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Safety and Efficacy of Carbon Nanoparticle-Labeled Lymph Node Dissection in Radical Resection of Gastric Cancer: A Systematic Review and Meta-Analysis

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Abstract

Objective: In this meta-analysis, we investigated the safety and efficacy of carbon nanoparticle (CNP) trace-guided lymph node (LN) dissection during radical gastrectomy. **Methods:** Literature on CNP tracing compared with non-CNP tracing in radical gastric cancer (GC) surgery was searched from PubMed, EMBASE (Ovid platform), Web of Science, and the Cochrane Library from the establishment of the library until October 2022. This meta-analysis was performed according to the preferred reporting items for systematic reviews and meta-analysis guidelines. Available data regarding the number of LNs dissected, number of metastatic LNs dissected, other surgical outcomes, and postoperative complications were analyzed in a pooled manner. Stata software (version 12.0) was used for the present meta-analysis. **Results:** This analysis included 7 studies with a total of 1827 GC patients (551 and 1276 in the CNP and non-CNP groups, respectively). The results of the meta-analysis showed that the CNP group had more intraoperative LNs detected [weighted mean difference (WMD) = 6.67, 95% confidence interval (CI): 3.71–9.62], more LN metastases (WMD = 1.60, 95% CI: 0.09-3.12), and less intraoperative bleeding (WMD = 11.33, 95% CI: 6.30-16.37) than the non-CNP group, all with statistically significant differences ($P < .05$). For postoperative complications (odds ratio [OR] = 0.88, 95% CI: 0.52-1.48) and operative time (WMD = −11.60, 95% CI: −40.53-17.34), there was no statistically significant difference between the 2 groups ($P > 0.05$). **Conclusions:** CNP was a significant tracer for the LNs of GC. It increased the number of LNs harvested while reducing intraoperative blood loss, without increasing the operative time or postoperative complications. CNP tracer-guided lymphadenectomy is considered safe and effective for gastrectomy.

Keywords

gastric cancer, carbon nanoparticles, gastrectomy, lymph node, meta-analysis

Abbreviations

CIs, confidence intervals; CNPs, carbon nanoparticles; GC, gastric cancer; LNs, lymph nodes; NMS, Newcastle–Ottawa Quality Assessment Scale; ORs, odds ratios; RCTs, randomized controlled trials; SD, standard deviation; WMDs, weighted mean differences

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Introduction

Gastric cancer (GC) is one of the most common malignancies in the world and the third leading cause of cancer-related deaths.[1] Currently, radical GC surgery is the only means to cure locally progressive GC; however, lymph node (LN) metastasis in most GC patients greatly affects survival and prognosis.[2–4] LN metastasis is an independent risk factor for tumor recurrence after radical GC surgery, and standardized and thorough LN

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dissection is directly related to the clinical prognosis of GC patients. Therefore, strengthening intraoperative LN tracing and dissection is the key direction of GC treatment.[5–8]

Carbon nanoparticles (CNPs) are the most widely used and well-studied vehicles for LN visualization and lymphoma-targeting chemotherapy in GC.[9,10] The CNPs can follow the flow of lymphatic vessels around the tumor, accumulate in the LNs, and stain black.[11] This improves the intraoperative clearance and postoperative detection of LNs, especially micro LNs. Several studies[12–16] have confirmed that nanocarbon helps improve the rate and number of LNs detected during radical surgery for GC. However, as the application of CNP in lymphadenectomy for patients with GC is still in the preliminary stages, its safety and efficacy remain unclear.

We systematically analyzed and evaluated the clinical utility and safety of CNP in patients GC by reviewing relevant domestic and international literature, and by meta-analysis, with the aim of evaluating the value of CNP as a tracer in LN localization.

Materials and Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.[17]

Study Objective

In this meta-analysis, the primary endpoint was the total number of retrieved LNs, and the secondary endpoints included the number of metastatic LNs, operative time, intraoperative blood loss, and postoperative complications (such as anastomotic leaks, incision infections, pneumonia, and intestinal obstructions). The total number of LNs retrieved and number of metastatic LNs were used to assess the effectiveness of CNP tracer-guided LN dissection, operative time, intraoperative bleeding; postoperative complications and were used to assess its safety.

Search Strategy and Literature Inclusion Criteria

To identify all publications relevant to the safety and efficacy of CNP-labeled LN dissection in the radical resection of GC, we performed a comprehensive literature search using PubMed, EMBASE (Ovid platform), Web of Science, and Cochrane Library, from the inception of the library to October 16, 2022. The search terms were the following: "neoplasm, stomach" or "stomach neoplasm" or "neoplasms, stomach" or "gastric neoplasms" or "gastric neoplasm" or "neoplasm, gastric" or "neoplasms, gastric" or "cancer of stomach" or "stomach cancers" or "gastric cancer" "cancer, gastric" or "cancers, gastric" or "gastric cancers" or "stomach cancer" or "cancer, stomach" or "cancers, stomach" or "cancer of stomach" or "gastric cancer, familial diffuse" and "carbon nanoparticles" or "carbon nanotracers" or "CH-40" or "nano-carbon". The references of the included studies and related systematic reviews were tracked. Our research was limited to English language articles and not to time periods.

Eligible studies for this meta-analysis met the following criteria: patients were confirmed to have GC by pathological or histological examination; patients with and without CNP tracer-guided radical gastrectomy; articles with the most complete data for studies with duplicated data; retrospective and prospective research, as well as randomized controlled trials (RCTs); the full publication was written in English. The exclusion criteria were review articles, case reports, abstracts, editorials, letters, and meta-analyses. We also excluded articles without direct comparisons, those without sufficient data for analysis (even after contacting the study authors), and duplicate publications.

