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ORIGINAL RESEARCH

# Application of carbon nanoparticles in lymph node dissection and parathyroid protection during thyroid cancer surgeries: a systematic review and meta-analysis

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Lun Wang
Dong Yang
Jun-Yuan Lv
Dan Yu
Shi-Jie Xin

Department of Vascular and Thyroid Surgery, The First Affiliated Hospital, China Medical University, Shenyang, People's Republic of China

**Purpose:** To investigate whether carbon nanoparticles (CNs) are helpful in identifying lymph nodes and metastatic lymph nodes and in parathyroid protection during thyroid cancer surgery.

**Methods:** English and Chinese literature in PubMed, Cochrane Database of Systematic Reviews, EMBASE, ClinicalTrials.gov, China Biology Medicine Database, China National Knowledge Infrastructure, China Master's and Doctoral Theses Full-Text Database, Wanfang database, and Cqvip database were searched (till March 22, 2016). Randomized controlled trials (RCTs) that compared the use of CNs with a blank control in patients undergoing thyroid cancer surgery were included. Quality assessment and data extraction were performed, and a meta-analysis was conducted using RevMan 5.1 software. The primary outcomes were the number of retrieved central lymph nodes and metastatic lymph nodes, and the rate of accidental parathyroid removal.

**Results:** We obtained 149 relevant studies, and only 47 RCTs with 4,605 patients (CN group: n=2,197; blank control group: n=2,408) met the inclusion criteria. Compared with the control group, the CN group was associated with more retrieved lymph nodes/patient (weighted mean difference [WMD]: 3.39, 95% confidence interval [CI]: 2.73–4.05), more retrieved metastatic lymph nodes (WMD: 0.98, 95% CI: 0.61–1.35), lower rate of accidental parathyroid removal, and lower rates of hypoparathyroidism and hypocalcemia. However, the total metastatic rate of the retrieved lymph nodes did not differ between the groups (odds ratio: 1.13, 95% CI: 0.87–1.47, $P$=0.35).

**Conclusion:** CNs can improve the extent of neck dissection and protect the parathyroid glands during thyroid cancer surgery. And the number of identified metastatic lymph nodes can be simultaneously increased.

**Keywords:** carbon nanoparticles, lymph node tracer, thyroid cancer, parathyroid, meta-analysis

## Introduction

Thyroid cancer is a common malignant tumor, and its occurrence has been increasing appreciably over the last few decades.[1,2] Papillary thyroid carcinoma, the most common pathological type of thyroid carcinoma, is associated with an excellent prognosis if surgery is performed successfully.[3,4] However, complications and tumor metastasis often occur postoperatively. A multicenter revisit study of 25,634 patients with a history of ambulatory surgery revealed that the incidence of hypocalcemia was as high as 20.8%.[5] Moreover, the rate of postoperative cervical lymph node metastasis has been reported to be as high as 20%–90%.[6,7] Therefore, an effective method is urgently

Correspondence: Shi-Jie Xin
Department of Vascular and Thyroid Surgery, The First Affiliated Hospital, China Medical University, No 155 of Nanjing Street, Shenyang 110001, People's Republic of China
Tel +86 24 8328 3288
Fax +86 24 2270 3576
Email sjxin@cmu.edu.cn


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required to help identify and remove additional lymph nodes and decrease the risk of parathyroid injury.

Nanobiotechnology, a new field defined as biomedical applications of nanosized systems, which involves nanostructure and nanomaterials, has emerged as a key player among various disciplines of biomedical science. Nanomaterials, which measure 1–1,000 nm, have unique physical and chemical properties such as small-size effect, large surface area, high reactivity, and quantum effects. In addition, they have been certified as breaking a new ground in disease detection,[8,9] imaging,[10,11] diagnosis,[12,13] and treatment.[12,14–16] Carbon-based nanoparticles are an important part of nanomaterials; they include carbon nanotubes, fullerene, and graphene and its derivatives.[17] Due to their unique physical and chemical properties, carbon-based nanoparticles have broad applications in the biomedical field. Above all, structure or surface modifications of carbon-based nanoparticles result in different effects.

In recent years, with the development of nanotechnology, nanomaterials or nanosized products have been used in surgeries. Carbon nanoparticles (CNs) suspension (China Food and Drug Administration approval H20041829; Lai Mei Pharmaceutical Co, Chongqing, People's Republic of China), which comprises nanosized polymeric carbon granules with an average diameter of 150 nm (Figure 1),[18] ensures that these CNs pass through the lymphatic vessels (diameter: 120–500 nm) rather than blood capillaries (diameter: 20–50 nm) due to their molecular size. Hence, the lymph nodes and thyroid glands can be stained with CNs but not the parathyroid glands. Therefore, as revealed in Figure 2,[19] CNs have been used as lymph node tracers during thyroid surgeries in the People's Republic of China in recent years, but there is no report about their usage in other countries. Previous studies have demonstrated that CNs could help visualize the lymph nodes and preserve the parathyroid. In addition, a meta-analysis has also been published to support this viewpoint.[20] However, controversy still exists about the usefulness of CNs. Liu et al reported that CNs are not beneficial for parathyroid protection during thyroid cancer surgery and that the usage of CNs results in a significantly prolonged operation time.[18] Before 2014, all articles published on the usage of CNs in thyroid cancer surgeries were in Chinese, and there were only limited randomized controlled trials (RCTs) reported. Accordingly, a considerable amount of non-RCTs were included in the previous meta-analysis.[20] However, in recent years, more RCTs have been published. Hence, another meta-analysis is needed to determine whether CNs are helpful in thyroidectomy.

