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ABOUT COVER

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META-ANALYSIS

Neoadjuvant chemotherapy for patients with resectable colorectal cancer liver metastases: A systematic review and meta-analysis

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Abstract

BACKGROUND

In recent years, neoadjuvant chemotherapy (NAC) has been increasingly used in patients with resectable colorectal liver metastases. However, the efficacy and safety of NAC in the treatment of resectable colorectal liver metastases (CRLM) are still controversial.

AIM

To assess the efficacy and application value of NAC in patients with resectable CRLM.

METHODS

We searched PubMed, Embase, Web of Science, and the Cochrane Library from inception to December 2020 to collect clinical studies comparing NAC with non-NAC. Data processing and statistical analyses were performed using Stata V.15.0 and Review Manager 5.0 software.

RESULTS

In total, 32 studies involving 11236 patients were included in this analysis. We divided the patients into two groups, the NAC group (that received neoadjuvant chemotherapy) and the non-NAC group (that received no neoadjuvant chemotherapy). The meta-analysis outcome showed a statistically significant difference in the 5-year overall survival and 5-year disease-free survival between the two groups. The hazard ratio (HR) and 95% confidence interval (CI) were HR = 0.49, 95%CI: 0.39-0.61, P = 0.000 and HR = 0.48 95%CI: 0.36-0.63, P = 0.000. The duration of surgery in the NAC group was longer than that of the non-NAC group [standardized mean difference (SMD) = 0.41, 95%CI: 0.01-0.82, P = 0.044)]. The meta-analysis showed that the number of liver metastases in the NAC group was significantly higher than that in the non-NAC group (SMD = 0.73, 95%CI:

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0.02-1.43, *P* = 0.043). The lymph node metastasis in the NAC group was significantly higher than that in the non-NAC group (SMD = 1.24, 95%CI: 1.07-1.43, *P* = 0.004).

CONCLUSION

We found that NAC could improve the long-term prognosis of patients with resectable CRLM. At the same time, the NAC group did not increase the risk of any adverse event compared to the non-NAC group.

Key Words: Colorectal neoplasm; Neoadjuvant chemotherapy; Systematic review; Randomized controlled trials; Meta-analysis; Colorectal liver metastases

Core Tip: Although hepatectomy is currently recommended as the most reliable treatment for colorectal liver metastasis, there are still a great number of patients who have recurrences and metastases after surgical resection. In recent years, neoadjuvant chemotherapy (NAC) has been increasingly used in patients with resectable colorectal liver metastases (CRLM). However, the efficacy and safety of NAC in the treatment of CRLM are still controversial. Therefore, we conducted a systematic review and meta-analysis to assess the value of NAC in patients with CRLM.

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INTRODUCTION

Colorectal cancer (CRC), one of the most common malignant tumors in Japan[1], is also the leading cause of death among cancer patients in Europe and the United States [2]. A report[3] showed that colorectal cancer ranked third among solid cancers in men and second among women, which explained why it is one of the most common malignancies in the world. Every year, many people are diagnosed with colorectal cancer, and the number grows every year. Compared to other organs, colorectal cancer seems more likely to metastasize to the liver. As the largest substantive organ in the human body, the importance of the liver is evident. Therefore, many deaths of patients with colorectal cancer are caused by liver metastasis[2,4,5].

Hepatectomy is currently recommended as the most reliable treatment for colorectal liver metastasis, and hepatic resection can provide significant long-term benefit with 5-year survival rates approaching 50% in many reports[6-9]. However, only 10%-20% of those patients have the opportunity to undergo surgical resection of metastatic colorectal cancer (CRLM) as more than 80% of the patients are not suitable for liver resection because of advanced disease at the time of diagnosis[10-12]. Although hepatectomy remains the only treatment that can ensure prolonged survival[13], there are still a great number of patients who have recurrences and metastases after surgical resection[14]. Many studies have reported that more than half of patients experience a recurrence after hepatectomy[15-17].

In recent years, neoadjuvant chemotherapy (NAC) has been highly effective, and response rates of 50%-80% have been reported[18-20]. Modern systemic chemotherapy has been widely used to increase the cure rate of patients with resectable tumors and to transform some unresectable metastases to enable surgery[21-23]. However, NAC does not show an overall survival benefit for patients with resectable CRLM, and a subset of patients experience disease progression during treatment[10,13,24]. In recent years, some studies have reported that NAC had no significant survival benefit for patients with resectable CRLM[25-27]. At the same time, NAC has also attracted extensive attention for its potential damage to the liver[28,29], and it remains unclear whether the presence of chemotherapy-induced liver injury or impaired liver

functional reserve affects the long-term outcomes. Thus, the efficacy and safety of NAC in patients with resectable colorectal cancer liver metastasis remain controversial. Therefore, the purpose of this meta-analysis was to evaluate the application value of NAC in patients with colorectal cancer with liver metastases.

MATERIALS AND METHODS

Search strategy

Up to December 2020, four major databases including PubMed, Embase, Web of Science, and the Cochrane Library were searched. The study was designed and conducted in accordance with the standardized Systematic Reviews and Meta-Analyses (PRISMA) guidelines[30] and PRISMA-P guidelines[31]. We used the following keywords in the retrieval process "Colorectal Neoplasm", "Neoplasms, Colorectal", "Colorectal Tumor", "Neoadjuvant Chemotherapies", "Neoadjuvant Therapies", "Neoadjuvant Chemotherapy", "Neoadjuvant chemotherapy", and " Colorectal liver metastases", "Colonic liver metastases", "Rectal liver metastases". The search for PubMed strategy is provided in the Supplementary Table 1.

Inclusion and exclusion criteria

Two investigators (Zhang Y and Ge L) independently reviewed the title and abstract of the included studies, using the inclusion and exclusion criteria. The Inclusion criteria were: (1) Patients with colorectal cancer with liver metastasis confirmed by computed tomography imaging and pathology; (2) Reports with at least one of the outcome measures below; (3) Studies in which patients with extrahepatic metastases were excluded; and (4) Study designs including clinical, randomized controlled trials (RCTs) or observational studies. The exclusion criteria were: (1) Patients with extrahepatic metastases; (2) Patients with preoperative evaluations indicating non-resectable tumors; and (3) Document types including reviews, meta-analyses, letters, case reports, conference abstracts, or duplicate publications.

Data extraction

Two investigators (Zhang Y and Ge L) extracted the baseline characteristics, major outcome indicators, and secondary outcome indicators from the included and consistent studies. The baseline characteristics included the name of the first author of the included study, country, type of study, and general characteristics of the patients in each group. The major outcome indicators included survival outcomes, including 5-year overall survival (OS) and 5-year disease-free survival (DFS). The secondary outcome indicators included the duration of surgery, blood loss, the length of hospital stay, the number of liver metastases, the size of the largest metastasis, synchronous liver metastases, perioperative complications, bile leakage, surgical site infection, liver failure, blood transfusions, major liver resection, lymph node metastasis, and R0 liver resection. The outcome indicators in this meta-analysis are presented in detail in the results section.

Quality assessment

We used the Cochrane risk of bias tool for RCTs[32] and the Newcastlee Ottawa Scale (NOS)[33] criterion for cohort studies to assess the quality of the included studies. Any discrepancy between the two reviewers was resolved by discussion and mutual agreement. If necessary, disagreements were resolved by discussion and consultation with the third researcher (Ma SX).

Statistical analysis

Stata version 15.0 (Stata Corporation, College Station, TX, United States) and Review Manager 5.0 (Cochrane Collaboration's Information Management System) software were used for the statistical analyses. The odds ratio (OR) and 95% confidence interval (CI) were employed to analyze the dichotomous variables, such as adverse event outcomes and synchronous metastasis. Meanwhile, the standardized mean difference (SMD) with a 95%CI was used to analyze the continuous variables, such as the duration of surgery and blood loss. In addition, the hazard ratio (HR) was used as a summary statistical measure of survival outcome (5-year OS and 5-year DFS). We used Cochran's Q test and I^2 to evaluate heterogeneity between the studies. An I^2 of greater than 50% was considered to indicate significant heterogeneity. In this case, a random-effects model and sensitivity analysis or subgroup analysis were needed to analyze the

source of the heterogeneity.

Possible publication bias was assessed using funnel plots, Egger's, and Begg's tests. All statistical values were calculated by the 95%CI, and a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Studies retrieved and characteristics

A flow diagram of the study selection is shown in Figure 1, according to PRISMA. Initially, a total of 1526 potentially eligible studies were identified, and then repeated studies, case reports, meeting abstracts, reviews, meta-analyses, and other unrelated studies were excluded. Finally, 32 studies were included in this meta-analysis, which involved 11236 patients (NAC group = 4791; non-NAC group = 6445). The study included 31 retrospective cohort studies[1,3,6-9,34-58] and one RCT[59], in which NAC was compared with non-NAC for patients who underwent surgery for the treatment of CRLM.

The characteristics of the included studies and the summary results of the NOS scores are shown in Table 1. Quality evaluation of all observational studies was conducted using the NOS scale, and the scores ranged from six to nine stars. In general, studies with a score of 6 were considered of high quality. The quality evaluation of the one RCT is presented in Figure 2, which showed that the overall quality of the one RCT was good. The meta-analysis results are shown in Table 2.

Survival results

Twenty two studies[1,3,7,9,35-39,41,42,44,47-52,54,57-59] reported 5-year OS (Figure 3A). The results of the meta-analysis showed a significant survival benefit in the NAC group (HR = 0.49, 95%CI: 0.39-0.61, P = 0.000, I^2 = 0.0%).

Thirteen included studies[6,7,35,37,38,44,46,48,50-52,54,58] reported 5-year DFS (Figure 3B). The results of the meta-analysis showed a significant survival benefit in the NAC group (HR = 0.48, 95%CI: 0.36-0.63, P = 0.000, I^2 = 0.0%). Compared to the non-NAC groups, there were significant DFS benefits in the NAC groups.

Perioperative results

Eight studies[1,7,9,34,35,40,42,43] with 4396 patients assessing the duration of surgery showed an increase in surgery duration (Figure 4) in the NAC group (SMD = 0.41, 95%CI: 0.01-0.82, P = 0.044, I^2 = 95.9%). The meta-analysis of Europe and America studies (SMD = 0.49, 95%CI: -0.01-0.98, P = 0.054) and Asia studies (SMD = 0.17, 95%CI: -0.12-0.45, P = 0.247). The results showed no heterogeneity in the subgroup of Asia studies (χ^2 = 0.01, I^2 = 0.0%, P = 0.918).

