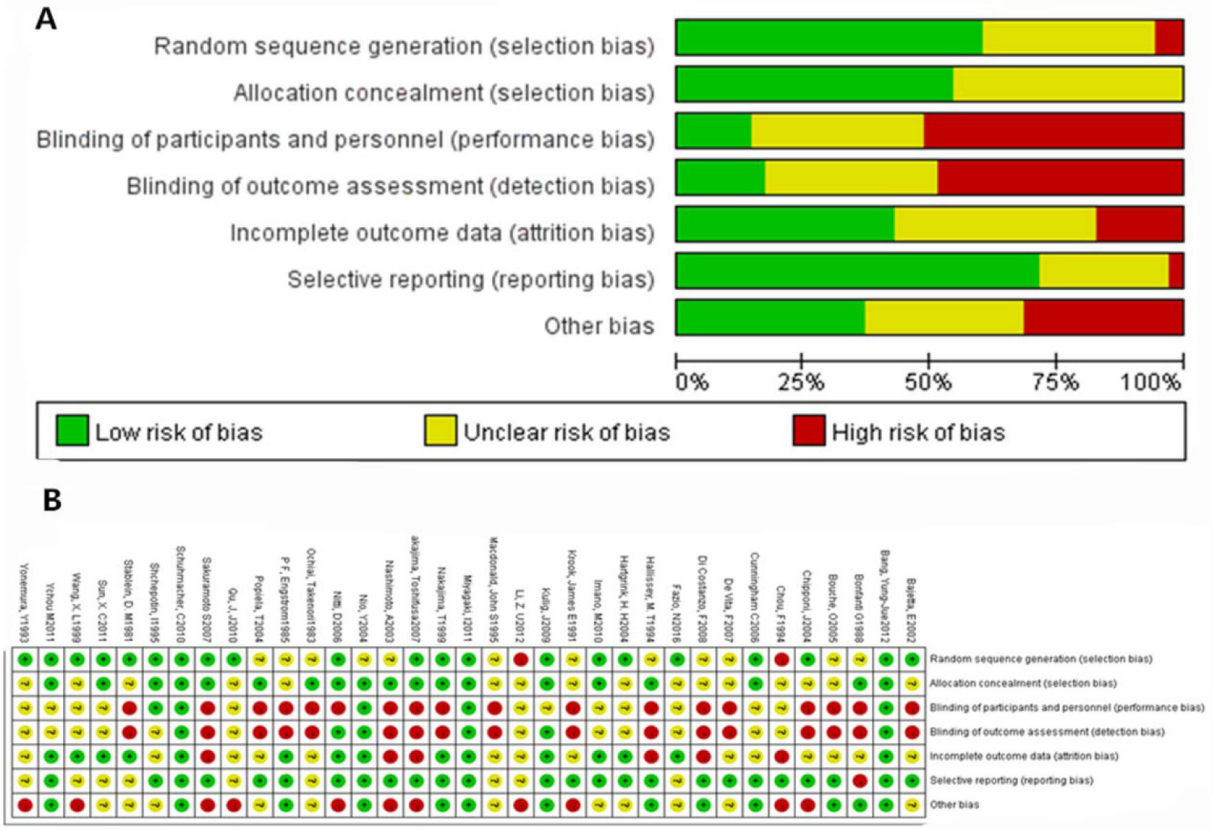

Figure 2. Quality assessments of the included studies. **(A)** Performance bias of the studies included. RCTs quality evaluation showed high risk in performance bias. **(B)** Detection bias of the studies included. RCTs quality evaluation showed high risk in detection bias.

Results of simple meta-analysis

Heterogeneity test was performed to calculate the combined effect value based on the p value of Q test and the I^2 statistic value, using appropriate effect model. From the result of direct compared meta-analysis, we found NAC was better than PAC in 1-year survival rate (I^2=0, p=0.4085, fixed effect model, OR=2.28, 95% CI:1.27-4.04). Both NAC+surgery and surgery+PAC were better than surgery alone in 1-year survival rate (NAC+surgery vs surgery: I^2=67.6%, p=0.005, random effect model , OR=1.88, 95% CI:1.09-3.24; surgery+PAC vs surgery: I^2=0, p=0.9322, fixed effect model, OR=1.28, 95% CI:1.10-1.49). NAC was better than PAC in 3-year survival rate (I^2=0, p=0.6979, fixed effect model, OR=2.10, 95% CI:1.09-4.03). Both NAC+surgery and surgery+PAC were better than surgery alone in 3-year survival rate (NAC+surgery vs surgery: I^2=68.3%, p=0.0043, random effect model, OR=1.66, 95% CI:1.05-2.62; surgery+PAC vs