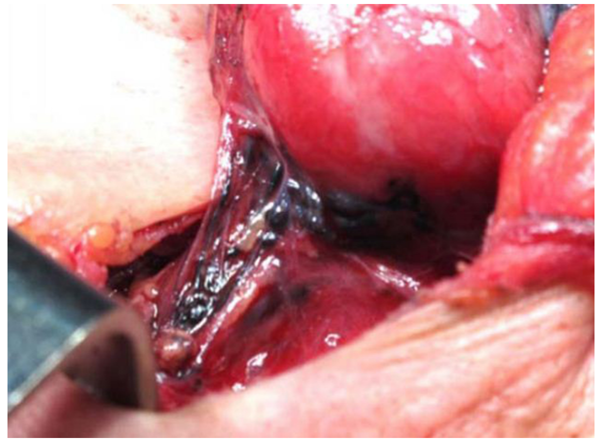


**Figure 2** Intraoperative view of the black-stained clusters of lymph nodes by CN injection.
**Notes:** Reproduced with permission of John Wiley and Sons, from Zhu Y, Chen X, Zhang H, et al. Carbon nanoparticle-guided central lymph node dissection in clinically node-negative patients with papillary thyroid carcinoma. *Head Neck*. 2016;38(6):840–845. © 2015 Wiley Periodicals, Inc.[19]
**Abbreviation:** CN, carbon nanoparticle.

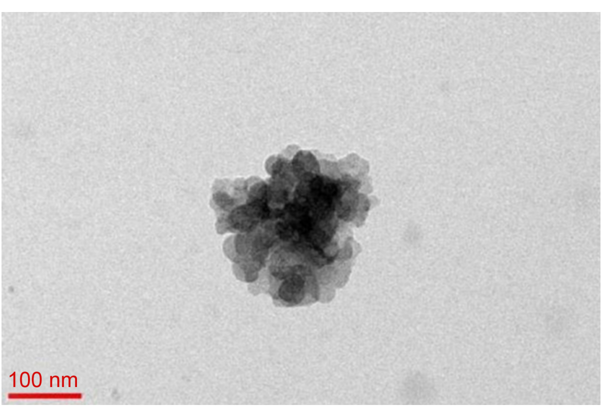



**Figure 1** Transmission electron microscopic image of CNs.
**Notes:** The main active component of CNs is nanosized polymeric carbon granules with an average diameter of 150 nm. Republished with permission of SAGE Publications, Inc., from Liu X, Chang S, Jiang X, Huang P, Yuan Z. Identifying parathyroid glands with carbon nanoparticle suspension does not help protect parathyroid function in thyroid surgery: a prospective, randomized control clinical study. *Surg Innov*. 2016;23(4):381–389. © The Author(s) 2016; permission conveyed through Copyright Clearance Center, Inc.[18]
**Abbreviation:** CN, carbon nanoparticle.

With this in mind, the present systematic review and meta-analysis was designed to confirm whether CNs are indeed helpful in thyroid cancer surgery, that is, whether CNs can really improve the extent of thyroidectomy and neck dissection and help identify metastatic lymph nodes while preserving the parathyroid glands, as compared with the performance of blank controls.

# Methods

## Search strategy

The following English and Chinese databases were searched systematically by 2 investigators independently (till March 22, 2016): PubMed, Cochrane Database of Systematic Reviews, EMBASE, ClinicalTrials.gov, China Biology Medicine Database, China National Knowledge Infrastructure, China Master's and Doctoral Theses Full-Text Database, WANFANG database, and Cqvip database. RCTs on initial thyroid cancer surgeries that compared the use of CNs with a blank control were included. Our search terms included (nano-carbon) or (carbon particle) or (carbon nanoparticle) or (carbon nanoparticles) or (lymph node tracer) or (lymphatic tracer) or (lymphography) and (thyroid or thyroidea). To resolve any disagreement between the 2 investigators, a third reviewer was invited to assess any discrepant items.

## Inclusion criteria

The studies selected were RCTs on thyroid cancer surgeries that included: 1) patients who underwent initial surgery and with a confirmed pathology diagnosis and 2) a control group not injected with anything before thyroidectomy and a CN group injected with CNs.

## Exclusion criteria

Non-independent clinical controlled trials, non-RCTs, studies with a patient number $<10$, or studies with incomplete data were excluded.

## Observation indexes

The primary outcomes were the number of retrieved central lymph nodes and metastatic lymph nodes per patient, and the rate of accidental parathyroid removal. Other outcomes extracted from the identified RCTs included the staining rate of lymph nodes, the number of metastatic lymph nodes in all retrieved lymph nodes, and the rate of postoperative transient or permanent hypoparathyroidism and hypocalcemia. All included articles reported at least 1 of the outcomes.

## Quality assessment

To evaluate the quality of these studies, the Jadad scoring system was applied in the RCTs. The scoring system included 3 items: descriptions of the dropouts and withdrawals (0 or 1 point), blinding (0–2 points), and randomization (0–2 points). The maximum score was 5 points. RCTs that scored 3–5 points were considered to be of high quality, whereas a score of 0–2 was considered to indicate low quality.