Data Extraction

Two reviewers (ZCL and WJH) independently extracted relevant data from the eligible studies using a per-design data form. Disagreements were resolved by discussion. Data retrieved from each publication included the basic characteristics of each study, such as the first author, year of publication, country, number of patients in the CNP and non-CNP groups, operative method, number of retrieved LNs, number of metastatic LNs, operative time, intraoperative blood loss, and postoperative complications. Unless the standard deviation (SD) could be obtained from reading the publication, we recalculated the SD from published data using Cochrane's official recommended "data conversion tool". This tool is an Excel conversion template created by Amy Drahota and Elaine Bellor based on the formulas provided in the Cochrane Handbook.[18]

Quality Assessment

Quality assessment of each eligible study was performed by the same reviewers (ZCL and WJH) who extracted the data. They independently read and scored each publication according to the Newcastle–Ottawa Quality Assessment Scale (NOS).[19] This method assesses 3 parameters of quality: selection (0-4 points), comparability (0-2 points), and outcome assessment (0-3 points), with total scores ranging from 0 to 9. A study with a total score greater than 7 was considered high quality in the present meta-analysis.

Statistical Analysis

Odds ratios (ORs) and weighted mean differences (WMDs) with their corresponding 95% confidence intervals (CIs) were used to analyze dichotomous and continuous variables. Heterogeneity was tested using the Q statistic and the I^2 test. If the P value was more than 0.1 or I^2 was less than 50%, then all included studies lacked heterogeneity; thus, the Mantel–Haenszel method (fixed effect model) was used to merge the studies. Otherwise, a random effects model was adopted. For the source of heterogeneity, a sensitivity analysis

of each study and subgroup analysis were used for secondary analysis. Egger's or Begg's tests were used to evaluate publication bias. Subgroup analyses were performed for different countries, sample sizes, operation methods, and study designs. Statistical analyses were performed using STATA version 12.0 (StataCorp, College Station). Statistical significance for 2-sided tests was set at $P < .05$.

Results

Literature Search and Study Baseline Characteristics

A total of 115 abstracts were identified using the search strategy. After screening these abstracts, 7 studies[12–16,20,21] involving 1827 patients (551 in the CNP group and 1276 in the non-CNP group) with GC were eligible and included in the present meta-analysis. The process of selecting studies is illustrated in Figure 1. All the research was published between 1998 and 2022 and came from 2 different nations (Italy and China). The sample sizes ranged from 26 to 1199 patients. Patient characteristics and baseline data are presented in Table 1. The mean NOS score of all included studies was 7.6, indicating high methodological quality of the included studies.

Characteristics of CNP Injection

The characteristics of CNP injections are shown in Table 2. Most studies have used endoscopy for submucosal injections, which were performed during or a few days before surgery. No CNP-related complications were reported in any of the studies.

Number of LNs Detected

The primary outcome of this study was the assessment of the CNP tracer-guided number of retrieved LNs after radical gastrectomy. The number of intraoperative LNs detected was addressed in all 7 included studies. The results of the heterogeneity analysis showed that $P < .05$ and $I^2 = 96.4\%$, indicating heterogeneity among studies; therefore, the random effects model was used for analysis. The combined results showed a statistically significant difference in the number of LNs detected in the CNP group compared with the non-CNP group [WMD = 6.67, 95% CI = (3.71-9.62), $P < .01$], suggesting that CNP tracer-guidance had a positive effect on increasing the number of retrieved LNs. The forest plot is shown in Figure 2.

Number of Metastatic LNs Detected

Three of the included studies reported the number of LN metastases. The results of the heterogeneity analysis showed that $P = .65$ and $I^2 = 0.0\%$, indicating mild heterogeneity among the studies; thus, a fixed effects model was used for the combined analysis. The results showed that the number of detected LN metastases was higher in the CNP group compared with the non-nanocarbon group, and the difference was statistically significant [WMD = 1.60, 95% CI = (0.09-3.12), $P = .038$] (Figure 3).

Operative Time

Three studies reported the operative time. Meta-analysis showed no difference in operative time between the 2 groups (WMD = −11.60, 95% CI: −40.53-17.34, $P = .432$) with moderate heterogeneity ($P < .001$, $I^2 = 89.2\%$), as shown in Figure 4.

Intraoperative Blood Loss

Three studies reported intraoperative blood loss, all of which showed a statistically significant reduction in the CNP group compared with the non-CNP group. The meta-analysis showed a mean reduction in intraoperative bleeding of 11.33 mL in patients in the CNP group compared with the non-CNP group (WMD = 11.33, 95% CI: 6.30-16.37, $P < .01$) with low heterogeneity ($P = .806$, $I^2 = 0.0\%$) as shown in Figure 5.

Postoperative Complications

Postoperative complication rates were reported in 5 studies. The results of the heterogeneity analysis showed that $P > .05$ and $I^2 = 0.0\%$, indicating that the heterogeneity between studies was not statistically significant; therefore, the fixed effects model was used for the combined analysis. The results of the combined analysis showed that the incidence of postoperative complications in the CNP and non-CNP groups was not statistically significant [OR = 0.88, 95% CI: (0.52-1.48), $P = .623$; $P > .05$]. (Figure 6)

Sensitivity Analysis and Publication Bias

Sensitivity analysis were performed by sequentially omitting individual cohort analyses to assess the reliability and stability of our results. When we excluded any studies, the pooled WMDs and their corresponding 95% CIs were similar. Hence, our findings are relatively consistent and reliable (Figure 7). Egger's and Begg's tests were used to analyze the publication bias in our meta-analysis. There was no evidence of publication bias in the number of retrieved LNs (Egger test, $P = 0.721$; Begg test, $P = 0.902$) (Figure 8).

Subgroup Analysis

The results of subgroup analysis (based on sample size, country, operation method, and study design) are presented in Table 3. Subgroup analysis based on "country" suggested that CNP tracer-guided lymphadenectomy was significantly associated with an increasing number of retrieved LNs in China (WMD = 5.73, 95% CI: 3.39-8.07, $P < .01$), with significant heterogeneity ($I^2 = 88.5\%$, $P < .01$), and Italy (WMD = 9.80, 95% CI: 9.13-10.47, $P < .01$). In terms of "operation method," CNP