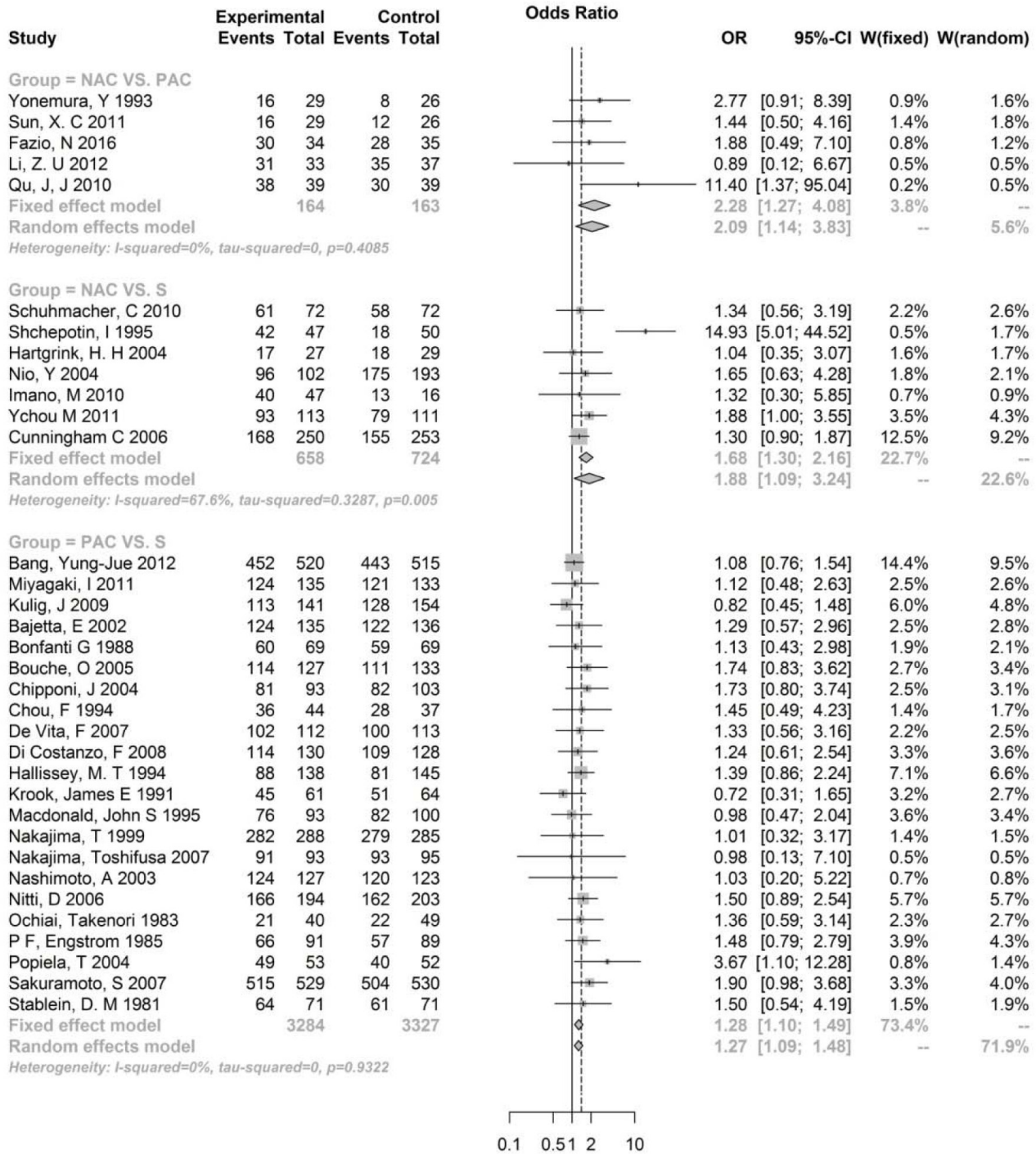

Figure 3. Pairwise comparison of 1-year survival rate.

surgery: I^2=39.1%, p=0.0321, random effect model, OR=1.28, 95% CI:1.10-1.48). For 5-year survival rate, NAC was better than PAC (I^2=37.8%, p=0.2048, fixed effect model, OR=2.04, 95% CI: 1.03-4.06), and both NAC + surgery and surgery + PAC were better than surgery only (NAC + surgery vs surgery: I^2=23.7%, p=0.2468, fixed effect model, OR=1.48, 95% CI:1.12-1.97; surgery + PAC vs surgery: I^2=38.7%, p=0.0339, random effect model, OR=1.28, 95% CI: 1.11-1.49) (Figures 3-5).

Results of the network meta-analysis

Inconsistency factors were applied for consistency test of 1-year survival data. Consistency model was conducted as log OR= -0.35, 95% CI:-1.15 to 0.23. PSRF values were between 1.00 and 1.02, indicating a complete convergence and stable result. It could be inferred from 1-year survival data that NAC + surgery was the optimal treatment for resectable gastric cancer (Table 3 and Figure 6A), and there was significant difference for NAC + surgery