## Statistical analysis

RevMan version 5.1 software was used for the statistical analyses. We measured the heterogeneity of the studies using the $I^2$ and $\chi^2$ tests. Statistical heterogeneity of the studies was defined as an $I^2$ value $<50\%$ or $P$-value $<0.10$. The random-effects model was applied if heterogeneity existed among the studies; otherwise, the fixed-effects model was adopted for the analyses. Weighted mean differences (WMDs) with 95% confidence intervals (CIs) were used for the continuous outcome variables, whereas risk differences (RDs) and odds ratios (ORs) with 95% CIs were calculated for the dichotomous outcome variables. To investigate possible bias, funnel plots were created. For all analyses, statistical differences were considered to exist between the 2 groups when $P$-value was $<0.05$.

# Results and discussion

Considering the complicated anatomic structure and lymphatic drainage, the cervical lymph node metastasis rate is amazingly high after thyroid cancer surgery.[6,7] Especially, in the central region of the neck and other places such as the central neck compartment and deep surface of the recurrent laryngeal nerve, which cannot be easily dissected, postoperative cervical lymph node metastasis is common. As a result, reoperation and surgical trauma are common in these patients. According to a previous report,[21] while the incidence of permanent hypoparathyroidism is 3%–10% after the first surgery for thyroid disease, it is as high as 9%–35% after reoperation. Kurmann et al reported that the incidence of permanent recurrent laryngeal nerve palsy was significantly higher in patients undergoing reoperation on the ipsilateral lobe compared to patients undergoing initial operation (3.8% vs 1.1%; $P$=0.03).[22] In addition, parathyroid injury has been considered inevitable for a long time, mostly due to its unique anatomy. The appearance of the parathyroid is similar to that of the cervical lymph nodes, and the location of the gland is close to the backside of the thyroid gland and varies greatly; for example, the parathyroid may hide within the thyroid lobes, thymus, or carotid sheath. Xu and Gu reported that 6.9%–46% of parathyroid glands were damaged during thyroid surgery.[23] Such damage may cause permanent or transient hypocalcemia and hypoparathyroidism, and will consequently affect the quality of life of the patients. Therefore, some technical methods are urgently needed to help us better visualize the lymph nodes and metastatic lymph nodes, and distinguish the parathyroid glands and preserve them.

CNs, which have a mean diameter of 150 nm and a lymphatic tendency, had been used as lymph node tracers clinically in other cancer surgeries before. Upon injection, CNs are rapidly devoured by macrophages, resulting in the lymph nodes, but not the capillaries, initially becoming black-stained. Subsequently, the thyroid tissue stains black, as do the surrounding lymph nodes, whereas any tissues without lymph vessel connections remain unstained. Some previous studies have demonstrated that CNs are beneficial for visualizing the lymph nodes and for distinguishing and preserving the parathyroid glands. On the contrary, other studies found no advantage of CNs.[18,24] In addition, some indexes, such as postoperative hypocalcemia, are easily influenced by confounding factors such as the postoperative therapeutic selection, calcium supplements, and individual differences. To date, no large-scale meta-analysis has been performed to clarify these diverging results. Therefore, our analysis was designed to resolve the problems.

## Literature search and study description

According to the search strategy, 149 references were obtained, and 47 RCTs met the inclusion criteria.[18,19,23–67] The flowchart of the literature search is shown in Figure 3. A total of 4,605 patients were included in the analysis, including 2,197 patients in the CN group and 2,408 patients in the blank control group. All patients had confirmed thyroid cancer by postoperative pathologic diagnosis and had been divided into the CN and blank control groups randomly. All of the CNs used in these studies were the same product.

The characteristics of all 47 RCTs are presented in Table 1. The Jadad scale system was used to assess the quality of the included studies (Table 2). Most investigators preferred multipoint injections (2–4 points) prior to the thyroidectomy, with a total dose of approximately 0.3–0.8 mL. Besides, according to our experience and the studies analyzed herein, no adverse reactions to CNs have been reported.

## Intervention effects

### Number of retrieved lymph nodes and metastatic lymph nodes, and metastatic rate of retrieved lymph nodes in the CN and blank control groups

Compared with the blank control groups, the use of CNs resulted in an increased number of retrieved lymph nodes, approximately 3.39 per patient (WMD =3.39, 95% CI =2.73–4.05, $P<0.00001$; Figure 4A). The number of retrieved metastatic lymph nodes per patient in the CN group was significantly higher than in the blank control group (WMD =0.98, 95% CI =0.61–1.35, $P<0.00001$; Figure 4B). However, interestingly, the total metastatic rate of the lymph nodes, metastatic rate of the stained lymph nodes, and metastatic rate of the unstained lymph nodes were not significantly different between the CN and blank control groups