Twelve of the 32 included studies[6,7,9,35,42-44,49,51,55-57] assessing the number of liver metastases (Figure 5) showed a significant statistical difference between the two groups (SMD = 0.73, 95%CI: 0.02-1.43, P = 0.043, I^2 = 98.0%), indicating that there were more liver metastases in the patients in the NAC group. The meta-analysis of Europe and America studies (SMD = 0.89, 95%CI: -0.07-1.86, P = 0.069) and Asia studies (SMD = 0.36, 95%CI: -0.14-0.86, P = 0.159). High heterogeneity was showed in the subgroup of Asia studies (χ^2 = 14.03, I^2 = 78.6%, P = 0.003).

Sixteen of 32 included studies[6,8,35,36,38,39,41-44,46,50-52,58,59] assessing the lymph node metastasis (Figure 6) showed a significant statistical difference between the two groups (SMD = 1.24, 95%CI: 1.07-1.43, P = 0.004, I^2 = 49.5%), indicating that there were more lymph node metastasis in the patients in the NAC group.

Six studies[40,42,45,53,56,57] reported the length of hospital stay (Figure 7), 13 studies[6,7,9,35,39,42-45,49,55-57] reported the size of the largest metastasis (Figure 8), and six studies[1,7,35,42,43,57] reported blood loss during surgery (Figure 9). The results of the meta–analysis showed no significant statistical difference between these three indicators in the two groups (SMD = 0.20, 95%CI: -0.61-1.02, P = 0.624, I^2 = 97.3%; SMD = -0.00, 95%CI: -0.31-0.30, P = 0.980, I^2 = 92.9%; SMD = 0.53, 95%CI: -0.05-1.10 P = 0.072, I^2 = 94.5%). The results showed that the length of hospital stay in the European and American study subgroup was highly heterogeneous (χ^2 = 158.33, I^2 = 97.5%, P = 0.000). The size of the largest metastasis in the Asian study subgroup was highly heterogeneous (χ^2 = 38, I^2 = 92.1%, P = 0.000). There was no heterogeneity in blood loss in the Asian study subgroup (χ^2 = 0.33, I^2 = 0.0%, P = 0.850).

Data were acquired from 19 studies[1,3,7,9,35-38,43-46,50,52-54,57-59] on synchronous metastases .The pooled results (Figure 10) showed that there was no statistical difference between the two groups (OR = 1.19, 95%CI: 0.90–1.58, P = 0.221, I^2 = 65.8%).

Table 1 Baseline characteristics of the included studies

Ref.		Study design	Patients (*n*)		Age (yr) mean ± SD/mean		Gender (M/F)		Clinical T stage	Synchronous/metachronous		Tumor location
			Neo chemo	No neo chemo	Neo chemo	No neo chemo	Neo chemo	No neo chemo		Neo chemo	No neo chemo	
Allen *et al*[58], 2003	2003	Retrospective	52	54	59	63	33/19	28/26	T1/T2/T3/T4	52/0	54/0	NR
Tanaka *et al*[57], 2003	2003	Prospective	48	23	57 (38-69)	59 (37-79)	28/20	17/6	NR	33/15	18/5	a.b
Aloia *et al*[56], 2006	2006	Retrospective	75	17	57 ± 12	60 ± 11.9	46/29	8/9	NR	NR	NR	NR
Hewes *et al*[54], 2007	2007	Retrospective	80	21	NR	NR	40/40	11/10	NR	25/55	7/14	NR
Aloysius *et al*[55], 2007	2007	Prospective	79	25	65 (61-72)	64 (60-70)	49/30	9/16	NR	NR	NR	NR
Mehta *et al*[53], 2008	2008	Retrospective	130	43	NR	NR	NR	NR	NR	51/79	17/26	NR
Tamandl *et al*[49], 2009	2009	Retrospective	29	41	75 ± 3	75 ± 3	16/13	28/13	T1/T2/T3/T4	NR	NR	NR
Boostrom *et al*[52], 2009	2009	Retrospective	44	55	64	57.5	28/16	30/25	NR	24/20	24/31	NR
Lubezky *et al*[51], 2009	2009	Prospective	37	19	63	66	NR	NR	NR	NR	NR	a.b
Scoggins *et al*[50], 2009	2009	Retrospective	112	74	59	68.5	67/45	38/36	T1/T2/T3/T4	19/93	9/65	a.b.c
Adam *et al*[48], 2010	2010	Prospective	169	1302	NR	NR	100/69	831/471	NR	NR	NR	a.b.c
Scartozzi *et al*[47], 2011	2011	Prospective	60	44	NR	NR	23/37	23/31	T1/T2/T3/T4	NR	NR	NR
Son *et al*[46], 2011	2011	Retrospective	20	206	NR	NR	15/5	134/72	T1/T2/T3/T4	12/8	126/80	a.b
Cucchetti *et al*[45], 2011	2011	Prospective	125	117	63.9 ±1 0.4	64.9 ± 9.8	27/20	27/20	T1/T2/T3/T4	19/28	19/28	NR
Spelt *et al*[43], 2012	2012	Retrospective	97	136	64 (33-90)	66.5 (30-88)	61/36	81/55	T1/T2/T3/T4	65/97	70/66	NR
Pinto *et al*[44], 2012	2012	Retrospective	205	205	58.9 ± 12	61.9 ± 12	128/77	144/61	T1/T2/T3/T4	123/82	105/100	NR
Nordlinger *et al*[59], 2013	2013	RCT	182	182	60.7 (9.35)	62.4 (9.63)	127/54	114/65	T1/T2/T3/T4	61/121	67/115	a.b.c
Araujo *et al*[42], 2013	2013	Retrospective	175	236	54.8 (47.5-62.3)	60.9 (51.1-67.6)	103/72	148/88	NR	NR	NR	a.b
Oh *et al*[41], 2013	2013	Prospective	15	15	54	63	12/3	11/4	T2/T3/T4	NR	NR	a.b
Scilletta *et al*[40], 2014	2014	Retrospective	52	129	64 ± 13	63 ± 9	29/23	74/55	NR	NR	NR	a.b.c
Zhu *et al*[39], 2014	2014	Retrospective	121	345	58.0 (35-72)	59.0 (28-84)	81/40	213/142	T1/T2/T3/T4	NR	NR	a.b
Bonney *et al*[37], 2015	2015	Retrospective	693	608	NR	NR	418/275	370/238	NR	693	608	NR
Schreckenbach *et al*[36], 2015	2015	Retrospective	117	71	61 (35–81)	69 (34-85)	86/31	74/26	NR	87/30	26/45	a.
Ayez *et al*[38], 2015	2015	Retrospective	65	154	63 (58-70)	66 (59-72)	47/18	95/59	NR	55/10	133/21	NR
Kim *et al*[6], 2017	2017	Retrospective	32	32	59 ± 10	59 ± 8	23/9	22/10	T2/T3/T4	NR	NR	a.b.

Strowitzki *et al*[3], 2017	2017	Prospective	125	125	NR	NR	NR	NR	NR	69/56	69/56	a.b.c.
Inoue *et al*[7], 2018	2018	Retrospective	61	61	66 (33-89)	63 (41-85)	31/30	32/29	NR	30/31	30/31	NR
Kumar *et al*[8], 2018	2018	Prospective	176	271	62 (30-82)	63 (29-86)	105/71	168/103	NR	NR	NR	NR
Makowiec *et al*[9], 2018	2018	Retrospective	106	228	64 (25-80)	64 (33-87)	64/42	158/70	NR	68/38	94/134	a.b
Hirokawa *et al*[1], 2019	2019	Prospective	20	117	67 (28-76)	68 (38-89)	13/7	70/47	T1/T2/T3/T4	6/14	36/81	a.b
Ratti *et al*[35], 2019	2019	Retrospective	73	73	62 (37-84)	60 (35-86)	39/34	41/32	T1/T2/T3/T4	73/0	73/0	a.b
Wiseman *et al*[34], 2019	2019	Retrospective	1416	1416	60 ± 7	61 ± 12	836/580	803/613	NR	NR	NR	NR

M: Male; F: Female; NAC group: Neoadjuvant chemotherapy group; non-NAC group: No neoadjuvant chemotherapy group; NR: Not reported; a: Colon; b: Rectum; c: Other.

The meta-analysis of Europe and America studies (OR = 1.28, 95%CI: 0.91-1.80, P = 0.153) and Asia studies (OR = 0.91, 95%CI: 0.58-1.44, P = 0.685). The results showed no heterogeneity in the subgroup of Asia studies (χ^2 = 0.54, I^2 = 0.0%, P = 0.910).

Fourteen studies[1,9,34-36,40,42-44,46,50,53,56,59] reported major liver resection (Figure 11), seven studies[1,7,9,42,44,50,52] reported R0 liver resections (Figure 12), and five studies[7,34,35,45,53] reported blood transfusions (Figure 13). The results of the meta-analysis showed no significant statistical difference between the three indicators in the two groups (OR = 1.09, 95%CI: 0.97-1.22, P = 0.143, I^2 = 0.0%; OR = 0.85, 95%CI: 0.61-1.18, P = 0.336, I^2 = 4.6%; OR = 1.07, 95%CI: 0.90-1.29, P = 0.438).

The assembled data from 17 studies[3,7,9,34,35,39-43,49-51,53,54,56,59] assessing perioperative complications showed no statistically significant difference between the groups (OR = 1.00, 95%CI: 0.76-1.31, P = 0.989, I^2 = 69.1%, Figure 14). The meta-analysis of Europe and America studies (OR = 0.98, 95%CI: 0.72-1.33, P = 0.885) and Asia studies (OR = 1.11, 95%CI: 0.53-2.30, P = 0.783). The results showed high heterogeneity in the subgroup of Europe and America studies (χ^2 = 44.37, I^2 = 73.0%, P = 0.000).

Ten studies[7,34,35,39,41,43,50,51,53,59] reported bile leakage (Figure 15), eight studies[7,34,40,41,43,50,53,59] reported surgical site infections (Figure 16), and seven studies[34,35,41,43,50,53,59] reported liver failure (Figure 17). The results of the meta–analysis showed no significant statistical difference between the three indicators in the two groups (OR = 1.10, 95%CI: 0.84-1.43, P = 0.481, I^2 = 0.00%; OR = 0.94, 95%CI: 0.76–1.16, P = 0.571, I^2 = 27.7%; OR = 1.04, 95%CI: 0.76-1.42, P = 0.329, I^2 = 13.4%).

Publication bias

We used Begg's and Egger's regression tests to explore the publication bias of the studies in our meta-analysis and a funnel plot based on the NAC was generated to assess publication bias (Figure 18). Publication bias was not observed [Begg's test (P = 0.888) and Egger's tests (P= 0.676)].