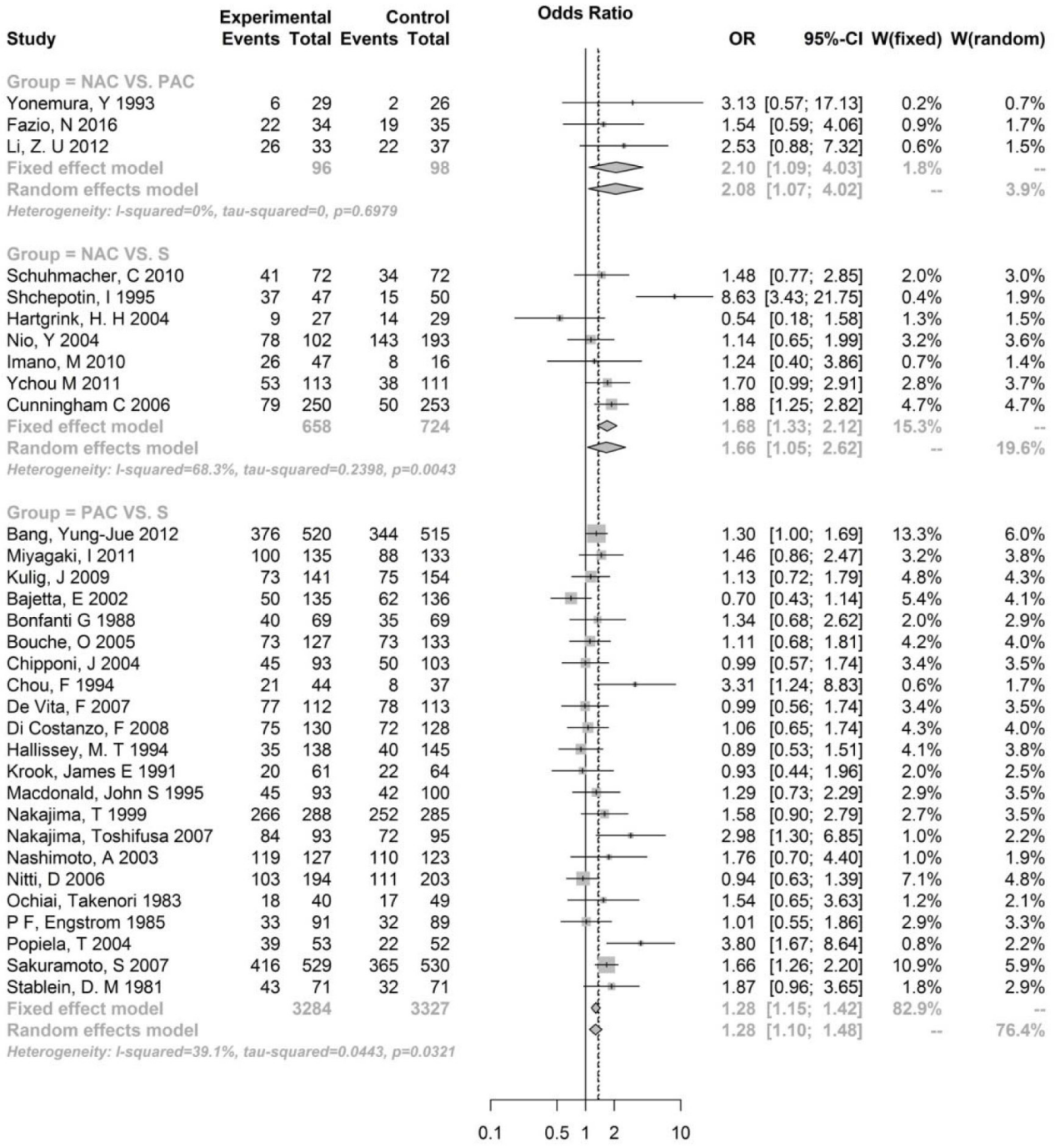

Figure 4. Pairwise comparison of 3-year survival rate.

compared with surgery + PAC or surgery alone. Figure 7A shows mesh construction of 1-year survival data.

Inconsistency factors were applied for consistency test of 3-year survival data. Consistency model was conducted as log OR= -0.28, 95% CI:-1.12 to 0.29. PSRF values were between 1.00 and 1.02, indicating a complete convergence and stable result. It could be inferred from 3-year survival data that NAC + surgery was the optimal treatment for resectable gastric cancer (Table 3 and Figure 6B), The difference of NAC + surgery compared with surgery + PAC or surgery was statistically significant. Figure 7B shows mesh construction of 3-year survival data.

For 5-year survival data, inconsistency factors were applied for consistency test. Consistency model was conducted as log OR= -0.38, 95% CI:-1.14 to 0.23. PSRF values were between 1.00 and 1.01, indicating a complete convergence and stable result. Combined with probability sequence diagram, it could be inferred from 5-year survival data that NAC + surgery may be a better treatment for resectable gastric cancer (Table 3 and Figure 6C).