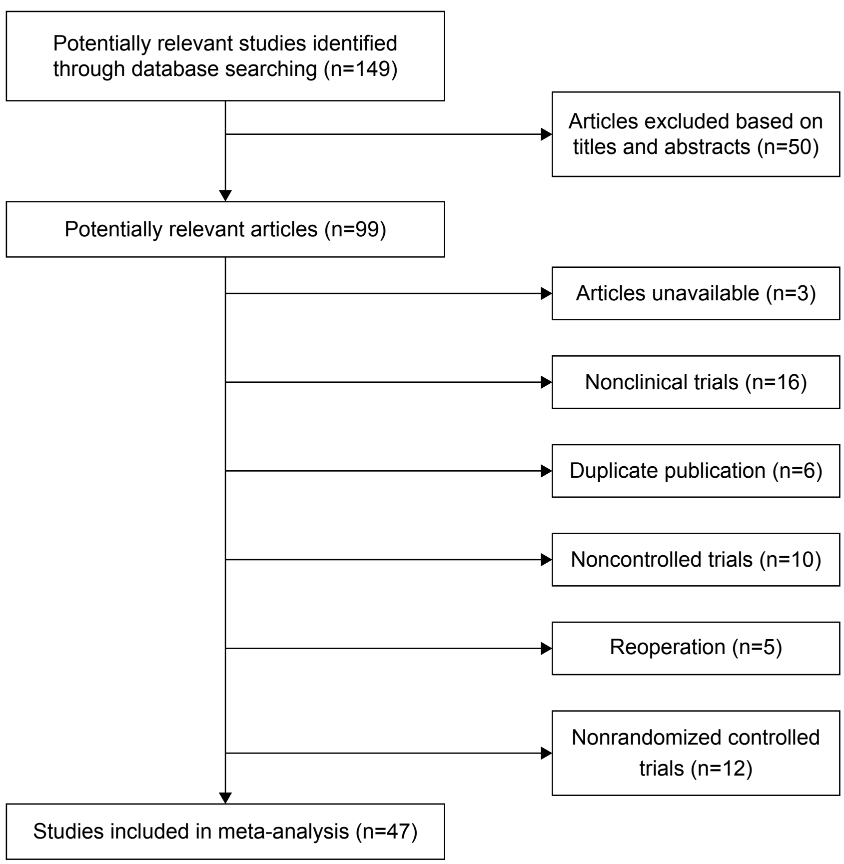



**Figure 3** Flowchart of the literature search.

**Table 1** Characteristics of the 47 RCTs included in the meta-analysis

| Study | n | Male/female | | Age, years, mean (SD) | | Injection site | Dose (mL) | Waiting time | Staining rate (%) | Indices[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CNs | BL | CNs | BL | | | | | |
| Chen et al (2016)[25] | 173 | 15/72 | 13/73 | 33.46 (4.58) | 34.32 (4.36) | Upper, middle, and lower points of the thyroid | 0.3 | 5–10 min | NA | 1, 4–6 |
| Zhang et al (2016)[26] | 37 | 3/14 | 3/17 | 41.1 (8.7) | 43 (7.2) | In the bilateral thyroid | 0.2–0.4 | 5–20 min | 95.5 | 1–4 |
| Liu et al (2016)[18] | 156 | 16/62 | 17/61 | NA | NA | Upper, middle, and lower parts of the lobes | 0.4–0.8 | NA | NA | 4, 6 |
| Li (2015)[27] | 40 | 4/16 | 8/12 | 47.9 (11.2) | 49.5 (12.4) | Top of the tumor | 0.4–0.8 | 3 min | NA | 4 |
| Feng and He (2015)[28] | 60 | 0/30 | 0/30 | NA | NA | 4 points around the tumor | 0.8 | NA | NA | 4–6 |
| Guo et al (2015)[29] | 59 | 9/21 | 8/21 | 35 (9.5) | 32 (8.2) | Upper, middle, and lower points of the bilateral thyroid | 0.6 | 20 min | NA | 6 |
| Duan et al (2015)[30] | 80 | 14/26 | 15/25 | 40.4 (7.18) | 42.5 (7.65) | 3–5 points around the thyroid | 0.3–0.5 | 30 min | 95.7 | 1, 2, 4, 5 |
| Chen and Wu (2015)[31] | 96 | 11/37 | 16/32 | 46.1 (10.9) | 45.8 (12.6) | NA | NA | NA | NA | 1, 5, 6 |
| Du et al (2015)[32] | 118 | 19/41 | 18/40 | 42.7 (10.6) | 43.5 (10.8) | Upper and middle points of the thyroid | 0.4 | 5 min | NA | 4–6 |
| Wang et al (2015)[33] | 120 | NA | NA | NA | NA | Upper and middle points of the thyroid | 0.2 | 15 min | NA | 1–6 |
| Liu and Qing (2015)[34] | 66 | 12/21 | 11/22 | 46.11 (2.09) | 45.63 (2.7) | Upper, middle, and lower points of the thyroid | 0.3 | 20 min | NA | 4–6 |
| Shao et al (2015)[35] | 60 | NA | NA | NA | NA | Multipoint injection of the tumor | 0.4–1.2 | 10 min | NA | 1, 5, 6 |
| Fu (2015)[43] | 250 | NA | NA | NA | NA | 4–6 points around the tumor | 0.8–1.2 | 15–20 min | NA | 5 |
| Wu et al (2015)[36] | 245 | 11/79 | 33/122 | NA | NA | Top and middle points of the tumor | 0.2–0.6 | 5–10 min | NA | 4–6 |
| Li et al (2015)[37] | 52 | NA | NA | NA | NA | 4 points of the bilateral thyroid | 1.0 | 10 min | NA | 4–6 |
| Chu et al (2015)[38] | 57 | 10/18 | 8/21 | 46.28 (12.635) | 40.39 (1.711) | Upper, middle, and lower points of the ipsilateral thyroid | 0.3–0.6 | 10 min | NA | 1, 4 |
| Wang et al (2015)[39] | 88 | 10/34 | 9/35 | 36.6 (11.2) | 36.8 (11.4) | Upper, middle, and lower points of the thyroid | 0.3–0.8 | NA | NA | 1 |
| Wu et al (2015)[40] | 86 | NA | NA | NA | NA | Upper, middle, and lower points of the thyroid | 0.6–1.2 | 30 min | 82.9 | 1–3 |
| Yin et al (2015)[41] | 80 | 17/23 | 18/22 | NA | NA | Upper, middle, and lower points of the thyroid | 0.6 | 5 min | NA | 4–6 |