Table 2 Meta-analysis results

Outcome indicators	No. of study	Patients (*n*)		HR/OR/SMD (95%CI)	*P* value	Heterogeneity		
		NAC	non-NAC			χ^2	I^2	*P* value
5-year overall survival	22	2580	4218	0.49 (0.39-0.61)	*P* < 0.01	14.38	0.00%	*P* = 0.853
5-year disease free survival	13	1643	2864	0.48 (0.36-0.63)	*P* < 0.01	5.68	0.00%	*P* = 0.931
Duration of surgery	8	1980	2396	0.41 (0.01-0.82)	*P* < 0.05	172.79	95.90%	*P* = 0.000
Number of liver metastases	12	1017	1096	0.73 (0.02-1.43)	*P* < 0.05	549.46	98.00%	*P* = 0.000
Blood loss during surgery	6	474	646	0.53 (-0.05-1.10)	*P* = 0.072	90.12	94.50%	*P* = 0.000
Length of hospital stay (d)	6	605	565	0.01 (-0.61-1.02)	*P* = 0.624	184.79	97.30%	*P* = 0.000
Size of largest metastases (cm)	13	1226	1539	0.03 (-0.31-0.30)	*P* = 0.980	168.39	92.90%	*P* = 0.000
Synchronous metastases	19	2355	2553	1.17 (0.90-1.58)	*P* = 0.221	43.91	65.80%	*P* = 0.000
Major liver resection	14	2780	3133	1.06 (0.97-1.22)	*P* = 0.143	5.21	0.00%	*P* = 0.970
Lymph node metastasis	16	1523	2128	1.24 (1.07-1.43)	*P* < 0.05	29.26	49.50%	*P* = 0.013
R0 liver resection	7	723	976	0.85 (0.61-1.18)	*P* = 0.336	6.29	4.60%	*P* = 0.391
Perioperative complications	17	2886	3161	1.00 (0.76-1.31)	*P* = 0.980	51.82	69.10%	*P* = 0.000
Bile leakage	10	2244	2364	1.10 (0.84-1.43)	*P* = 0.481	4.77	0.00%	*P* = 0.782
Surgical site infection	8	2065	2056	0.94 (0.76-1.16)	*P* = 0.571	9.68	27.70%	*P* = 0.208
Liver failure	7	2025	1939	1.04 (0.76-1.42)	*P* = 0.813	5.77	13.40%	*P* = 0.329
Blood transfusion	5	1805	1710	1.07 (0.90-1.29)	*P* = 0.438	5.95	32.80%	*P* = 0.203

NAC: Neoadjuvant chemotherapy group; non-NAC: No neoadjuvant chemotherapy group; HR: Hazard ratio; OR: Odds ratio; SMD: Standard mean difference.

Sensitivity analysis

Sensitivity analysis of the primary outcomes with high heterogeneity (continuous variables and individual dichotomous variables) was performed to explore their potential source and assess the robustness of the outcomes. After ignoring each included study in turn for each outcome, the results of those indicators were stable. The result of the sensitivity analysis showed in Supplementary Figure 1.

DISCUSSION

A previous meta-analysis comprising 18 studies with a total of 6254 patients concluded that NAC improved the survival of patients with initially resectable CRLM [60]. Our meta-analysis evaluated the safety and efficiency of NAC and found that NAC could provide significant survival benefits for patients with resection of CRLM, consistent with previous studies. This conclusion was also confirmed with recent findings concerning the association between NAC and survival outcomes[10,11,24]. Therefore, we performed this systematic review and meta-analysis to provide an updated viewpoint on this subject.

In this meta-analysis, we analyzed 5-year OS and 5-year DFS. For cancer patients, one of the essential indicators for evaluating a treatment is survival outcomes such as the 5-year OS and the 5-year DFS, which may reflect whether a treatment could benefit those patients. In this study, one study[59] conducted a phase 3 clinical RCT to compare the survival outcomes of patients treated with or without NAC. The results of the study indicated that the 5-year OS was 51.2% (95%CI: 43.6-58.3) in the perioperative chemotherapy group *vs* 47.8% (95%CI: 40.3-55.0) in the surgery-only group. The results of this phase 3 clinical RCT showed no difference in OS with the addition of perioperative chemotherapy compared to surgery alone for patients with resectable liver metastases from colorectal cancer. However, NAC had an obvious DFS advantage. The perioperative chemotherapy group that subsequently underwent hepatectomy (83%) experienced 9.2% longer PFS (*P* = 0.025) compared to the group undergoing surgery only.

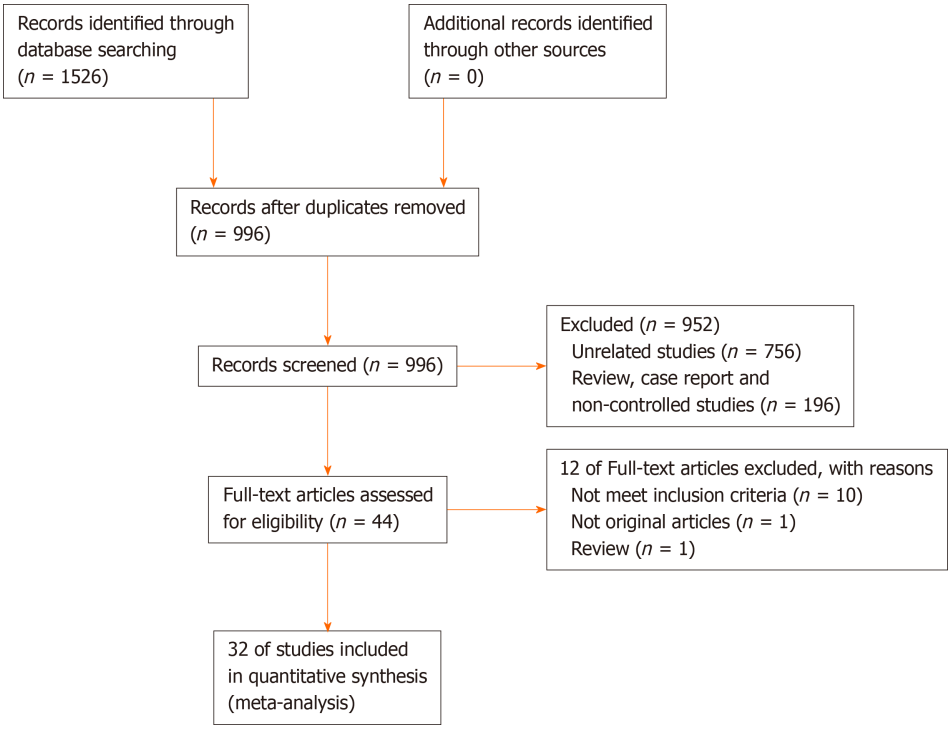

Figure 1 Study identification and selection flow.

Many previous studies have compared the survival outcomes of patients treated with or without NAC. However, the findings are not consistent. A study from Japan[1] showed that the overall survival after initial treatment was significantly worse in the NAC group (5.56 years) than that in the non-NAC group. Moreover, a South Korea study[46] reported that the DFS rates in the NAC and non-NAC groups were 23% and 39%, respectively, and the patient survival rates were 42% and 66% ($P > 0.05$), respectively. One study[19] showed that although NAC can transform a small number of patients with initially inoperable liver metastases into a resectable state, very few patients meet this criterion, and the long-term outcomes of these patients are not significantly different from those of patients who do not receive NAC. However, another South Korean study[6], reported that the DFS rate was significantly higher in the preoperative chemotherapy group than in the primary resection group. The 3-year DFS rates were 34.2% and 16.8%, respectively, and this was also consistent with our findings. Therefore, the discussion and controversy surrounding this conclusion have never stopped, so large sample clinical trials are needed to confirm further it.

High heterogeneity was observed in the continuous variables, such as blood loss and the number of liver metastases, which may be related to study design, ethnic differences, inconsistent measurement methods, and different reporting methods. The included original studies were mostly from Europe and America, which may affect the accuracy and credibility in the measurement results. There were also fewer patients in the NAC group than in the non-NAC group. Therefore, the size of the patient sample was likely to contribute to this result. In addition, a major reason may be the use of neoadjuvant chemotherapy drugs[61]. One study's multivariate analysis of all study factors potentially contributing to the increased intraoperative transfusion rates determined that preoperative chemotherapy was the only independent prognostic factor[56]. This was most likely related to blood vessel damage caused by preoperative chemotherapy.

Because of the high heterogeneity in the pooled data for continuous variables and individual dichotomous variables, subgroup analysis was conducted according to the different study regions, and we performed a sensitivity analysis to explore their potential source and assess the robustness of the outcomes. After ignoring each included study in turn for each outcome, the results of those indicators were stable.

Our meta-analysis showed that NAC could increase the duration of surgery and that the NAC group had more liver metastases and lymph node metastasis. Moreover, the number of liver lesions invaded by tumor cells and the number of lymph nodes invaded are closely related to the patient prognosis. In this case, the surgical methods involved may be completely different[62,63]. Several previous studies reported that

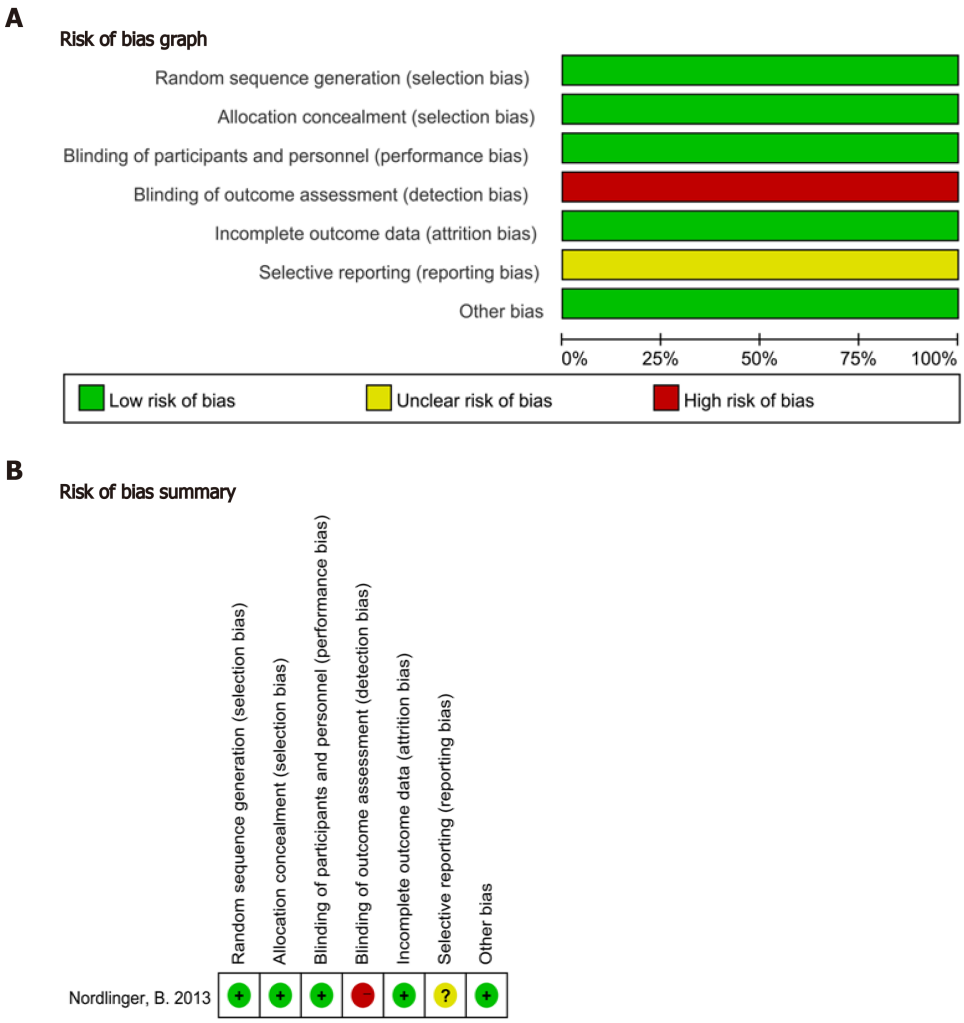

Figure 2 Quality assessment of 1 randomized controlled trial. A: Risk of bias graph; B: Risk of bias summary.