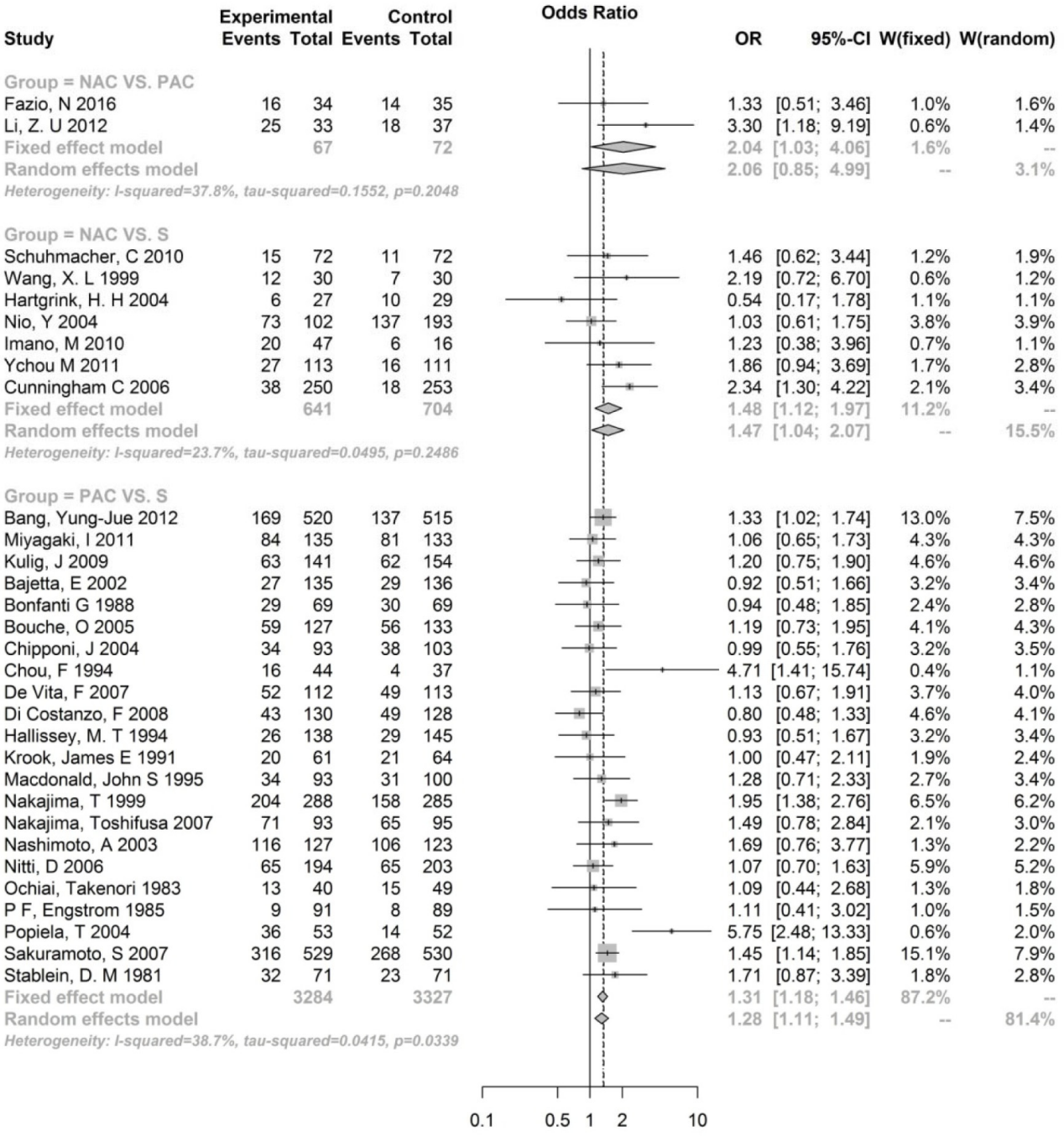

Figure 5. Pairwise comparison of 5-year survival rate.

But there was no statistical significance between NAC + surgery and surgery + PAC. Figure 7C shows mesh construction of 5-year survival data.

Discussion

NAC and PAC are important multidisciplinary strategies raising the survival rate of resectable gastric cancer. MAGIC trial published in 2006 was the first successful phase III clinical trial of multidisciplinary treatment for resectable gastric cancer [37]. Based on the results of this trial, NAC of gastric cancer was adopted in NCCN guideline from 2007 to now. In 2011, FNCLCC/FFCD trials [15] confirmed that NAC increased the survival rate and surgical resection rate. ACTS-GC was the first phase III clinical trial verifying PAC could prolong survival of gastric carcinoma patients. The study of Sakuramoto et al. including 1059 D2 radical surgery of stage II and III gastric cancer reported results of ACTS-GC phase III clinical trial in 2007 [14], showing that 3-year survival rate was significantly higher in PAC group than surgery alone (80.5% vs 70.1 %, HR 0.68, 95% CI 0.52 to 0.87). Furthermore, Sasako et al. reported 5 years follow-up data in 2011 [13], which showed that 5-year survival rate of PAC group was significantly higher than surgery alone group (71.7 vs 61.1%, HR 0.669, 95% CI 0.54 to 0.828). Bang et al. reported multicenter phase III clinical trials of gastric cancer which accepted PAC (CLASIC research) [41]. In this study, 1035 patients were randomly divided into the PAC group (oxaliplatin combined with capecitabine) and surgery-alone group, and showed that 3-year disease-free survival (DFS) in PAC group was significantly higher than surgery-alone group (74 vs 59% HR 0.56, 95% CI 0.44-0.72, p<0.0001). Five-year survival was reported in 2014 [16]: 5-year survival rate was obviously higher in PAC group than surgery-alone group (78 vs 69%, HR 0.66, 95% CI 0.51-0.85, p=0.0015). MAGIC trial and FNCLCC/FFCD trials provided evidence for NAC, and ACTC-GC and CLASIC provided evidence for PAC.