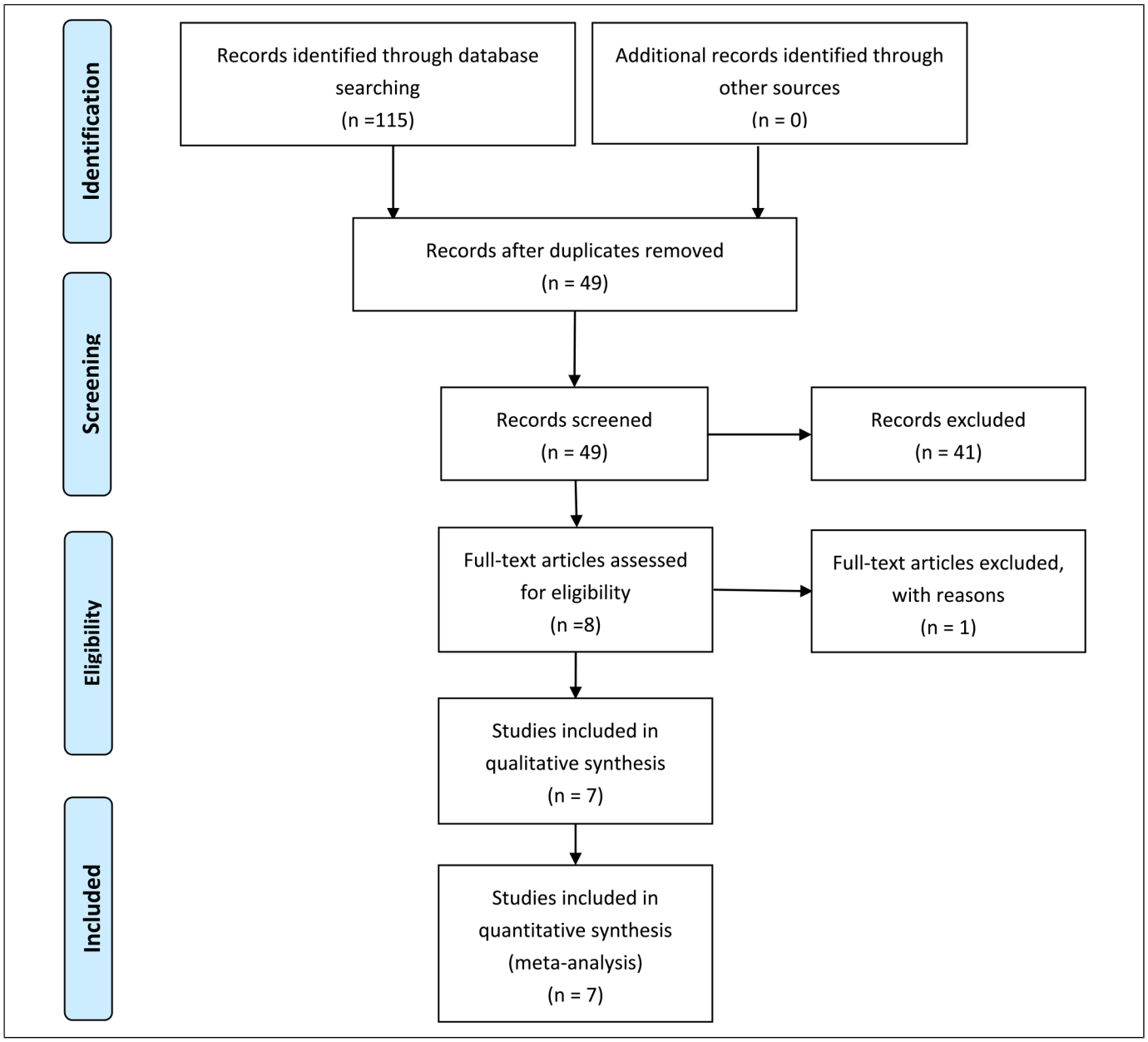

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram of the meta-analysis.

tracer-guided had a positive effect on increasing the number of retrieved LNs in all kinds of operations (open gastrectomy: WMD = 9.80, 95% CI: 9.13-10.47, $P < .01$; laparoscopic surgery: WMD = 3.92, 95% CI: 3.29-4.54, $P < .01$; open or robot laparoscopic: WMD = 7.90, 95% CI: 4.42-11.39, $P<.05$). Regardless of whether the sample size was >60 (WMD = 4.31, 95% CI: 1.95-6.66, $P<.01$) or ≤60 (WMD = 9.84, 95% CI: 9.18-10.50, $P < .01$), CNP tracer-guidance showed a positive effect on increasing the number of LNs compared to non-CNP. We found that CNP tracer guidance could increase the number of LN harvested in the retrospective study (WMD = 5.71, 95% CI: 4.80-6.61, $P < .01$) with no significant heterogeneity ($I^2 = 0.0\%$, $P = .881$) and the prospective study (WMD = 7.11, 95% CI: 6.59-7.63, $P < .01$) with significant heterogeneity ($I^2 = 97.4\%$, $P < .01$).

Discussion and Conclusions

Recently, with the development of nanotechnology in medicine, nanocarbons have been used in clinical practice. It is not only convenient to stain but also has high lymphatic tropism. Thus, it has become an ideal lymphatic tracer in current clinical practice.[22–24] CNP injection is critical for effective LN imaging in radical GC surgery.[9] Most studies[12,14–16,20] used endoscopy for submucosal injections, which were performed around the primary tumor within 3 days before the procedure. This

Table 1. Characteristics of Included Studies.