NAC could affect the blood supply to liver tissue and lead to the fibrosis of liver cells. Consequently, this affects the duration of surgery and the amount of blood loss[56,64-67]. In our meta-analysis, the results of the pooled data on blood loss were not statistically significant. Since the data on blood loss were only generated from six studies, this result may be affected by the small limited number of included studies and the insufficient sample size.

In this study, the safety of NAC was also one of the key points of our discussion. In this study, there was no statistical significance in the combined effect size in terms of the incidence of surgical site infection, bile leakage, and liver failure.

Liver failure is a very common and highly fatal complication after NAC[68]. Additionally, NAC has been proven to cause tissue damage to the liver, including vascular lesions of liver parenchyma and steatosis of liver tissue[53,56,63]. Pathologically, these histologic lesions are inextricably linked to the occurrence and prognosis of postoperative complications of NAC[68-70]. However, it should be noted that patients with severe complications such as liver failure often received extensive chemotherapy before surgery, which is also closely associated with confounding factors like type, dose, and duration of chemotherapy drugs[71]. In this study, the combined effect size of liver failure was not statistically significant because of the above confounding factors and the small sample, as the combined effect size of liver failure was only obtained from the research data of seven different studies.

Many studies have shown that a positive margin (< 1 mm) is an indicator of a poor prognosis[72-76]. Although there is a consensus[59] that patients with a negative surgical margin (R0) have a better prognosis, differences remain in the range of the optimal surgical margin of liver lesions during perioperative systemic treatment and its relationship with the survival prognosis of patients. Moreover, Miller *et al*[77] evaluated the optimal margin of resection, which confirmed the importance of R0 resection for CRLM in the modern era of chemotherapy and suggested that patients

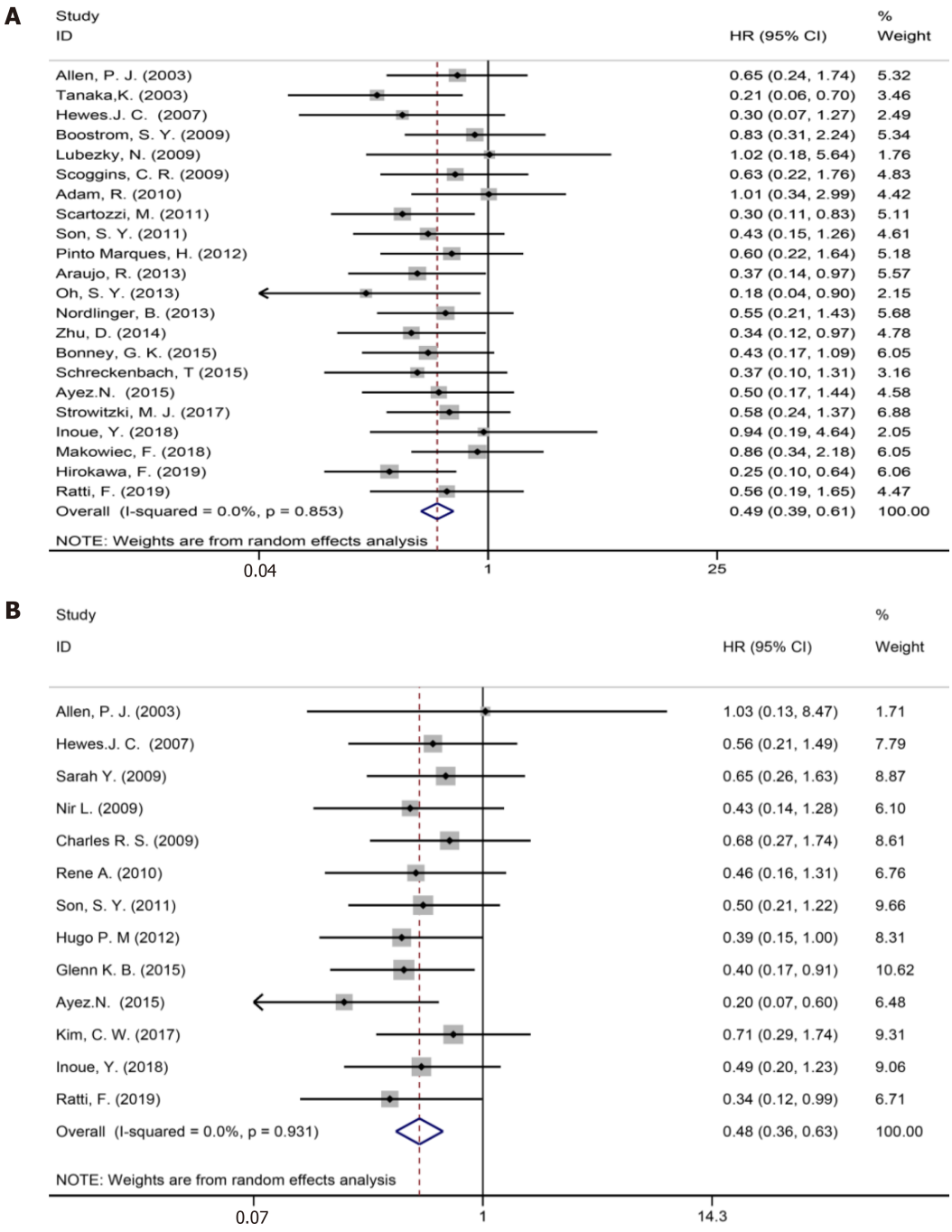

Figure 3 Result of 5-year overall survival and disease-free survival. A: 5-year overall survival for all patients and two groups; B: 5-year disease-free survival for all patients and two groups.

with positive margin should receive additional post-resection chemotherapy to improve survival. However, this study did not find an advantage in long-term survival of patients with a larger margin of resection. In addition, other studies showed that among patients undergoing NAC following R0 and R1 resection, no significant difference was found in OS or recurrence-free survival after surgery[21,71].

In this study, we present the pooled analysis of the impact of NAC on long-term oncology outcomes after liver metastases were resected. In 2016, the safety and effectiveness of NAC in the treatment of colorectal cancer was systematically evaluated[60]. Contrasted to previous studies, our research incorporated more original studies and sensitivity analysis, and more indicators were performed.

Some studies[48,78] have shown that additional adjuvant chemotherapy can significantly improve and prolong the survival period of patients with liver metastases after complete resection. The NCCN guidelines[79] recommend that the duration of peri-operative chemotherapy, including neoadjuvant chemotherapy, should not exceed 6 mo. Moreover, European Society for Medical Oncology guidelines[80]

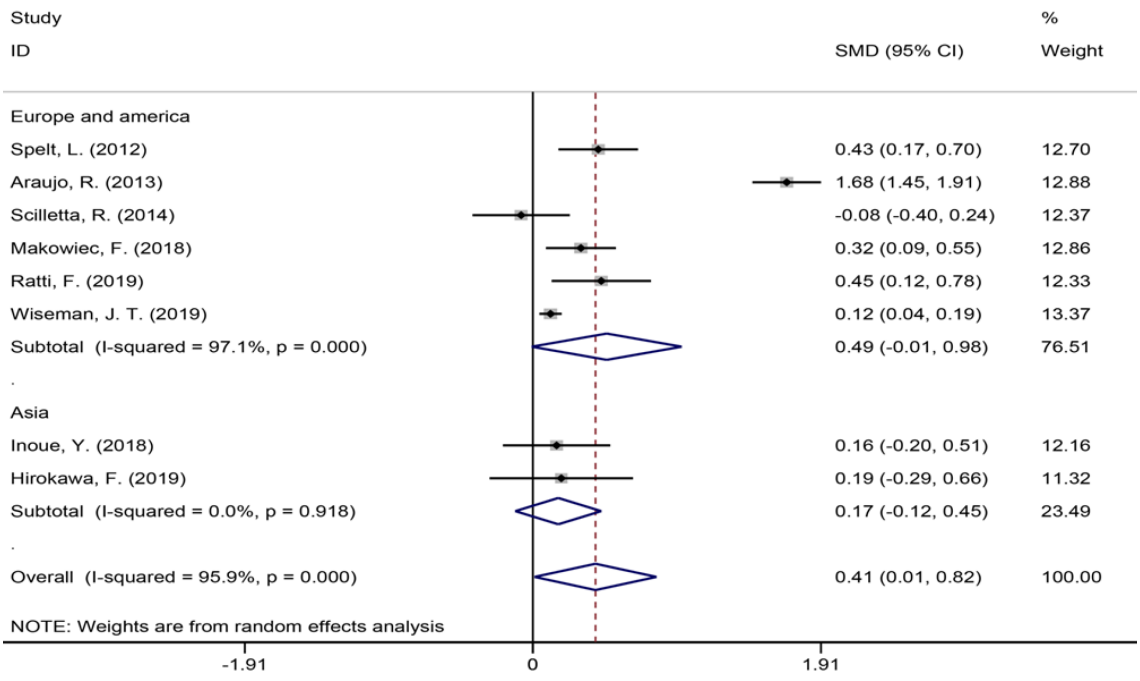

Figure 4 Duration of operation for all patients and by study region subgroups.