In order to elucidate whether NAC or PAC could provide better survival benefit for resectable gastric cancer we made this meta-analysis of randomized controlled trials. In the present study, we searched 5 RCTs which directly compared NAC with PAC. Of the 5 RCTs, 4 were from Asia while 1 was from Europe. The results of meta-analysis showed that compared with PAC, NAC might bring a greater survival benefit for resectable gastric cancer patients. NAC was obviously better than PAC in 1-year, 3-year and 5-year survival rate. The limitation for this simple meta-analysis was that only 5 RCTs were included, while most of them were small-sample RCTs. To get additional evidence for the evidence-based medicine, a network meta-analysis composed of 35 RCTs was made. Among them, 8 RCTs compared NAC + surgery with surgery alone, 22 RCTs compared surgery alone with surgery + PAC and the other 5 RCTs compared NAC with PAC directly. The results of network meta-analysis showed that NAC + surgery was statistically better than surgery + PAC in 1-year and 3-year survival, and there was no statistically significant difference between NAC + surgery and

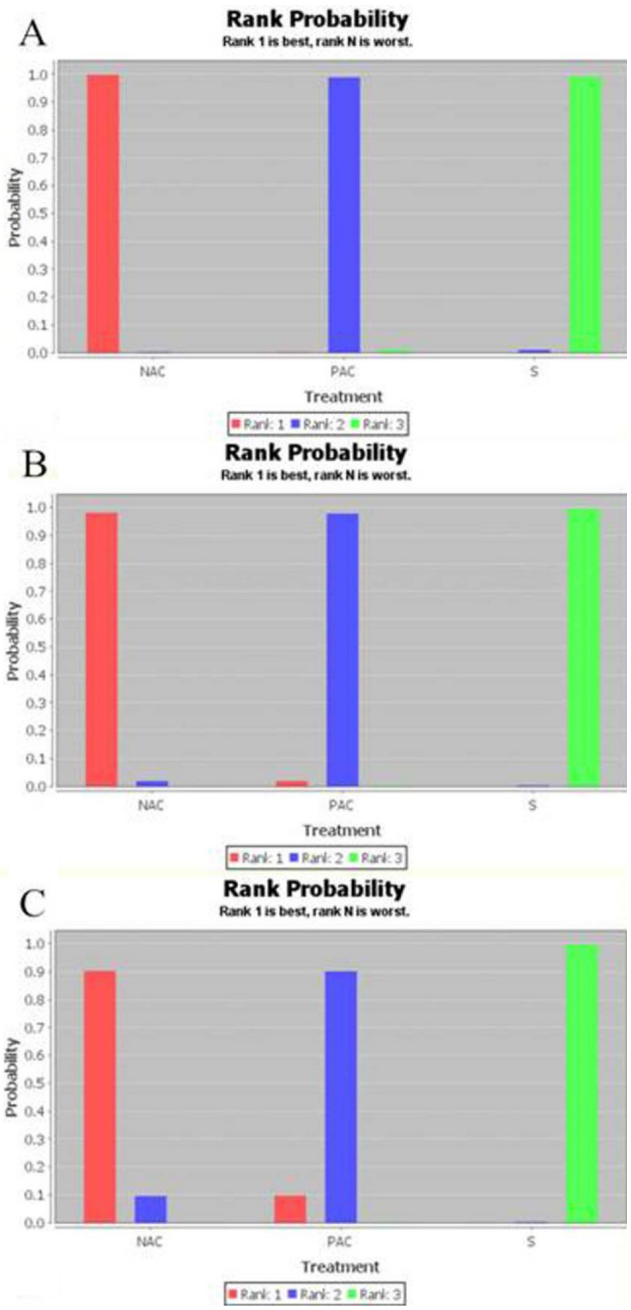

Figure 6. Probability sequence diagram of survival benefit. **(A)** Probability sequence diagram of 1-year survival benefit. **(B)** Probability sequence diagram of 3-year survival benefit. **(C)** Probability sequence diagram of 5-year survival benefit.