Study	Country	Study design	Intervention: Comparison (n)	Operation method	Study interval	NOS	Lymph nodes (LNs) detected ($\bar{\chi}$±S) (n)		LN metastasis ($\bar{\chi}$±S) (n)		Operative time (min)		Intraoperative blood loss (ml)		Complications (n)	
							CNP	nCNP	CNP	nCNP	CNP	nCNP	CNP	nCNP	CNP	nCNP
Catarci et al 1998[12]	Italy	P	21:24	Open gastrectomy	November 1994 to December 1996	7	35.3±1.24	25.5±1.02	NR	NR	NR	NR	NR	NR	None	none
Li et al 2016[13]	China	P	15:15	Open gastrectomy	December 2013 to June 2014	8	38.33±12.86	28.27±12.86	NR	NR	214.7 ± 42.9	212.9 ± 55.7	110.0 ± 63.2	98.7 ± 66.2	5	3
Wang et al 2016[20]	China	R	35:15	NR	October 2014 to August 2015	8	45.7 ± 14.5	39.2 ± 11.7	7.3 ±8.5	6.1 ±7.6	NR	NR	NR	NR	NR	NR
Mu et al 2020[21]	China	P	30:30	Open gastrectomy	January 2015 to January 2016	7	34.1 ± 9.8	22.6 ± 3.7	20.9 ± 17.5	23.6 ± 19.7	252.9 + 35.4	250.3 + 29.9	266.7 ± 115.5	260.0 ± 116.3	1	2
Feng et al 2021[14]	China	R	214:985	Laparoscopic	January 2014 to December 2019	8	27.9 ± 6.5	22.2 ± 4.0	NR	NR	185.9 ± 27.8	218.7 ± 69.2	NR	NR	8	38
Yang et al 2021[15]	China	P	80:80	Open or laparoscopic	January 2020 to January 2021	7	39.96±13.06	32.06±9.13	4.80 ±5.97	3.05 ±4.09	NR	NR	NR	NR	7	9
Zhao et al 2022[16]	China	P	LTG:99:77; LSG:81:50	Laparoscopic	June 2018 to February 2021	8	LTG:34.95 ±4.81; LSG:32.65 ±3.82	LTG:31.90 ±4.47; LSG:30.88 ±2.69	NR	NR	NR	NR	LTG:71.13 ± 21.33;LSG:90.70 ± 31.77	LTG:61.53 ± 20.38;LSG:75.69 ± 20.18	LTG:3; LSG:0	LTG:2; LSG:2

Abbreviations: CNPs, carbon nanoparticles; LTG, laparoscopic total gastrectomy; LSG, laparoscopic subtotal gastrectomy; nCNPs, non-carbon nanoparticles; NR, not reported; NOS, Newcastle–Ottawa Quality Assessment Scale; P, prospective; R, retrospective study.

Table 2. Characteristics of CNP Injection.

Study	The method of CNP injection	The time of CNP injection	CNP injection site	CNP injection concentration	CNP injection dose	Complications related to CNP
Catarci et al 1998[12]	Endoscopy	24 to 72 h before surgery	submucosal injections (each cardinal point adjacent to the lesion)	50 mg/mL	0.2 mL in each cardinal point adjacent to the lesion, 0.8 mL in total	None
Li et al 2016[13]	Surgery	During surgery	5 points around the tumor on average (subserosa of the stomach)	50 mg/mL	0.2 mL at each cardinal point adjacent to the lesion, 1 mL in total	None
Wang et al 2016[20]	Endoscopy	Before surgery	4 points surrounding the tumor from the outside of the stomach (subserous and muscular)	NR	1 mL in total	None
Mu et al 2020[21]	Surgery	During surgery	No. 12b LN	50 mg/mL	0.2 mL	None
Feng et al 2021[14]	Endoscopy	24 to 48 h before surgery	4 points on the anal side, oral side, left side and right side of the gastric cancer lesion about 0.5 cm–1.0 cm from the boundary (submucosal)	50 mg/mL	0.2 mL at each cardinal point	None
Yang et al 2021[15]	Endoscopy	24 h before surgery	4 points of 0.5–1 cm from the edge of the tumor (the submucosa on the cardia side, the pylorus side, the large curved side, and the small curved side)	50 mg/mL	0.25 mL at each point	None
Zhao et al 2022[16]	Endoscopy	1 to 2 days before surgery	2–4 points were selected 0.5–1.0 cm from the tumor edge. submucosal surface	NR	2.0 mL in total	None

Abbreviations: CNP, carbon nanoparticle; NR, not reported; Complications related to CNP, hemorrhage perforation.

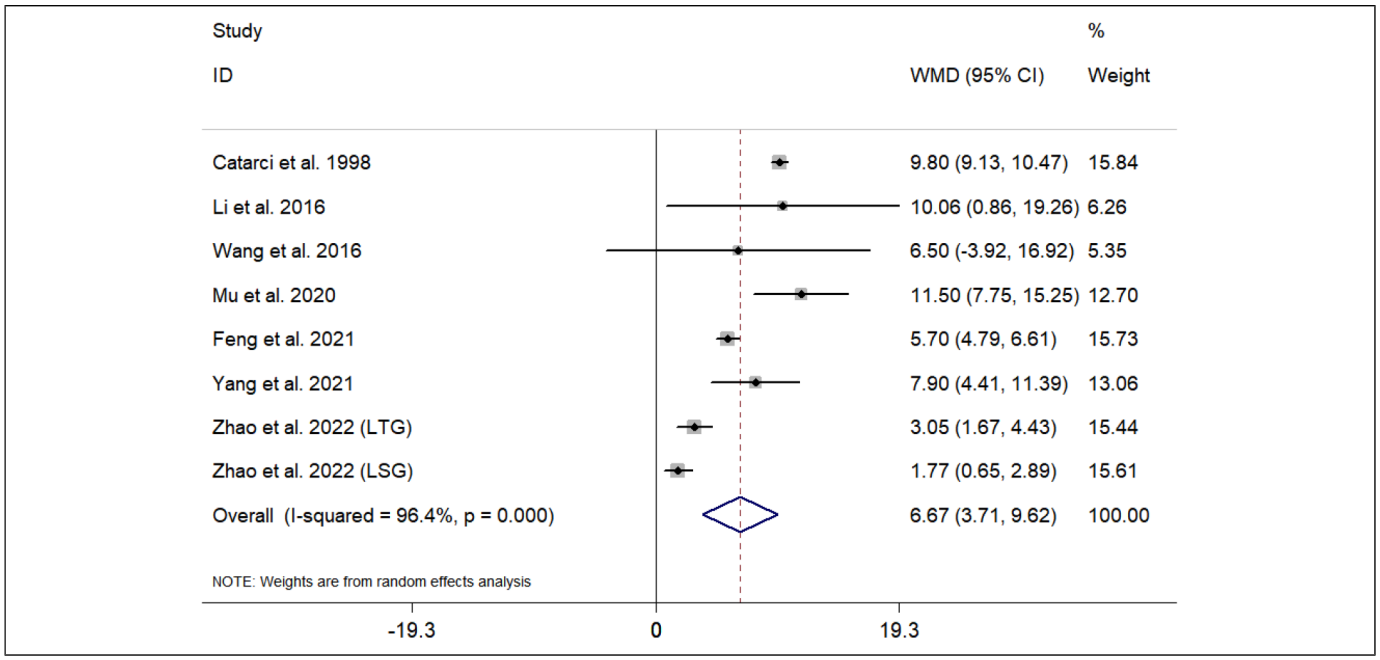

Figure 2. Forest plot of weighted mean difference (WMD) for the number of intraoperative lymph nodes (LNs) detected.