| Li et al (2015)[42] | 72 | 9/27 | 10/26 | NA | NA | 2–4 points around the thyroid | NA | 15 min | 84 | 1–6 |
| Xu and Gu (2016)[23] | 114 | 5/52 | 4/53 | 45.37 (10.71) | 42.68 (14.43) | Around the tumor | 0.5 | 5–10 min | NA | 1, 4–6 |
| Wang et al (2015)[64] | 55 | 1/27 | 2/25 | 30.25 (6.04) | 29.44 (6.27) | In the thyroid gland | 0.1–0.2 | 2–3 min | 85 | 1, 4–6 |
| Zhu et al (2016)[19] | 162 | 14/67 | 16/65 | 46.75 (12.09) | 44.31 (10.73) | 1–2 points in the thyroid gland | 0.1–0.2 | Few minutes | 92.75 | 1–6 |
| Gu et al (2015)[65] | 100 | 10/40 | 6/44 | 46.98 (9.027) | 47.76 (13.912) | Upper and lower points of the thyroid | 0.2–0.3 | 3–5 min | NA | 1, 2, 4–6 |
| Liu et al (2014)[44] | 47 | 3/20 | 5/19 | 37.79 (11.2) | 33.94 (7.76) | Upper, middle, and lower points of the thyroid | 0.6 | 1 day | NA | 1, 4–6 |
| Chen et al (2014)[45] | 72 | 5/31 | 8/28 | 38.23 (10.67) | 34.64 (8.75) | Upper, middle, and lower points of the thyroid | 0.4/0.6 | 30 min | 95.4 | 1, 2, 4 |
| Gao and Zhao (2014)[46] | 100 | 12/38 | 9/41 | 42 (1.28) | 41 (1.36) | 3–4 points around the tumor | 0.53–1 | 30 min | 95.56 | 1–5 |
| Yang et al (2014)[47] | 379 | 23/155 | 27/174 | 42.3 (8.5) | 44.2 (7.3) | Upper and lower points of the tumor or the thyroid gland | 0.1–0.3 | 3–5 min | NA | 1, 6 |
| Wang and Rang (2014)[48] | 70 | NA | NA | 44.3 (8.8) | 45.2 (7.9) | 4 points in the contralateral thyroid gland | 0.4–0.8 | 15–20 min | NA | 1, 2, 4–6 |
| Liu et al (2014)[49] | 55 | 5/21 | 9/20 | 36.58 (11.31) | 33.58 (7.77) | In the ipsilateral thyroid | 14 days | NA | NA | 1, 4–6 |
| Du (2014)[50] | 40 | 4/16 | 8/12 | 47.9 (10.12) | 49.5 (12.4) | Top point of the thyroid gland | 0.4–0.8 | 3 min | NA | 1, 4–6 |
| Zhao (2014)[51] | 183 | 23/79 | 19/62 | NA | NA | Upper and lower points of the thyroid | 0.1–0.2 | 5 min | 73.5 | 1, 2 |
| Chun (2014)[52] | 67 | 6/27 | 11/23 | 41.06 (12.84) | 44.65 (12.84) | Upper, middle, and lower points of the thyroid | 0.1–0.3 | 3–5 min | 86.8 | 1, 5 |
| Liu (2014)[53] | 184 | 23/53 | 30/78 | 46.5 (12.8) | 47.2 (13.5) | Multipoint injection of the tumor | 0.8 | NA | NA | 5, 6 |
| Zhang et al (2014)[54] | 72 | 12/24 | 10/26 | NA | NA | Upper and lower points of the thyroid | 0.2–0.4 | 5 min | NA | 4–6 |
| Shen et al (2014)[55] | 109 | NA | NA | NA | NA | Around the tumor | 0.2 | 10 min | 90.5 | 1, 2, 4 |
| Shao et al (2014)[57] | 29 | NA | NA | NA | NA | Upper, middle, and lower points of the thyroid | 0.3–0.6 | 15 min | NA | 4–6 |
| Long et al (2014)[56] | 150 | 15/60 | 12/63 | 41.4 (1.62) | 42.1 (2.56) | Upper, middle, and lower points of the ipsilateral thyroid | 0.3 | 20 min | NA | 1, 2, 6 |
| Tian et al (2014)[66] | 100 | 5/45 | 11/39 | 36.4 (2.5) | 44.5 (5.8) | Upper, middle, and lower points of the thyroid | 0.6 | 10–15 min | NA | 1, 2, 4–6 |

(*Continued*)