Table 3. Comparison of survival benefits of the three therapeutic methods

One-year survival	NAC	0.63 (0.42, 0.85)	0.50 (0.35, 0.65)
	1.59 (1.18, 2.37)	PAC	0.80 (0.66, 0.96)
	2.01 (1.53, 2.89)	1.25 (1.04, 1.52)	S
Three-year survival	NAC	0.71 (0.50, 0.98)	0.55 (0.40, 0.74)
	1.41 (1.02, 1.99)	PAC	0.78 (0.65, 0.92)
	1.81 (1.35, 2.48)	1.29 (1.09, 1.53)	S
Five-year survival	NAC	0.79 (0.55, 1.11)	0.62 (0.45, 0.84)
	1.26 (0.90, 1.80)	PAC	0.78 (0.67, 0.92)
	1.62 (1.20, 2.24)	1.28 (1.09, 1.49)	S

NAC: neoadjuvant chemotherapy group; PAC: postoperative adjuvant chemotherapy group; S: surgery-alone group. Data in the cross points show comparison between any 2 groups. For example, 1.59 represented the OR value, and the numbers in parentheses (e.g 1.18, 2.3) represent 95% CI of NAC vs PAC in 1-year survival.

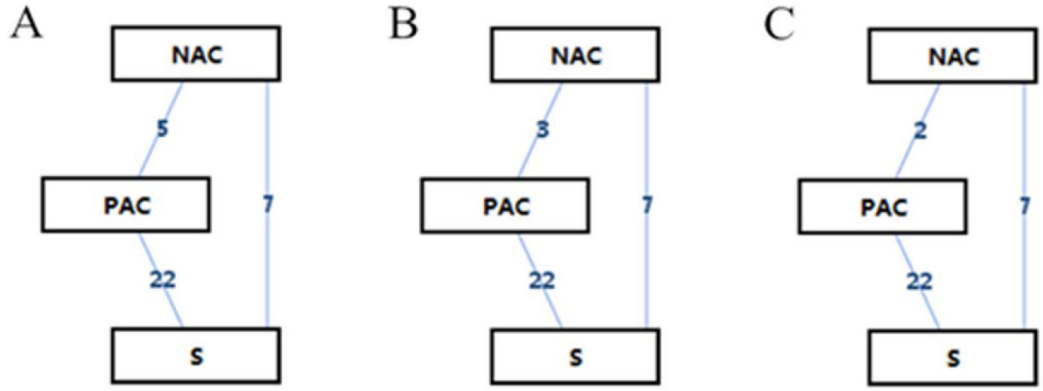

Figure 7. Mesh construction of survival data. The number under blue line is proportional to the number of studies included in the pairwise comparisons. **(A)** Mesh construction of 1-year survival data. **(B)** Mesh construction of 3-year survival data. **(C)** Mesh construction of 5-year survival data.

surgery + PAC in 5-year survival. ADDIS software could rank the intervention measures according to MCMC algorithm [46]. As shown in Figure 6, NAC + surgery ranked first in Probability Sequence Diagram of 1-, 3- and 5-year survival data. Based on the above results, we inferred that NAC could bring more survival benefits than PAC for resectable gastric cancer patients.

Our study showed that NAC had a better survival advantage than PAC for gastric cancer patients. Furthermore, some studies confirmed that NAC reduced tumor staging and improved R0 resection rate [47]. But the clinical research about survival benefit that NAC brings to gastric cancer patients is not enough till now. The reasons are the following: Firstly, MAGIC and FNCLCC/FFCD trials are the main evidence of evidence-based medicine of NAC. But for the deficiency of these trials, especially MAGIC trial acting as the base of American and European guidelines, is questioned by some authors [48]. For example, only 37.6% cases received D2 lymph node dissection in MAGIC trial. FNCLCC study recommended D2 lymph node dissection to patients, but statistical description was not conducted for surgical method. Furthermore, only 42% of the patients finished the whole treatment plan in MAGIC trial. In FNCLCC/FFCD study, more than grade 3 adverse effects appeared in 38% of the patients receiving PAC. Besides, low esophageal cancer patients were included in both researches. Secondly, in addition to MAGIC and FNCLCC/FFCD trials, RCTs with large samples were lacking. Many studies on gastric cancer patients receiving NAC only reported surgical resection rate, chemotherapeutic safety, effects on surgery, R0 resection rate, but lacked follow-up for survival. Thirdly, the meta-analysis of 8 RCTs about NAC + surgery included in our study suggested that though NAC + surgery was superior to surgery-alone group in 1-year, 3-year and 5-year survival rate, but significant heterogeneity was observed in 1-year survival (NAC + surgery vs surgery: I^2=67.6%, p= 0.005) and 3-year survival (NAC + surgery vs surgery: I^2=68.3%, p=0.0043). Only 5-year survival heterogeneity test showed no obvious heterogeneity (I^2=37.8%, p=0.2048). Therefore, the statistical results of 1-year and 3-year survival data of NAC + surgery in our meta-

analysis are not very definite, and further studies are needed.