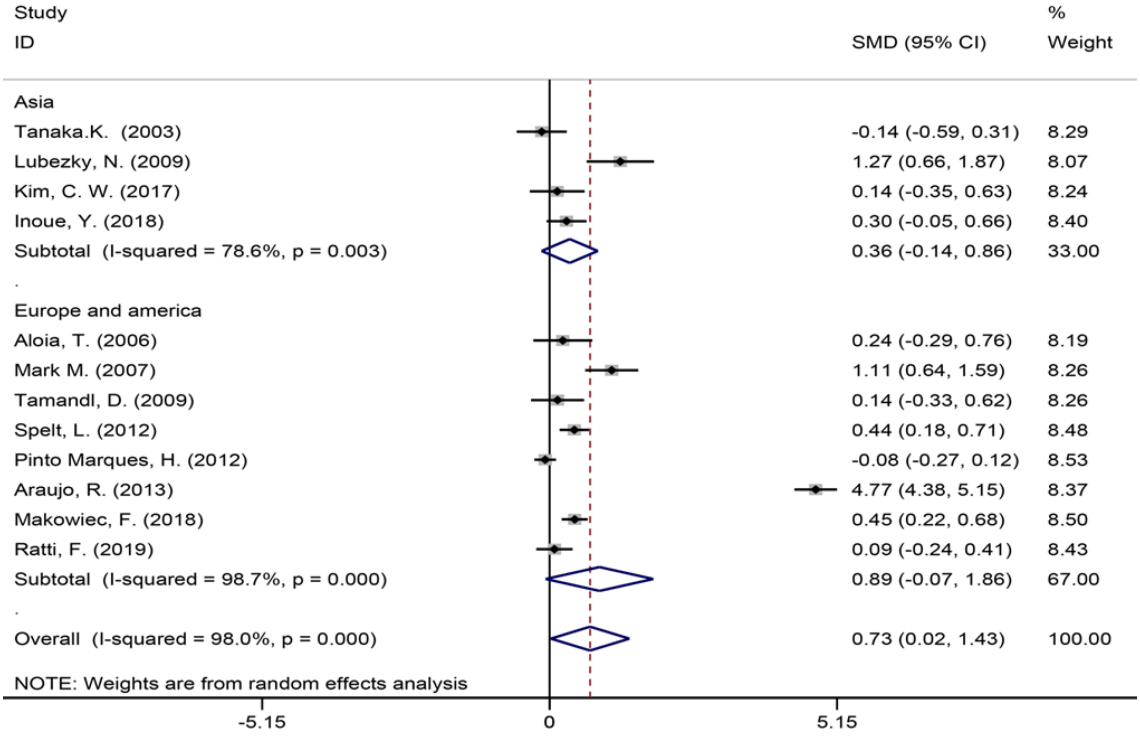

Figure 5 Number of liver metastases for all patients and by study region subgroups.

explicitly suggest that the perioperative treatment mode should be measured from two dimensions: Surgical technical standards and tumor prognosis. The latest NCCN guidelines for the treatment of colorectal cancer[81] recommend FOLFOX as the preferred preoperative chemotherapy option for patients with resectable CRLM and recommend postoperative adjuvant chemotherapy for patients with CRLM who have not received preoperative NAC treatment but have undergone complete surgical resection. Since the efficacy of NAC in patients with resectable CRLM remains controversial and to control for confounders, the role of NAC in patients with resectable CRLM was only discussed in this study. This is also the limitation of this study.

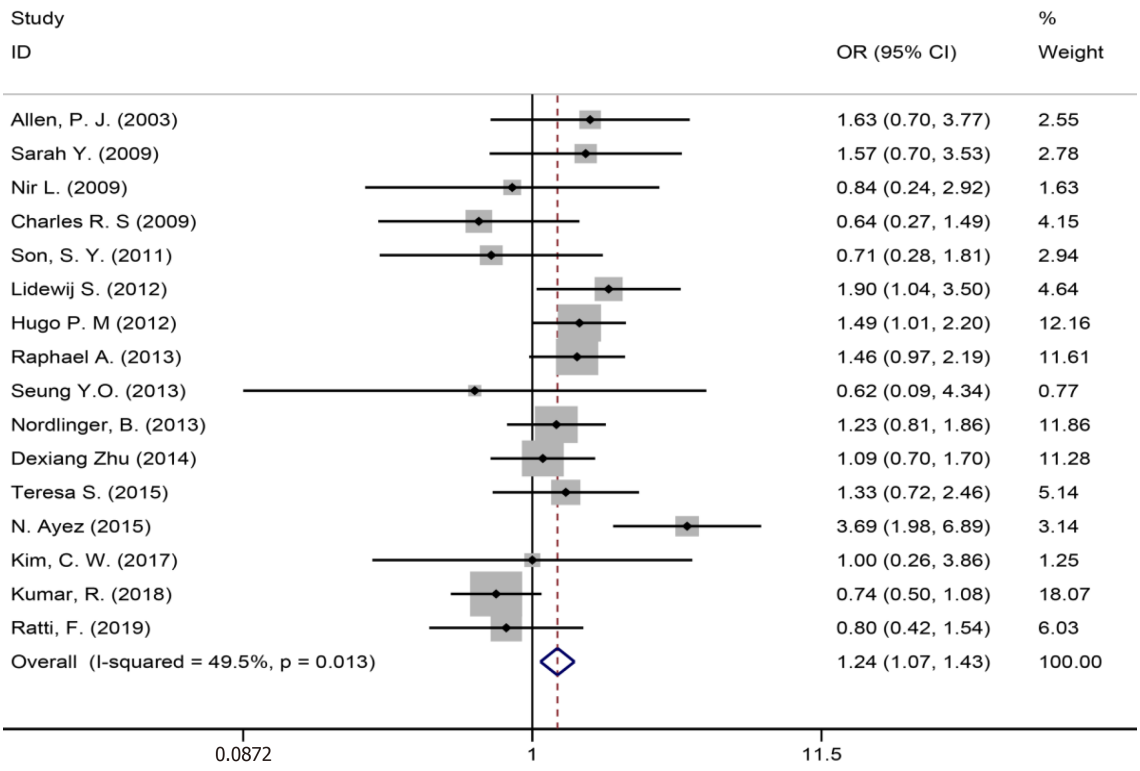

Figure 6 Lymph node metastasis for all patients and two groups.

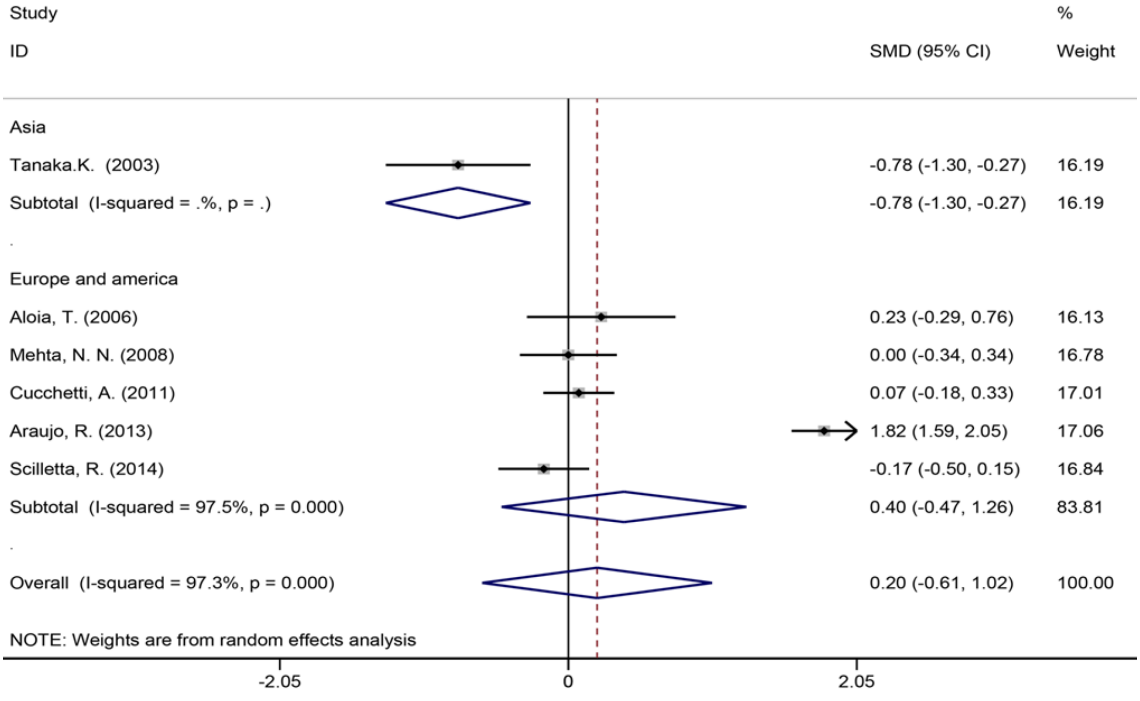

Figure 7 Length of hospital stay and by study region subgroups.

CONCLUSION

The results of this meta-analysis showed that NAC improved the long-term prognosis of the patients who underwent surgery for the treatment of colorectal liver metastases. At the same time, the NAC group did not increase the risk of any adverse event compared to the non-NAC group. Because this study was a secondary study and the included original research studies were mostly from Europe and America, it was impossible to control the differences among the original studies, which may have

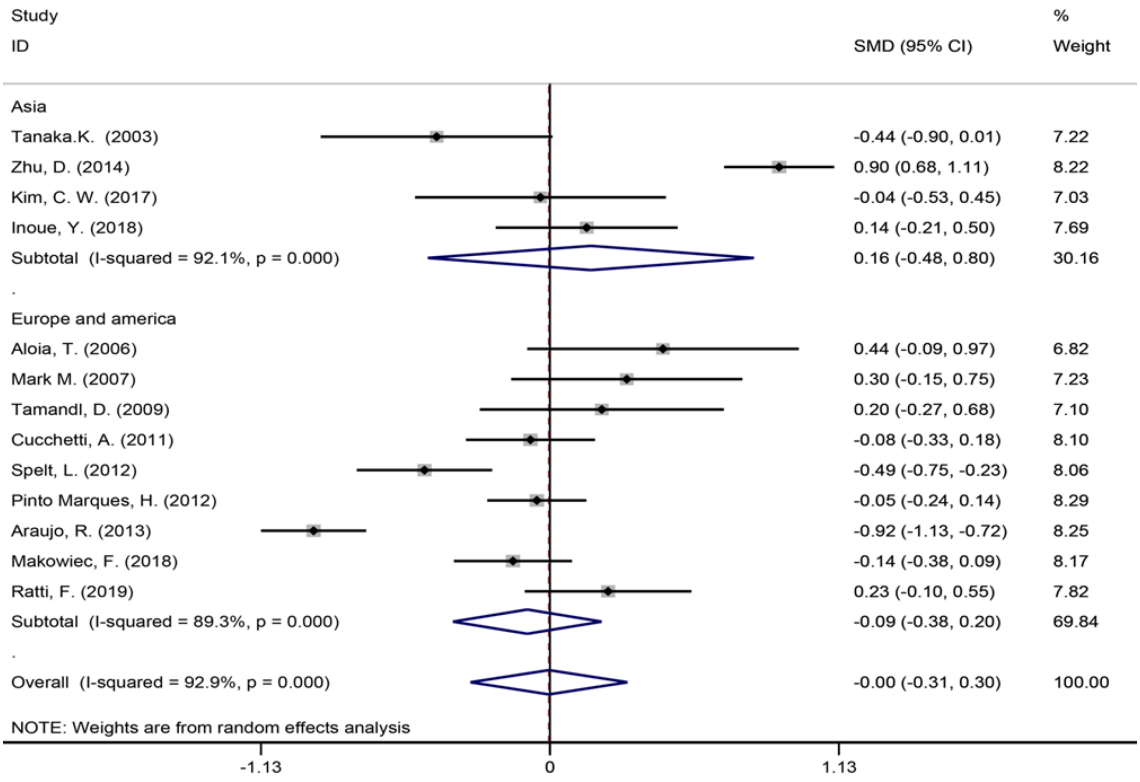

Figure 8 Size of the largest metastasis for all patients and by study region subgroups.