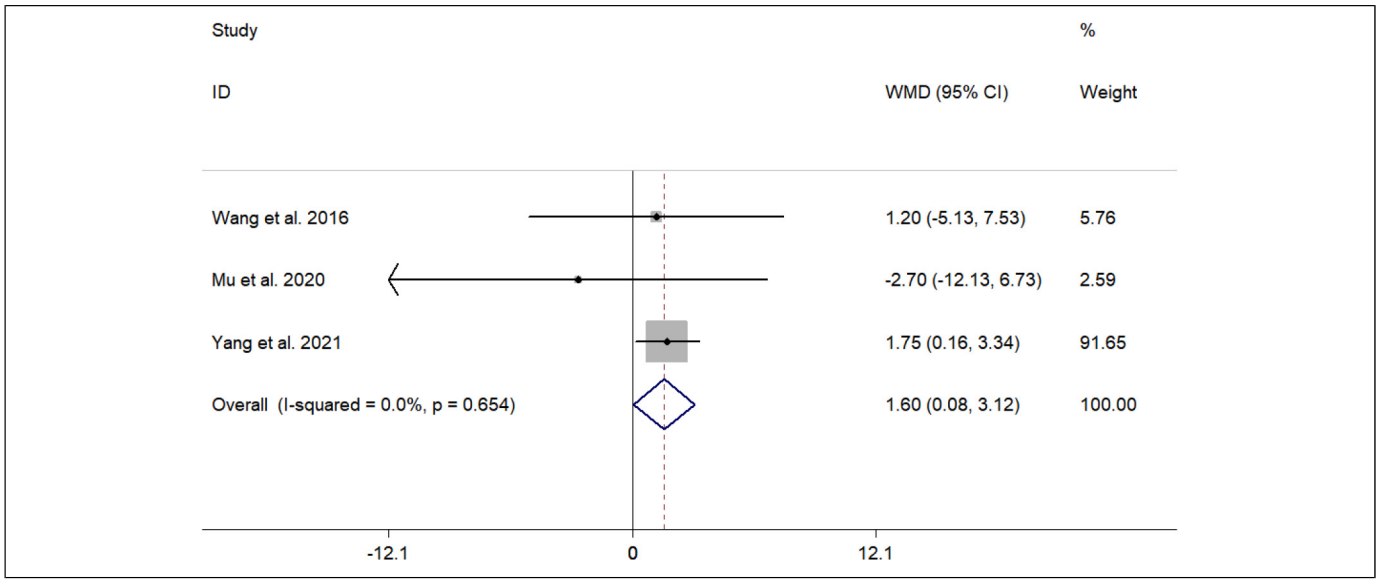

Figure 3. Forest plot of weighted mean difference (WMD) for the number of metastatic lymph nodes (LNs).

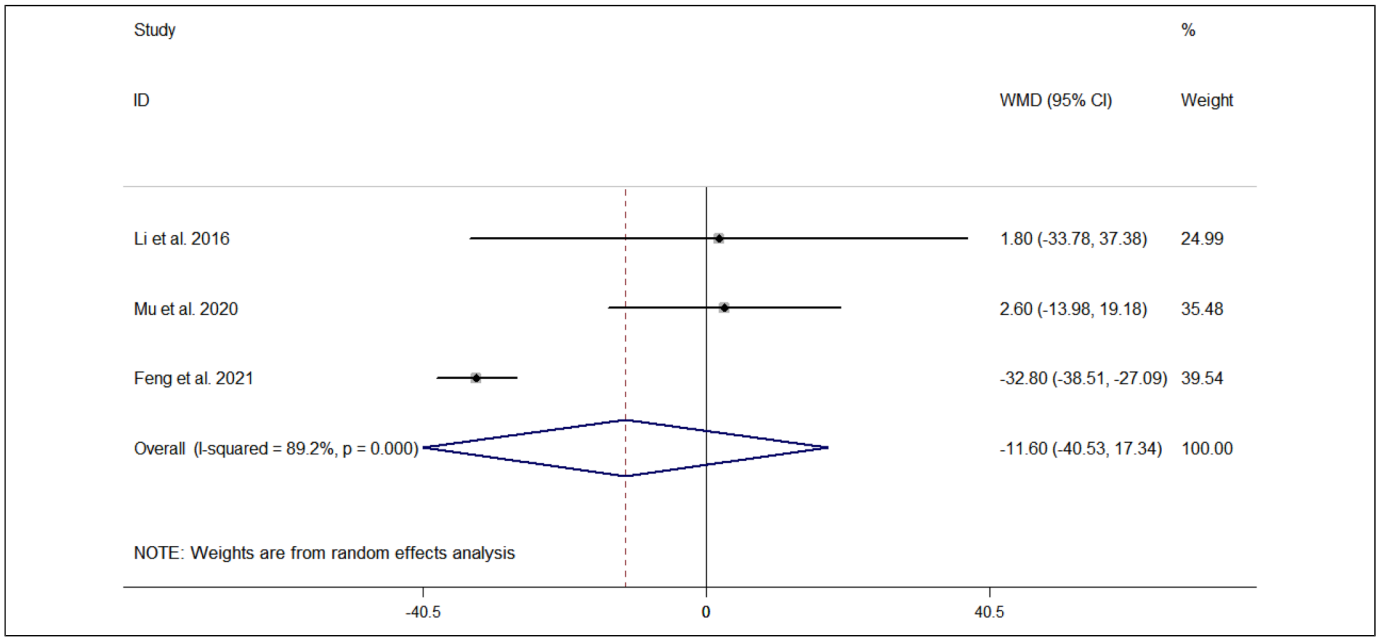

Figure 4. Forest plot of weighted mean difference (WMD) for operative time.

definitely increases patient discomfort, medical costs, and physician workload compared to intraoperative CNP injection studies.[13,21] However, for early stage tumors, it is difficult to identify the tumor location intraoperatively and subsequently perform CNP injection because the tumor does not break through the plasma layer. Therefore, endoscopic injection is undoubtedly a better choice. Regardless of the method of injection, the vast majority of studies have confirmed that CNP is a significant tracer for the LNs of GC and increases the number of LNs harvested while reducing intraoperative blood loss, without increasing the operative time or postoperative complications. CNP tracer-guided lymphadenectomy is considered safe and effective for gastrectomy. The above findings are consistent with the results of our meta-analysis. Additionally, the subgroup analyses based on country, sample source, operation method, and study design were consistent with the above results.