**Table 1** (*Continued*)

| Study | n | Male/female | | Age, years, mean (SD) | | Injection site | Dose (mL) | Waiting time | Staining rate (%) | Indices[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CNs | BL | CNs | BL | | | | | |
| Sun et al (2014)[67] | 80 | NA | NA | NA | NA | 2–4 points around the tumor | 0.2–0.8 | 15 min | 69.89 | 1–4 |
| Yang et al (2013)[58] | 43 | 1/20 | 1/21 | 32.48 (4.69) | 32.32 (5.35) | In the ipsilateral thyroid gland | 0.1 | 20 min | NA | 1, 2, 4, 5 |
| Yang et al (2013)[59] | 68 | 17/19 | 12/20 | 34.5 (9.1) | 33.9 (10.3) | 1–2 points around the tumor | 0.1–0.3 | 10 min | 91.7 | 1, 5 |
| Wu (2013)[60] | 55 | 5/21 | 9/20 | 36.58 (11.31) | 33.58 (7.77) | Upper, middle, and lower points of the ipsilateral thyroid | 0.6 | NA | NA | 1, 2, 4–6 |
| Huang et al (2013)[24] | 72 | 12/24 | 10/26 | 41.22 (2.53) | 40.69 (2.42) | Lower and upper points of the tumor | 0.2–0.4 | NA | NA | 5 |
| Bai et al (2013)[61] | 88 | 9/39 | 7/33 | 46.28 (9.2) | 45.39 (12.03) | Lower and upper points of the tumor | 0.2 | NA | NA | 1–6 |
| Zeng et al (2012)[62] | 80 | 0/40 | 0/40 | NA | NA | 4–6 points around the tumor | 1.0 | 20 min | NA | 5, 6 |
| Wang et al (2009)[63] | 36 | 10/8 | 7/11 | NA | NA | 4–6 points around the tumor | 0.4–0.6 | 30 min | 95.2 | 2–4 |

**Notes:** [a]Observation indexes: differences in the following: 1) the number of retrieved lymph nodes, 2) the total metastatic rate of the retrieved lymph nodes, 3) the metastatic rate of stained/unstained lymph nodes, 4) the accidental parathyroid removal rate, 5) the postoperative transient or permanent hypoparathyroidism rate, and 6) the postoperative transient or permanent hypocalcemia rate between the CN and blank control groups.
**Abbreviations:** RCT, randomized controlled trial; SD, standard deviation; CN, carbon nanoparticle; BL, blank; NA, not available.

(OR =1.13, 95% CI =0.87–1.47, *P*=0.35; OR =1.33, 95% CI =0.91–1.94, *P*=0.14; and OR =0.55, 95% CI =0.23–1.36, *P*=0.20, respectively; Figure 5A–C).

In the present meta-analysis of these studies, we found that the number of retrieved lymph nodes per patient in the CN group was higher than that of the blank control group. This finding of an increasing number of retrieved lymph nodes corresponds to the improvement in the extent of neck dissection. Further, with increasing removal of dyed lymph nodes, metastatic lymph nodes will also be cleared away simultaneously. Hence, the number of metastatic lymph nodes in the CN group was statistically higher than that in the blank control group. Besides, 4 studies reported that the number of retrieved small lymph nodes (diameter $<5$ mm) was significantly higher in the CN group.[44,60,61,67] These findings suggest that CNs may help identify tiny, suspicious lymph nodes.

However, it should be noted that the total metastatic rate of the retrieved lymph nodes and the metastatic rate of stained or unstained lymph nodes did not significantly differ between the 2 groups, consistent with the findings of previous studies.[46,68] In Gao and Zhao study,[46] more metastatic lymph nodes were eliminated in the CN group (6±2.37 vs 4±2.49; $P<0.01$), but the rate of metastatic lymph nodes did not differ (45.97% vs 47.10%; $P>0.05$). In the study by Yan et al,[68] no increase in the number of sentinel lymph node metastasis-positive cases was observed with the utilization of CNs, as compared to that in the control group (36.8% vs 63.2%). Concerning the mechanism of CNs, it is considered that the tissue damage and inflammation caused by the tumor alter the lymphatic drainage channels of the thyroid, which in turn will affect the diffusion of CNs and the identification of metastatic lymph nodes. Thus, it is actually quite hard for CNs to distinguish metastatic lymph nodes among normal lymph nodes.

## Anatomic structure and physical function of the parathyroid in the CN and blank control groups

Compared with the blank control group, the use of CNs was associated with a lower rate of accidental parathyroid removal, approximately 22% (OR =0.22, 95% CI =0.16–0.30, $P<0.00001$; RD =–0.13, 95% CI =–0.15 to –0.11, $P<0.00001$; Figure 6). The transient and permanent hypoparathyroidism rates declined by approximately 31% and 24% in the CN group, respectively (transient hypoparathyroidism rate: OR =0.31, 95% CI =0.25–0.39, $P<0.00001$; RD =–0.15, 95% CI =–0.18 to –0.12, $P<0.00001$; Figure 7A; permanent hypoparathyroidism rate: OR =0.24,