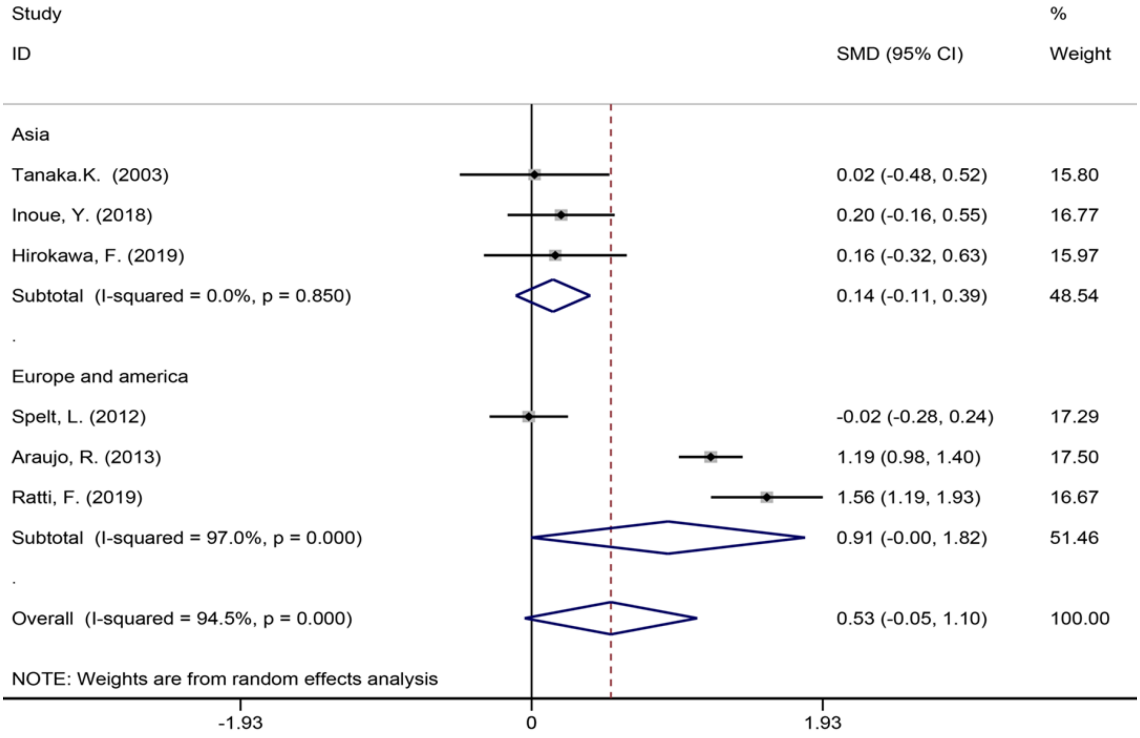

Figure 9 Blood loss during surgery for all patients and by study region subgroups.

affected the reliability of the results. In the future, well-designed prospective RCTs are warranted to define better the treatment effects using NAC.

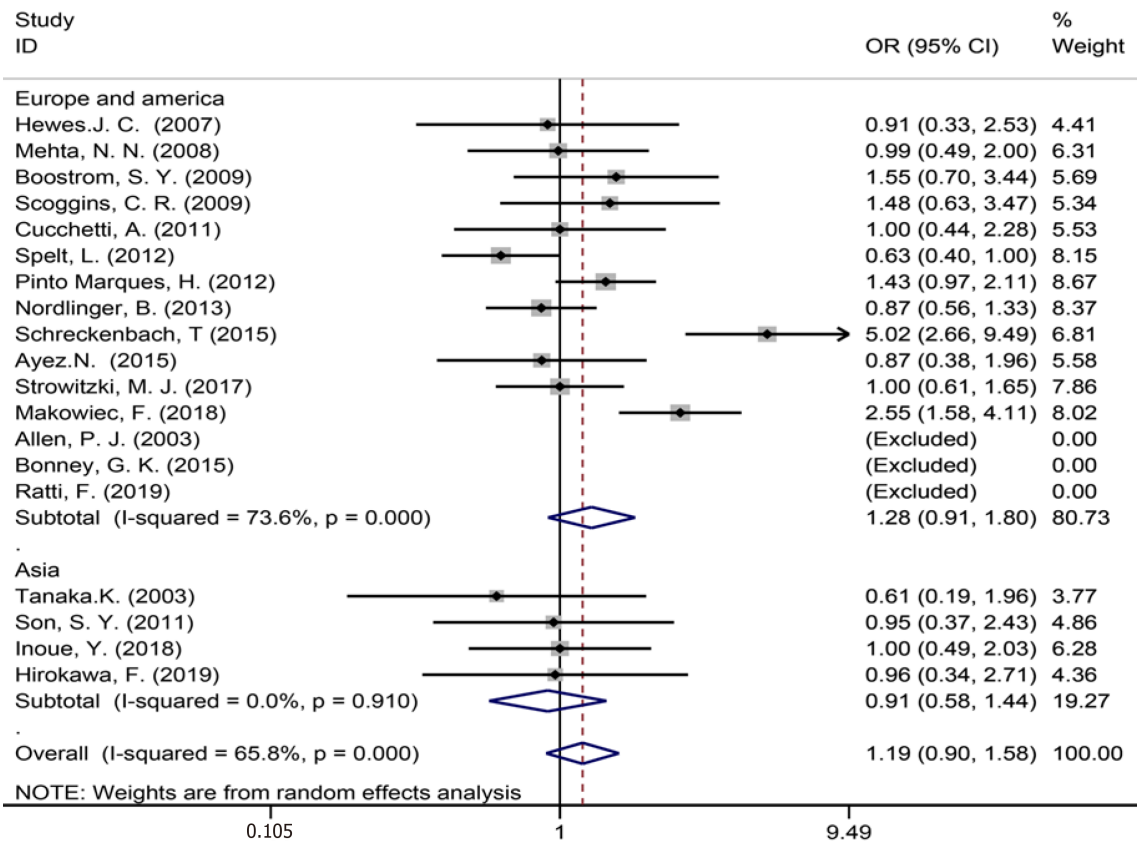

Figure 10 Synchronous metastases for all and by study region subgroups.

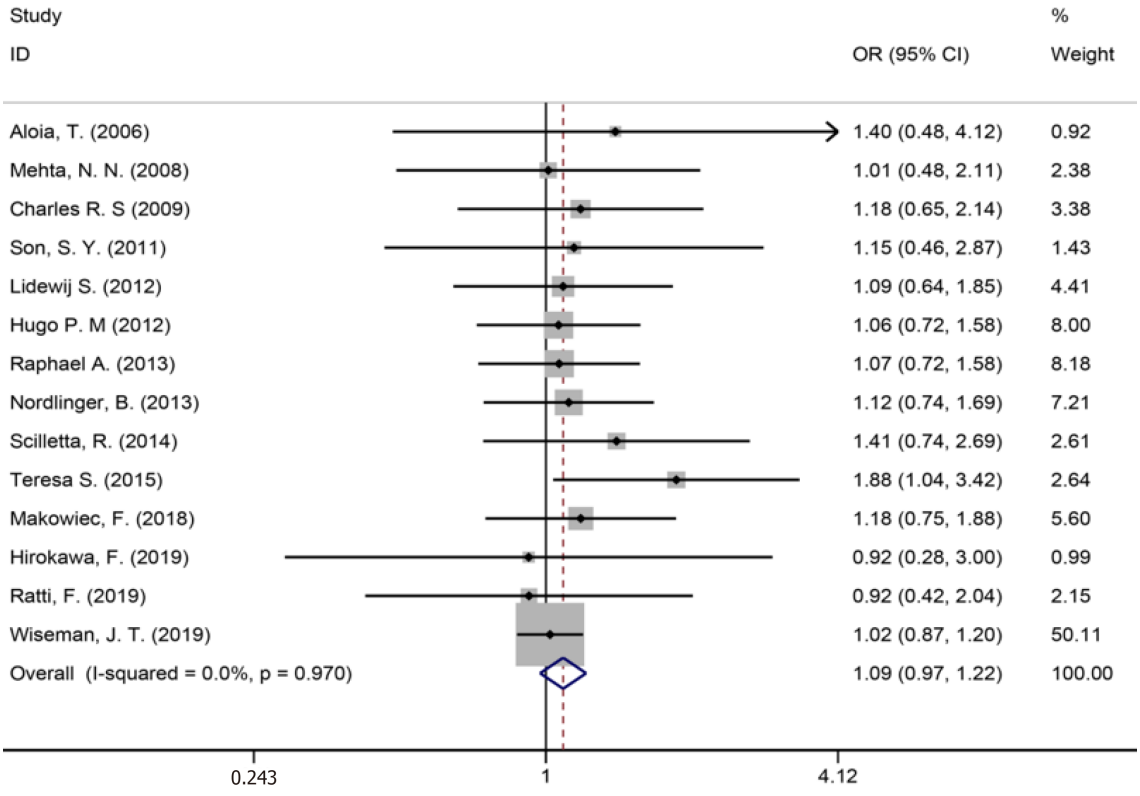

Figure 11 Major liver resection for all patients and two groups.