The main component of CNP is small molecular-weight CNPs with a diameter of 150 nm.[25] Since the basement membrane of capillary lymphatic vessels is incompletely developed, the gap between endothelial cells is 100 to 150 nm, while the gap between capillary endothelial cells is approximately 30 to 50 nm, and the particle size of nanocarbon is in the middle of both of them. Therefore, the

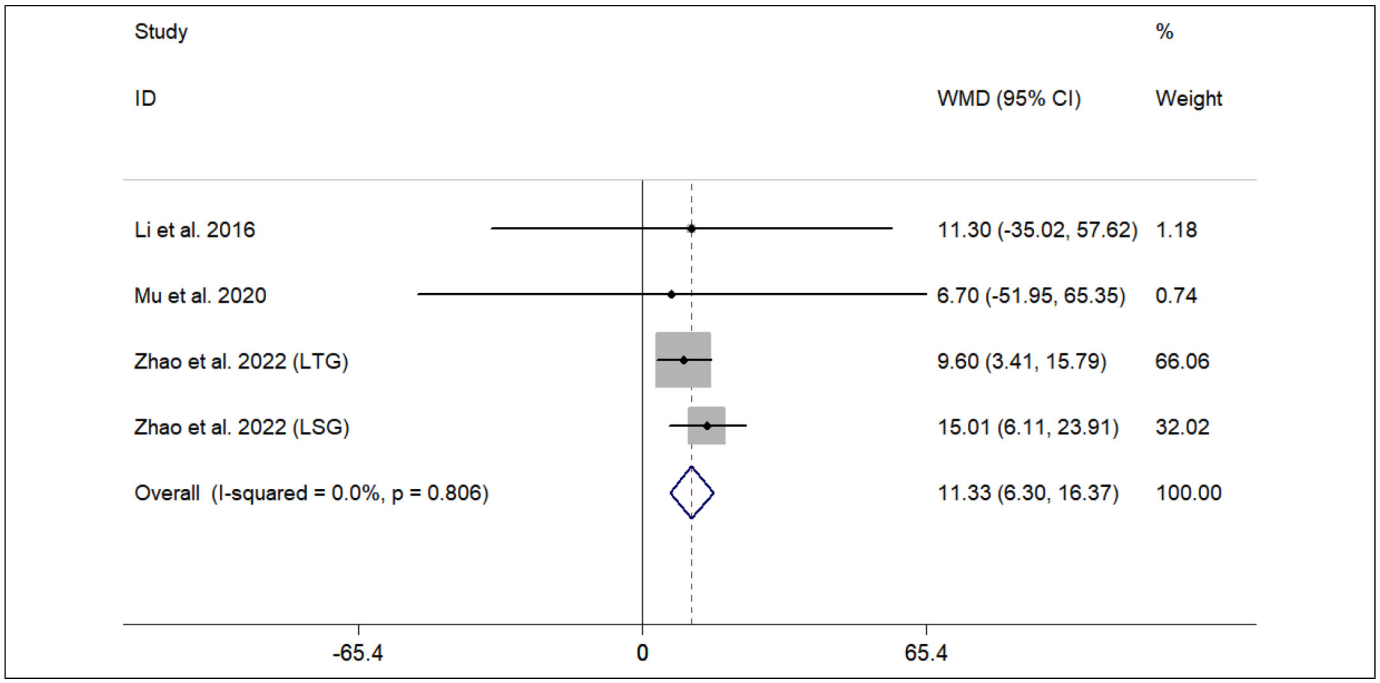

Figure 5. Forest plot of weighted mean difference (WMD) for intraoperative blood loss.