**Table 2** Quality assessment of the 47 randomized controlled trials included using the Jadad scale system

| Study | Randomization | Concealment of allocation | Blinding | Loss to follow-up (%) | Quality assessment |
|---|---|---|---|---|---|
| Chen et al (2016)[25] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Zhang et al (2016)[26] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Liu et al (2016)[18] | Computer-generated permuted | Only mentioned randomized | Unclear | 0 | 3 |
| Li (2015)[27] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Feng and He (2015)[28] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Guo et al (2015)[29] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Duan et al (2015)[30] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Chen and Wu (2015)[31] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Du et al (2015)[32] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Wang et al (2015)[33] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Liu and Qing (2015)[34] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Shao et al (2015)[35] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Fu (2015)[43] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Wu et al (2015)[36] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Li et al (2015)[37] | Random-number table | Only mentioned randomized | Unclear | 0 | 3 |
| Chu et al (2015)[38] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Wang et al (2015)[39] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Wu et al (2015)[40] | Random-number table | Only mentioned randomized | Unclear | 0 | 3 |
| Yin et al (2015)[41] | Random-number table | Only mentioned randomized | Unclear | 0 | 3 |
| Li et al (2015)[42] | Random-number table | Only mentioned randomized | Unclear | 0 | 3 |
| Xu and Gu (2016)[23] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Wang et al (2015)[64] | Computer-generated | Only mentioned randomized | Unclear | 0 | 3 |
| Zhu et al (2016)[19] | Computer-generated random-number tables | Only mentioned randomized | Unclear | 0 | 3 |
| Gu et al (2015)[65] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Liu et al (2014)[44] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Chen et al (2014)[45] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Gao and Zhao (2014)[46] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Yang et al (2014)[47] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Wang and Rang (2014)[48] | Random-number table | Only mentioned randomized | Unclear | 0 | 3 |
| Liu et al (2014)[49] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Du (2014)[50] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Zhao (2014)[51] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Chun (2014)[52] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Liu (2014)[53] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Zhang et al (2014)[54] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Shen et al (2014)[55] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Shao et al (2014)[57] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Long et al (2014)[56] | Odd or even number | Only mentioned randomized | Unclear | 0 | 1 |
| Tian et al (2014)[66] | Randomization chart | Only mentioned randomized | Unclear | 0 | 3 |
| Sun et al (2014)[67] | Computer-generated permuted block sequencing | Only mentioned randomized | Unclear | 0 | 3 |
| Yang et al (2013)[58] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Yang et al (2013)[59] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Wu (2013)[60] | No detailed description | Only mentioned randomized | Unclear | 15.4 | 3 |
| Huang et al (2013)[24] | Computer-generated permuted | Sealed envelopes | Single blinding | 0 | 3 |
| Bai et al (2013)[61] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Zeng et al (2012)[62] | No detailed description | Only mentioned randomized | Unclear | 0 | 2 |
| Wang et al (2009)[63] | Random-number table | Only mentioned randomized | Unclear | 0 | 3 |

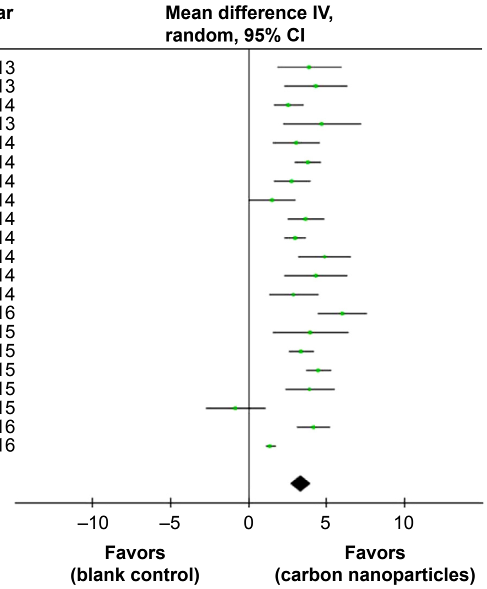
**Notes:** The Jadad scale was used to assess the quality of these RCTs. Thirteen studies included had a score of 3 points, which reflected the high quality of the study. The majority of studies had 2 points or lower. These studies can be considered to be of relatively low quality.
**Abbreviation:** RCT, randomized controlled trials.

95% CI =0.07–0.85, *P*=0.03; RD =–0.02, 95% CI =–0.03 to –0.00, *P*<0.02; Figure 7B). In addition, the rate of postoperative transient hypocalcemia in the blank control group was 30% higher than in the CN group (OR =0.30, 95% CI =0.25–0.38, *P*<0.00001; RD =–0.16, 95% CI =–0.18 to –0.13, *P*<0.00001; Figure 8A). On the other hand, the postoperative permanent hypocalcemia rate did not significantly differ between the CN and blank control groups

**A**

| Study or subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight (%) | Mean difference IV, random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Bai et al (2013)[61] | 7.6 | 4.1 | 48 | 3.7 | 4.9 | 33 | 3.9 | 3.90 (1.87, 5.93) | 2013 |
| Wu (2013)[60] | 9.96 | 4.53 | 26 | 5.62 | 2.58 | 29 | 4.0 | 4.34 (2.36, 6.32) | 2013 |
| Yang et al (2013)[59] | 8.99 | 2.24 | 36 | 6.41 | 1.56 | 32 | 5.5 | 2.58 (1.67, 3.49) | 2014 |
| Yang et al (2013)[58] | 9.67 | 5.26 | 21 | 4.95 | 2.54 | 22 | 3.3 | 4.72 (2.23, 7.21) | 2013 |
| Chen et al (2014)[45] | 8.67 | 3.15 | 36 | 5.61 | 3.36 | 36 | 4.7 | 3.06 (1.56, 4.56) | 2014 |
| Wang and Rang (2014)[48] | 11.4 | 1.88 | 35 | 7.6 | 1.59 | 35 | 5.6 | 3.80 (2.98, 4.62) | 2014 |
| Zhao (2014)[51] | 10.9 | 4.3 | 102 | 8.1 | 3.7 | 81 | 5.2 | 2.80 (1.64, 3.96) | 2014 |
| Chun (2014)[52] | 5.97 | 3.92 | 33 | 4.44 | 0.2 | 34 | 4.7 | 1.53 (0.03, 3.03) | 2014 |
| Gao and Zhao (2014)[46] | 9.45 | 3.16 | 50 | 5.75 | 2.75 | 50 | 5.2 | 3.70 (2.54, 4.86) | 2014 |
| Shen et al (2014)[55] | 9.7 | 1.7 | 45 | 6.7 | 1.9 | 64 | 5.8 | 3.00 (2.32, 3.68) | 2014 |
| Liu et al (2014)[44] | 10.43 | 3.64 | 23 | 5.54 | 1.79 | 24 | 4.4 | 4.89 (3.24, 6.54) | 2014 |
| Liu et al (2014)[49] | 9.96 | 4.53 | 26 | 5.62 | 2.58 | 29 | 4.0 | 4.34 (2.36, 6.32) | 2014 |
| Du (2014)[50] | 7.6 | 2.52 | 20 | 4.7 | 2.52 | 20 | 4.6 | 2.90 (1.34, 4.46) | 2014 |
| Zhu et al (2016)[19] | 10.07 | 6.46 | 81 | 4.04 | 2.84 | 81 | 4.6 | 6.03 (4.49, 7.57) | 2016 |
| Duan et al (2015)[30] | 10.86 | 7.39 | 40 | 6.88 | 2.37 | 40 | 3.4 | 3.98 (1.57, 6.39) | 2015 |
| Li et al (2015)[42] | 8.7 | 1.8 | 36 | 5.3 | 1.4 | 36 | 5.7 | 3.40 (2.66, 4.14) | 2015 |
| Chu et al (2015)[38] | 7.89 | 0.685 | 28 | 3.38 | 2.111 | 29 | 5.6 | 4.51 (3.70, 5.32) | 2015 |
| Wu et al (2015)[40] | 10.19 | 4.27 | 43 | 6.26 | 2.98 | 43 | 4.6 | 3.93 (2.37, 5.49) | 2015 |
| Gu et al (2015)[65] | 5.78 | 4.55 | 50 | 6.62 | 5.07 | 50 | 4.1 | –0.84 (–2.73, 1.05) | 2015 |
| Chen et al (2016)[25] | 9.71 | 4.32 | 87 | 5.54 | 2.54 | 86 | 5.3 | 4.17 (3.12, 5.22) | 2016 |
| Xu and Gu (2016)[23] | 0.6 | 0.98 | 57 | 4.58 | 0.6 | 57 | 6.1 | 1.42 (1.12, 1.72) | 2016 |
| **Total (95% CI)** | | | **923** | | | **911** | **100** | **3.39 (2.73, 4.05)** | |