At present, practical applications of NAC are not very clear, including how to select patients that may get benefit from NAC, how to choose the chemotherapy scheme, how to determine the time of surgery and how to avoid the adverse effects and tumor progression in patients with gastric cancer. In the studies of NAC, the clinical staging of tumors was generally late. Most of the patients had locally advanced stage, but the cases chosen for PAC were mostly I-III stage, although NCCN guideline indicated that NAC for T2 or more advanced stage patients was taken as the first choice. Combined with relevant studies and our clinical experience, we believe that T3/4 and N+patients without distant metastasis may benefit significantly from NAC. We believe that the evidence-based data for NAC of T2N0 patients is not sufficient. In recent years, many new drugs, including taxanes, oxaliplatin and S1 have been applied in NAC. Application of these new drugs has improved the efficiency and safety of chemotherapy for gastric cancer. Latest FLOT4 research, including 265 cases, used to evaluate its therapeutic effect showed that FLOT scheme including docetaxel and oxaliplatin was obviously superior to traditional chemotherapy regimens based on cisplatin and fluorouracil [49]. This study has significant impact on the choice of NAC scheme. For patients receiving NAC, the effect of the treatment should be evaluated in time instead of pursuing the maximum effect. Generally, the therapeutic effect of chemotherapy should be evaluated after two cycles and operation should be performed as soon as possible once the therapeutic purpose is achieved.

For PAC, two large-sample RCTs (ACTS-GC and CLASIC) provided evidence-based data. Our meta-analysis of 22 RCTs involving 6611 patients also confirmed that PAC could bring stable survival benefit to gastric cancer patients. However, the limitation for PAC is that the therapeutic effects cannot be observed. Some patients with PAC even received unnecessary treatment. The advantage for NAC is that the clinical and pathological responses of individuals to treatment can be observed and unnecessary chemotherapy can be avoided.

Quality evaluation of the 35 clinical researches included in our research showed that high risk existed in both performance bias and detection bias. Considering that the effect of these two aspects on survival data was limited, we believed that the overall quality of the included RCTs in this meta-analysis were relatively high.

In conclusion, NAC brings greater survival benefits than PAC to patients with resectable gastric cancer. However, a large-sample RCT comparing NAC and PAC directly is needed to verify our conclusions.

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Conflict of interests

The authors declare no conflict of interests.

References

1. McGuire S. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv Nutr 2016;7:18-9.
2. Choi AH, Kim J, Chao J. Perioperative chemotherapy for resectable gastric cancer: MAGIC and beyond. World J Gastroenterol 2015;21:7343-8.
3. Schuhmacher C, Gretschel S, Lordick F et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010;28:5210-8.
4. Hongzhen Q, Aizhen C, Hongqing X, Lin C. Meta-analysis on the curative effect of neoadjuvant chemotherapy for gastric cancer. Minerva Med 2015;106:247-54.
5. Cochrane Handbook for Systematic Reviews of Interventions. Online Kensaku 2014;35:154-5.
6. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820-6.
7. Hillege H BB, Valkenhoef Gv, Zhao J. ADDIS: an automated way to do network meta-analysis. In: University of Groningen, Research Institute SOM (Systems, Organisations and Management) 2012.
8. Van Valkenhoef G TT, Zwinkels T, De Brock B, Hillege H. ADDIS: a decision support system for evidence-based medicine. Decision Support Systems 2013;55: 459-75.