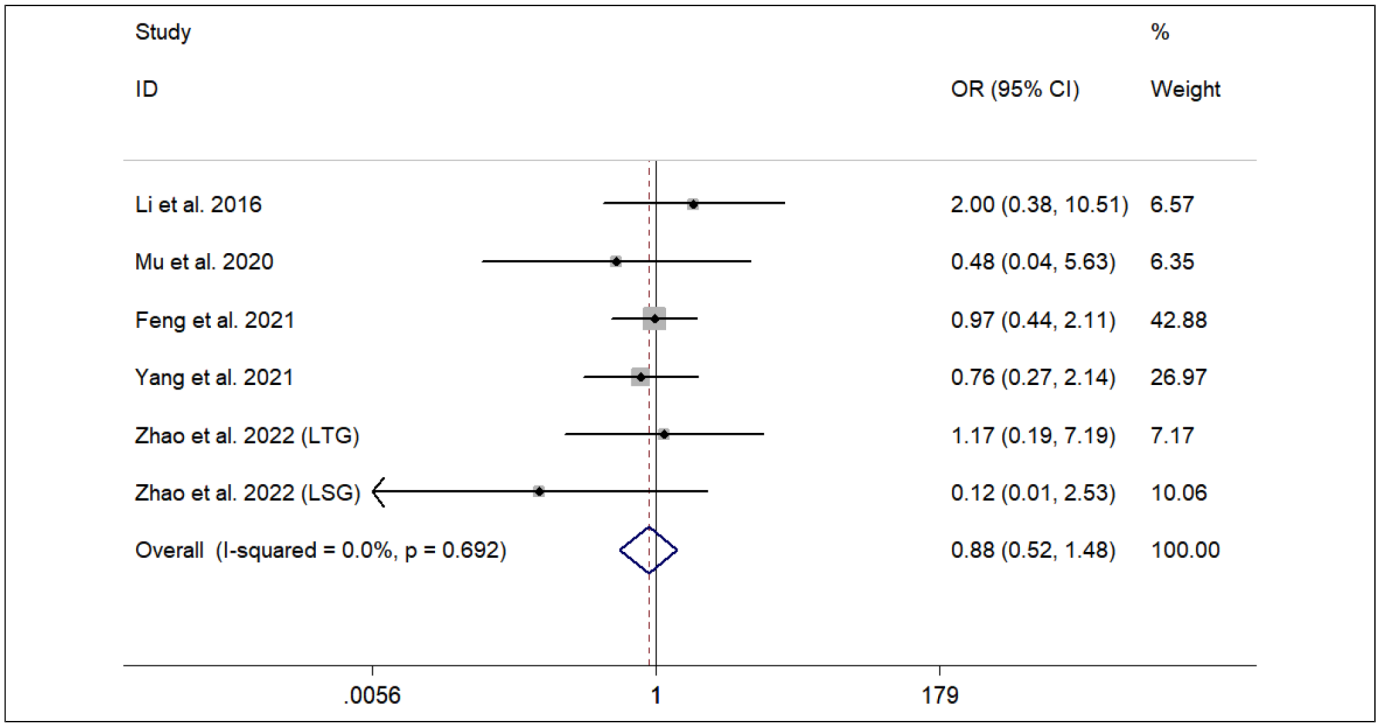

Figure 6. Forest plot of odds ratio (OR) for postoperative complications.

nanocarbon particles injected into the sub-plasma membrane of gastric tumors quickly drain into the surrounding lymphatic vessels and LNs and are phagocytosed by macrophages, resulting in a large number of charcoal particles remaining in the LNs and black staining of the LNs, which are easy to intraoperatively identify.[26] Thus, the CNP group was able to obtain higher numbers of LNs, which is consistent with the results [WMD = 6.67, 95% CI: (3.71-9.62), $P < .01$] in our meta-analysis. Previous studies[27,28,29] showed that a larger number of LN dissections was associated with better long-

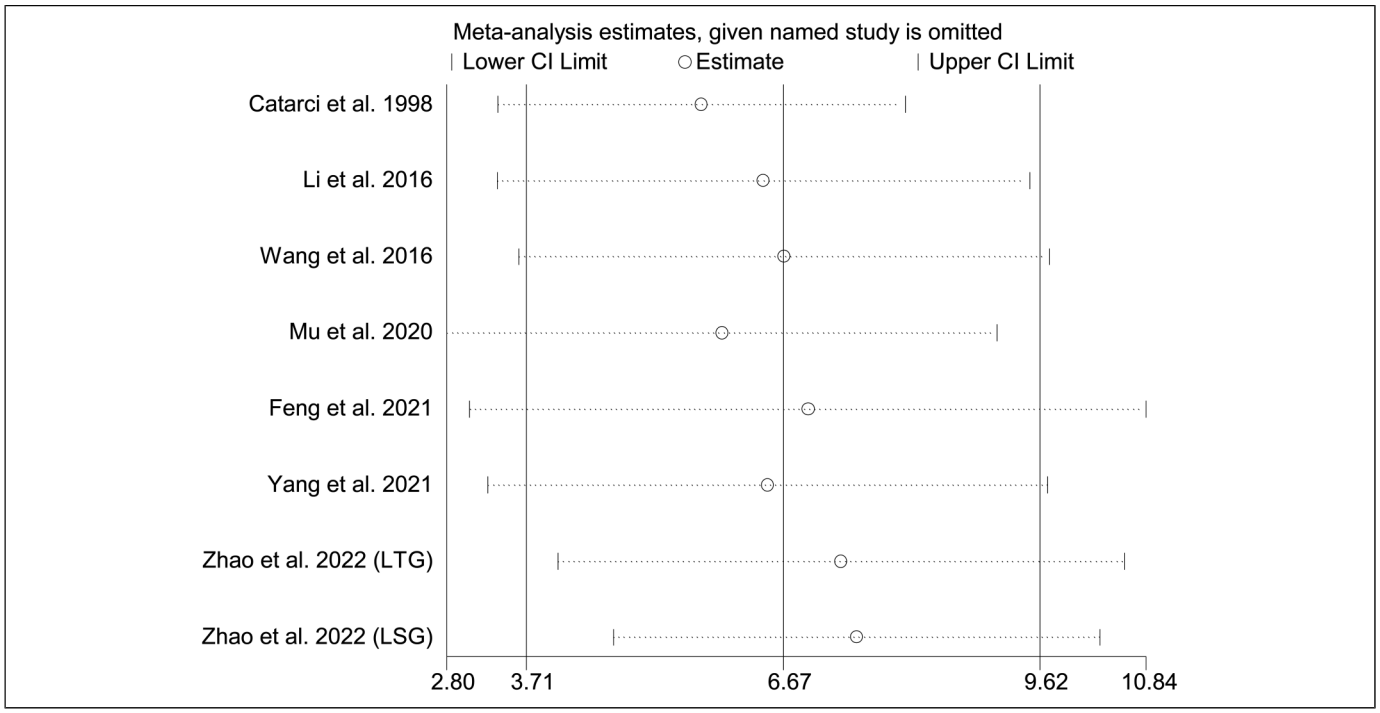

Figure 7. Sensitivity analysis of the intraoperative use of carbon nanoparticles (CNPs) and the number of lymph nodes (LNs) dissected.