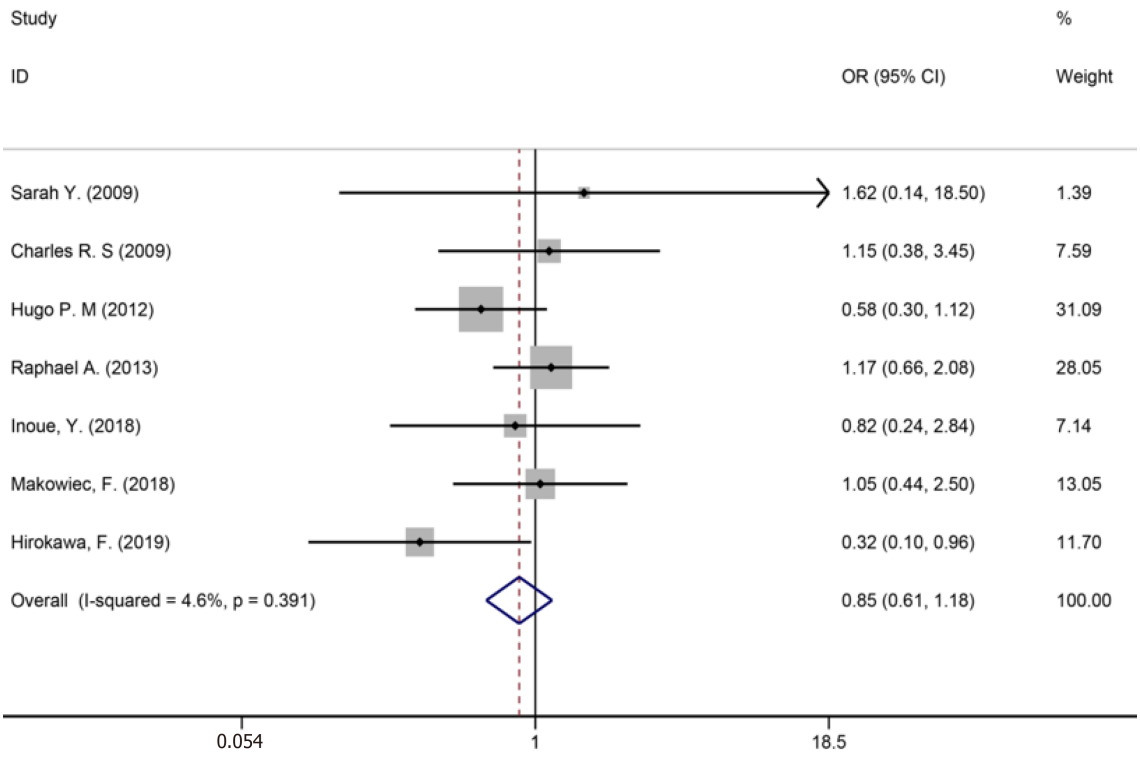

Figure 12 R0 liver resections for all patients and two groups.

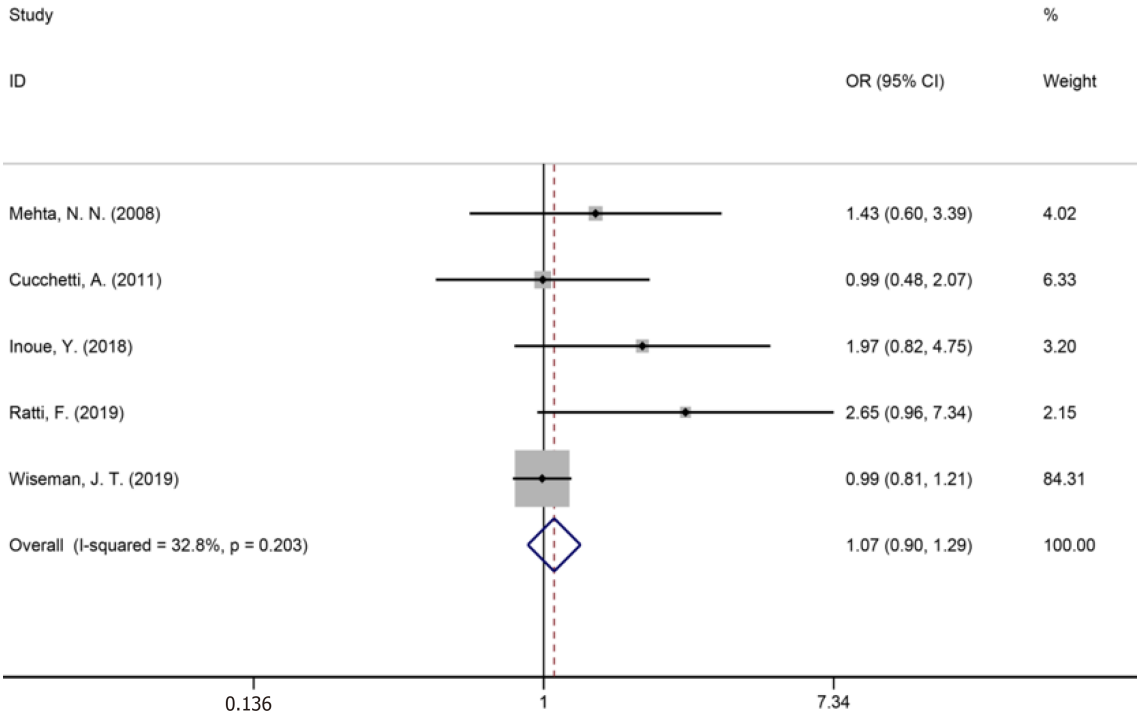

Figure 13 Blood transfusions for all patients and two groups.

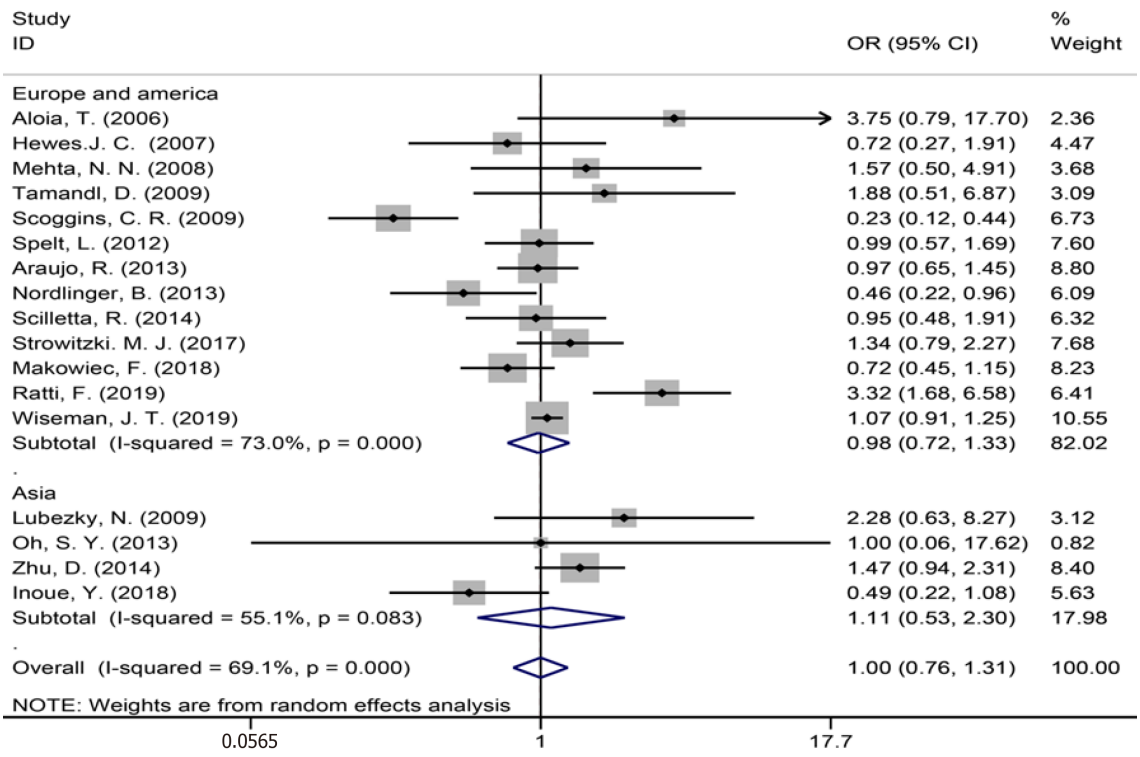

Figure 14 Perioperative complications for all patients and by study region.

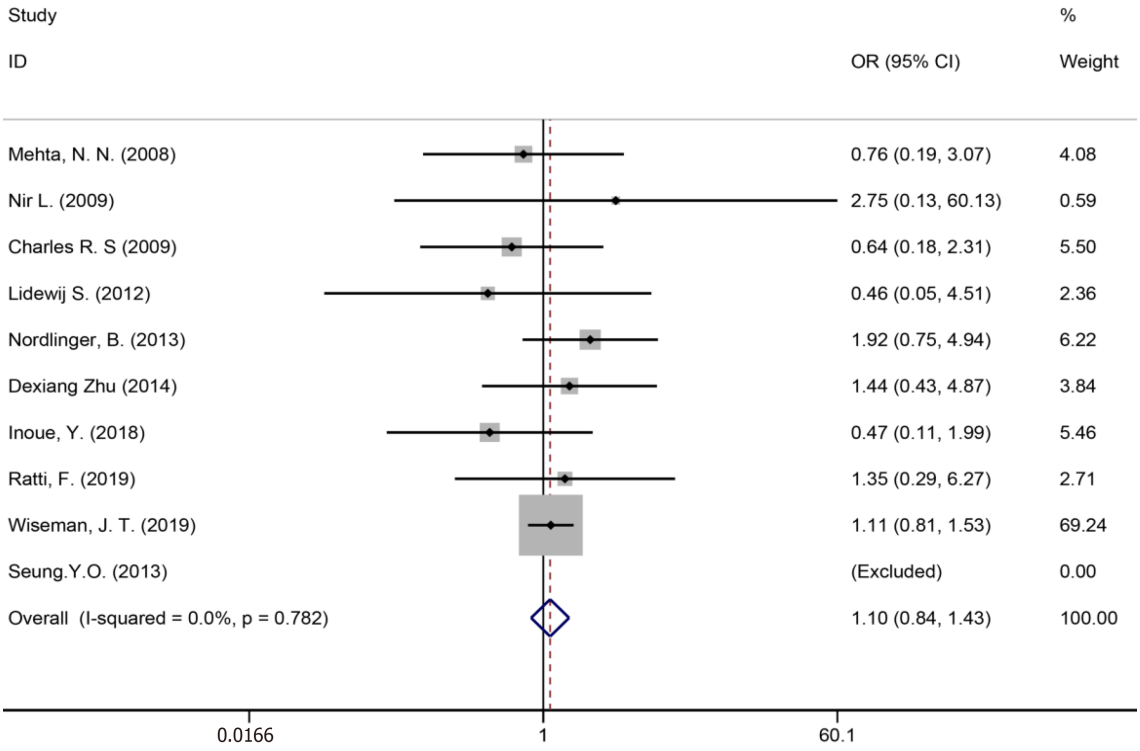

Figure 15 Bile leakage for all patients and two groups.