9. Brooks SP GA. General methods for monitoring convergence of iterative simulations. J Computat Graph Statistics 1998;7:434-55.
10. Wang XL, Wu GX, Zhang MD, Guo M, Zhang H, Sun XF. A favorable impact of preoperative FPLC chemotherapy on patients with gastric cardia cancer. Oncol Rep 2000;7:241-4.
11. Yonemura Y, Sawa T, Kinoshita K et al. Neoadjuvant chemotherapy for high-grade advanced gastric cancer. World J Surg 1993;17:256-61; discussion 261-252.
12. Li ZY, Koh CE, Bu ZD et al. Neoadjuvant chemotherapy with FOLFOX: improved outcomes in Chinese patients with locally advanced gastric cancer. J Surg Oncol 2012;105:793-9.
13. Shchepotin I, Evans S, Chorny V et al. Preoperative superselective intraarterial chemotherapy in the combined treatment of gastric carcinoma. Oncol Rep 1995;2:473-9.
14. Fazio N, Biffi R, Maibach R et al. Preoperative versus postoperative docetaxel-cisplatin-fluorouracil (TCF) chemotherapy in locally advanced resectable gastric carcinoma: 10-year follow-up of the SAKK 43/99 phase III trial. Ann Oncol 2016;27:668-73.
15. Ychou M, Boige V, Pignon JP et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.
16. Sun Z, Zhu RJ, Yang GF, Li Y. Neoadjuvant chemotherapy with FOLFOX4 regimen to treat advanced gastric cancer improves survival without increasing adverse events: a retrospective cohort study from a Chinese center. Sci World J 2014;2014:418694.
17. Sun XC, Lin J, Ju AH. Treatment of Borrmann type IV gastric cancer with a neoadjuvant chemotherapy combination of docetaxel, cisplatin and 5-fluorouracil/leucovorin. J Int Med Res 2011;39:2096-102.
18. Sasako M, Sakuramoto S, Katai H et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011;29:4387-93.
19. Sakuramoto S, Sasako M, Yamaguchi T et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810-20.
20. Popiela T, Kulig J, Czupryna A, Szczepanik AM, Zembala M. Efficiency of adjuvant immunochemotherapy following curative resection in patients with locally advanced gastric cancer. Gastric Cancer 2004;7:240-5.
21. Ochiai T, Sato H, Hayashi R, Asano T, Yamamura Y. Postoperative adjuvant immunotherapy of gastric cancer with BCG-cell wall skeleton. 3- to 6-year follow up of a randomized clinical trial. Cancer Immunol Immunother 1983;14:167-71.
22. Noh SH, Park SR, Yang HK et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:1389-96.
23. Nitti D, Wils J, Dos Santos JG et al. Randomized phase III trials of adjuvant FAMTX or FEMTX compared with surgery alone in resected gastric cancer. A combined analysis of the EORTC GI Group and the ICCG. Ann Oncol 2006;17:262-9.
24. Nio Y, Koike M, Omori H et al. A randomized consent design trial of neoadjuvant chemotherapy with tegafur plus uracil (UFT) for gastric cancer--a single institute study. Anticancer Res 2004;24:1879-87.
25. Nashimoto A, Nakajima T, Furukawa H et al. Randomized trial of adjuvant chemotherapy with mitomycin, Fluorouracil, and Cytosine arabinoside followed by oral Fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. J Clin Oncol 2003;21:2282-7.
26. Nakajima T, Nashimoto A, Kitamura M et al. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Gastric Cancer Surgical Study Group. Lancet 1999;354:273-7.
27. Nakajima T, Kinoshita T, Nashimoto A et al. Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. Br J Surg 2007;94:1468-76.
28. Macdonald JS, Fleming TR, Peterson RF et al. Adjuvant chemotherapy with 5-FU, adriamycin, and mitomycin-C (FAM) versus surgery alone for patients with locally advanced gastric adenocarcinoma: A Southwest Oncology Group study. Ann Surg Oncol 1995;2:488-94.
29. Kulig J, Kolodziejczyk P, Sierzega M et al. Adjuvant chemotherapy with etoposide, adriamycin and cisplatin compared with surgery alone in the treatment of gastric cancer: a phase III randomized, multicenter, clinical trial. Oncology 2010;78:54-61.
30. Krook JE, O'Connell MJ, Wieand HS et al. A prospective, randomized evaluation of intensive-course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. Cancer 1991;67:2454-8.
31. Imano M, Itoh T, Satou T et al. Prospective randomized trial of short-term neoadjuvant chemotherapy for advanced gastric cancer. Eur J Surg Oncol 2010;36:963-8.
32. Hartgrink HH, van de Velde CJ, Putter H et al. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. Eur J Surg Oncol 2004;30:643-9.
33. Hallissey MT, Dunn JA, Ward LC, Allum WH. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. Lancet 1994;343:1309-12.
34. Engstrom PF, Lavin PT, Douglass HO, Jr., Brunner KW. Postoperative adjuvant 5-fluorouracil plus methyl-CCNU therapy for gastric cancer patients. Eastern Cooperative Oncology Group study (EST 3275). Cancer 1985;55:1868-73.
35. Di Costanzo F, Gasperoni S, Manzione L et al. Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC. J Natl Cancer Inst 2008;100:388-98.
36. De Vita F, Giuliani F, Orditura M, et al. Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study). Ann Oncol 2007;18:1354-8.

37. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
38. Chou FF, Sheen-Chen SM, Liu PP, Chen FC. Adjuvant chemotherapy for resectable gastric cancer: a preliminary report. J Surg Oncol 1994;57:239-42.
39. Chipponi J, Huguier M, Pezet D et al. Randomized trial of adjuvant chemotherapy after curative resection for gastric cancer. Am J Surg 2004;187:440-5.
40. Bouche O, Ychou M, Burtin P et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). Ann Oncol 2005;16:1488-97.
41. Bang YJ, Kim YW, Yang HK et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315-21.
42. Bajetta E, Buzzoni R, Mariani L et al. Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian Trials in Medical Oncology (ITMO) Group. Ann Oncol 2002;13:299-307.
43. Adjuvant treatments following curative resection for gastric cancer. The Italian Gastrointestinal Tumor Study Group. Br J Surg 1988;75:1100-4.
44. Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. The Gastrointestinal Tumor Study Group. Cancer 1982;49:1116-22.
45. Qu JJ, Shi YR, Liu FR, Ma SQ, Ma FY. A clinical study of 5-fluorouracil/leucovorin combined with paclitaxel and oxaliplatin as neoadjuvant chemotherapy for advanced gastric cancer. Chin J Gastrointest Surg 2010;13:664-7.
46. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163-71.
47. Xu AM, Huang L, Liu W, Gao S, Han WX, Wei ZJ. Neoadjuvant chemotherapy followed by surgery versus surgery alone for gastric carcinoma: systematic review and meta-analysis of randomized controlled trials. PLoS One 2014;9:e86941.
48. Bringeland EA, Wasmuth HH, Gronbech JE. Perioperative chemotherapy for resectable gastric cancer - what is the evidence? Scand J Gastroenterol 2017;52:647-53.
49. Al-Batran SE, Hofheinz RD, Pauligk C et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 2016;17:1697-1708.