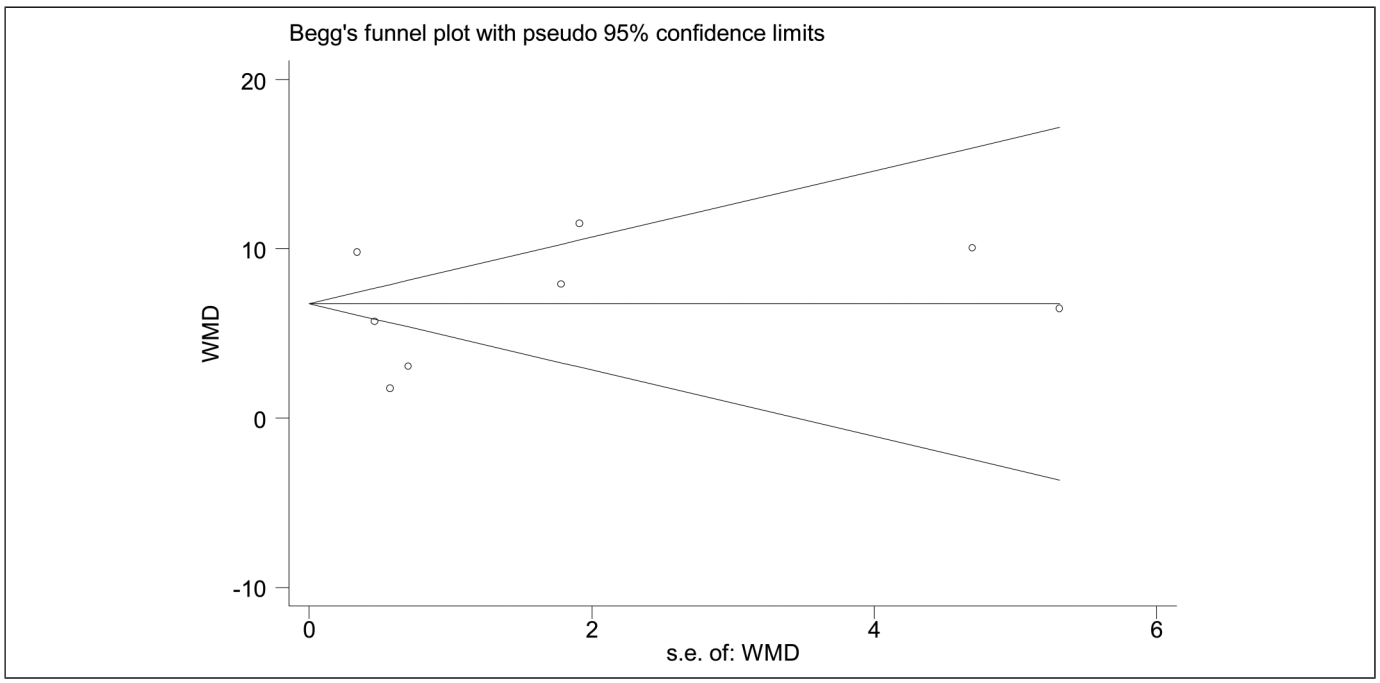

Figure 8. Funnel plots evaluating the relationship between the intraoperative use of carbon nanoparticles (CNPs) and the number of lymph nodes (LNs) dissected.

term survival of patients with GC. Therefore, CNP-trace-guided radical gastrectomy may have a better prognosis. Certainly, this needs to be further confirmed by high-quality evidence of long-term survival.

In this meta-analysis, we showed that the number of harvested LN metastases was higher in the CNP group than that in the non-CNP group [WMD = 1.60, 95% CI: (0.09-3.12), P = .038]. The reasons for this may be attributed to the

Table 3. Subgroup Analysis of WMD for the Number of Lymph Nodes (LNs) Dissected.

Items		No. of study	WMD	95% CI	*P* value
Country	China	6	5.73	3.39-8.07	<.001
	Italy	1	9.80	9.13-10.47	
Sample size	≤60	4	9.84	9.18-10.50	
	>60	3	4.31	1.95-6.66	
Operation method	Open gastrectomy	2	9.80	9.13-10.47	
	Laparoscopic	2	3.92	3.29-4.54	
	Open or laparoscopic	1	7.90	4.42-11.39	
Study design	Retrospective study	2	5.71	4.80-6.61	
	Prospective	5	7.11	6.59-7.63	

Abbreviations: No., number; WMD, weighted mean difference; 95% CI, 95% confidence interval.

following 2 points: (1) since the LN count is used as a quality measure for GC surgery,[30] the surgeon should obtain as many LNs as possible during the operation, and an increased total number of harvested LNs means a greater possibility of obtaining a higher number of metastatic LNs and (2) the metastatic LNs may change their original morphology,[31] making it easier for the CNPs to remain in the LNs, causing them to stain black. However, this needs to be confirmed through more rigorous experiments in the future.

In terms of intraoperative blood loss, our analysis showed a significant reduction in blood loss in the CNP group compared with that in the non-CNP group. This is most likely due to the fact that black staining of the LNs makes it easier for the surgeon to identify the vascular planes and to distinguish the vascular vessels from the surrounding lymphatic structures, thus reducing the risk of vascular injury.[16] Intraoperative blood loss, operative time, and postoperative complications are important factors in assessing the safety of surgery. The results of our meta-analysis did not show any difference between the 2 groups in terms of operative time and postoperative complications, probably because this is closely related to individual surgical proficiency and experience. This also indirectly proves the safety of nanocarbon.

Based on the available evidence, our study showed that the use of CNP during radical gastrectomy can extract more LNs, minimize intraoperative blood loss, and have short-term effectiveness similar to that of traditional radical gastrectomy. Through a comprehensive review of previous studies, we also found that in addition to being a tracer, nanocarbon may also be a mediator of targeted therapy for GC, which can be used to target residual and micro-metastases for targeted chemotherapy.[32] In summary, CNP-labeled may serve as a safe and effective method for LN tracing. It should be vigorously promoted in clinical practice, and different injection timings should be chosen according to different tumor stages. Larger prospective and standardized investigations should be conducted in the future to confirm our results.

This meta-analysis has some limitations. First, owing to the inherent weaknesses of retrospective studies, the homogeneity test for continuous variables revealed moderate heterogeneity. Second, because most of the included studies were conducted in Asia, the data from this meta-analysis are not applicable worldwide. Third, owing to the relatively small number of included studies and sample size, we were unable to pool the results based on tumor classification. Therefore, larger, multicenter, high-quality studies are urgently needed to confirm our findings. These limitations must be considered when evaluating the findings of our study.

Acknowledgments

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Author's Contribution

ZCL and DMX made substantial contributions to the conception and design for this work. ZCL and WJH collected all the data. ZCL and WJH were the major contributors in writing the manuscript. DMX and WQ performed the critical revision for this manuscript. All authors contributed to the article and approved the submitted version.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This article did not require an ethical board approval because the study data were downloaded from the open database.

Data Availability

Some or all data, models, or code generated or used during the study are available from the corresponding author upon reasonable request.

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