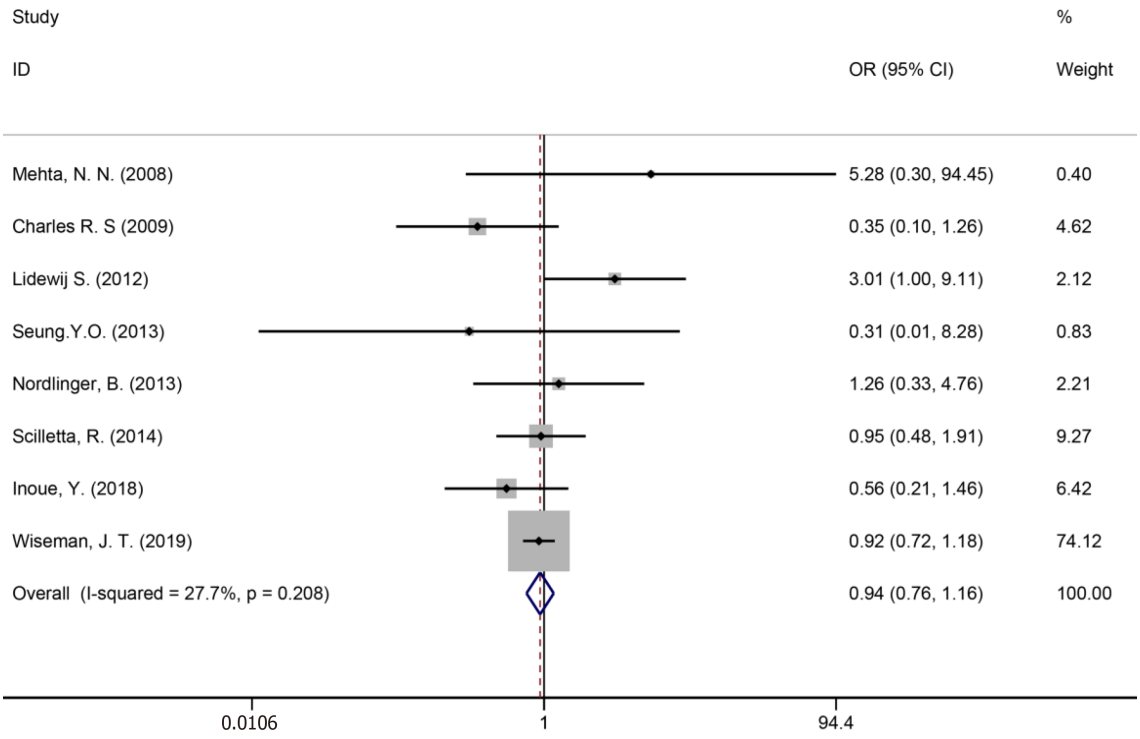

Figure 16 Surgical site infections for all patients and two groups.

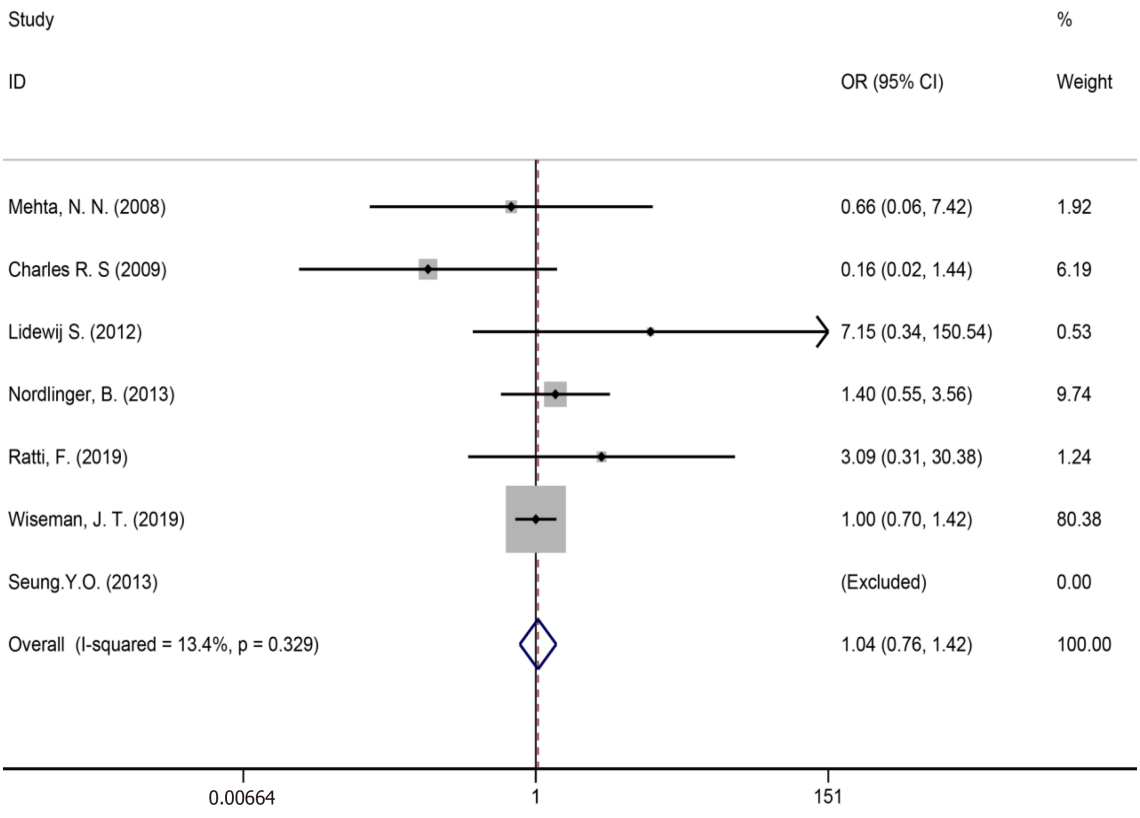

Figure 17 Liver failure for all patients and two groups.

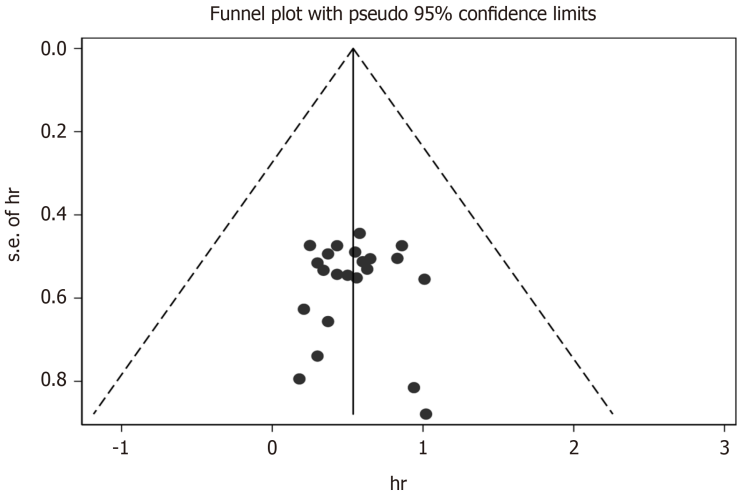

Figure 18 Funnel plot for potential publication bias of overall survival.

ARTICLE HIGHLIGHTS

Research background

Surgery is an effective method for the treatment of liver metastases from colorectal cancer, but the risk of recurrence and metastasis is higher after surgery. The use of neoadjuvant chemotherapy (NAC) for the treatment of resectable colorectal cancer liver metastases is still controversial.

Research motivation

Many previous studies have reported the efficacy of adding NAC in the surgical treatment of resectable liver metastases from colorectal cancer. However, their conclusions have been inconsistent. A randomized controlled trial has revealed that NAC can confer a significant survival advantage over disease-free survival (DFS). In order to solve this dispute systematically and comprehensively, it is necessary to conduct a meta-analysis.

Research objective

The purpose of this study is to use a systematic review and meta-analysis to evaluate the application value of NAC in patients with resectable colorectal cancer and liver metastases.

Research method

We searched PubMed, Embase, Web of Science, and the Cochrane Library to collect clinical studies comparing NAC with non-NAC. Data processing and statistical analyses were performed using Stata V.15.0 and Review Manager 5.0 software. The odds ratio (OR) and 95% confidence interval (CI) were employed to analyze the dichotomous variables. Meanwhile, the standardized mean difference (SMD) with a 95%CI was used to analyze the continuous variables. In addition, the hazard ratio (HR) was used as a summary statistical measure of survival outcome [5-year overall survival (OS) and 5-year DFS].

Research results

Thirty-two studies involving 11236 patients were included in this analysis, which included 31 retrospective cohort studies and one randomized controlled trial. Our results showed a statistically significant difference in the 5-year OS (HR = 0.49, 95%CI: 0.39-0.61 P = 0.000), 5-year DFS (HR = 0.48 95%CI: 0.36-0.63 P = 0.000), the duration of surgery (SMD = 0.41, 95%CI: 0.01-0.82, P = 0.044), the number of liver metastases (SMD = 0.73, 95%CI: 0.02-1.43, P = 0.043), and the number of lymph node metastasis (SMD = 1.24, 95%CI: 1.07-1.43, P = 0.004). However, our results showed no statistically significant difference in the combined effect size in terms of the incidence of surgical site infection (OR = 0.94, 95%CI: 0.76-1.16, P = 0.571, I^2 = 27.7%), bile leakage (OR = 1.10, 95%CI: 0.84-1.43, P = 0.481, I^2 = 0.00%), and liver failure (OR = 1.04, 95%CI: 0.76-1.42, P = 0.329, I^2 = 13.4%).

Research conclusions

NAC can significantly improve the long-term survival advantages of colorectal liver metastases patients, including 5-year OS and 5-year DFS. At the same time, it does not increase the incidence of postoperative bile leakage, surgical site infection, liver failure, and other complications.

Research perspectives

This study had several limitations: First, the included original research studies were mostly from Europe and America, which may affect the accuracy and credibility when comparing studies from different regions. Second, the representative sample size was relatively low. Furthermore, most of the studies that we included were observational studies, which may adversely affect the quality of the study results. Moreover, this study was a secondary study, and it was impossible to control the differences among the original studies, which may have affected the reliability of the results. Finally, colorectal liver metastases is a heterogeneous disease, and differences in tumor biology and expressed proteins may cause significant bias.

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