Heterogeneity: $\tau^2$=1.86; $\chi^2$=163.75, *df*=20 (*P*<0.00001); $I^2$=88%
Test for overall effect: *Z*=10.04 (*P*<0.00001)




**B**

| Study or subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight (%) | Mean difference IV, random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Yang et al (2013)[58] | 1.23 | 1.57 | 21 | 0.55 | 0.79 | 22 | 10.0 | 0.68 (–0.07, 1.43) | 2013 |
| Liu et al (2014)[44] | 8.92 | 3.38 | 23 | 4.47 | 1.91 | 24 | 4.1 | 4.45 (2.87, 6.03) | 2014 |
| Gao and Zhao (2014)[46] | 0.6 | 2.37 | 50 | 0.4 | 2.49 | 50 | 8.0 | 2.00 (1.05, 2.95) | 2014 |
| Long et al (2014)[56] | 2.86 | 0.13 | 75 | 1.87 | 0.09 | 75 | 16.9 | 0.99 (0.95, 1.03) | 2014 |
| Duan et al (2015)[30] | 0.5 | 4.15 | 40 | 2.64 | 1.52 | 40 | 5.1 | 2.36 (0.99, 3.73) | 2015 |
| Zhu et al (2016)[19] | 2.74 | 3.66 | 81 | 1.68 | 2.4 | 81 | 8.0 | 1.06 (0.11, 2.01) | 2016 |
| Chu et al (2015)[38] | 2.21 | 3.348 | 28 | 0.86 | 1.302 | 29 | 5.3 | 1.35 (0.02, 2.68) | 2015 |
| Gu et al (2015)[65] | 1.66 | 2.353 | 50 | 3.06 | 4.501 | 50 | 4.9 | –1.40 (–2.81, 0.01) | 2015 |
| Wu et al (2015)[40] | 3.88 | 0.49 | 43 | 3.81 | 3.43 | 43 | 7.3 | 0.07 (–0.97, 1.11) | 2015 |
| Chen et al (2016)[25] | 1.3 | 1.59 | 87 | 0.57 | 0.74 | 86 | 14.5 | 0.73 (0.36, 1.10) | 2016 |
| Xu and Gu (2016)[23] | 0.96 | 0.77 | 57 | 0.47 | 0.5 | 57 | 15.8 | 0.49 (0.25, 0.73) | 2016 |
| **Total (95% CI)** | | | **555** | | | **557** | **100** | **0.98 (0.61, 1.35)** | |

Heterogeneity: $\tau^2$=0.21; $\chi^2$=60.04, *df*=10 (*P*<0.00001); $I^2$=83%
Test for overall effect: *Z*=5.18 (*P*<0.00001)

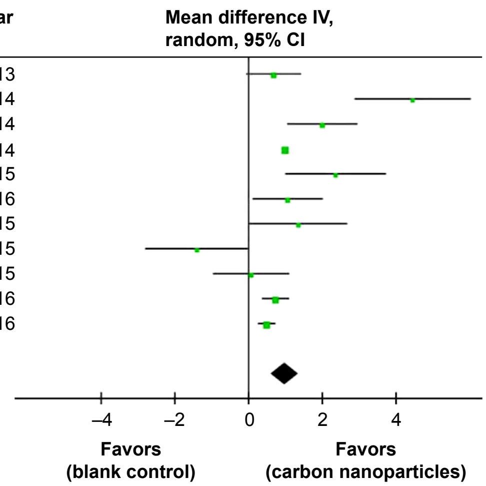


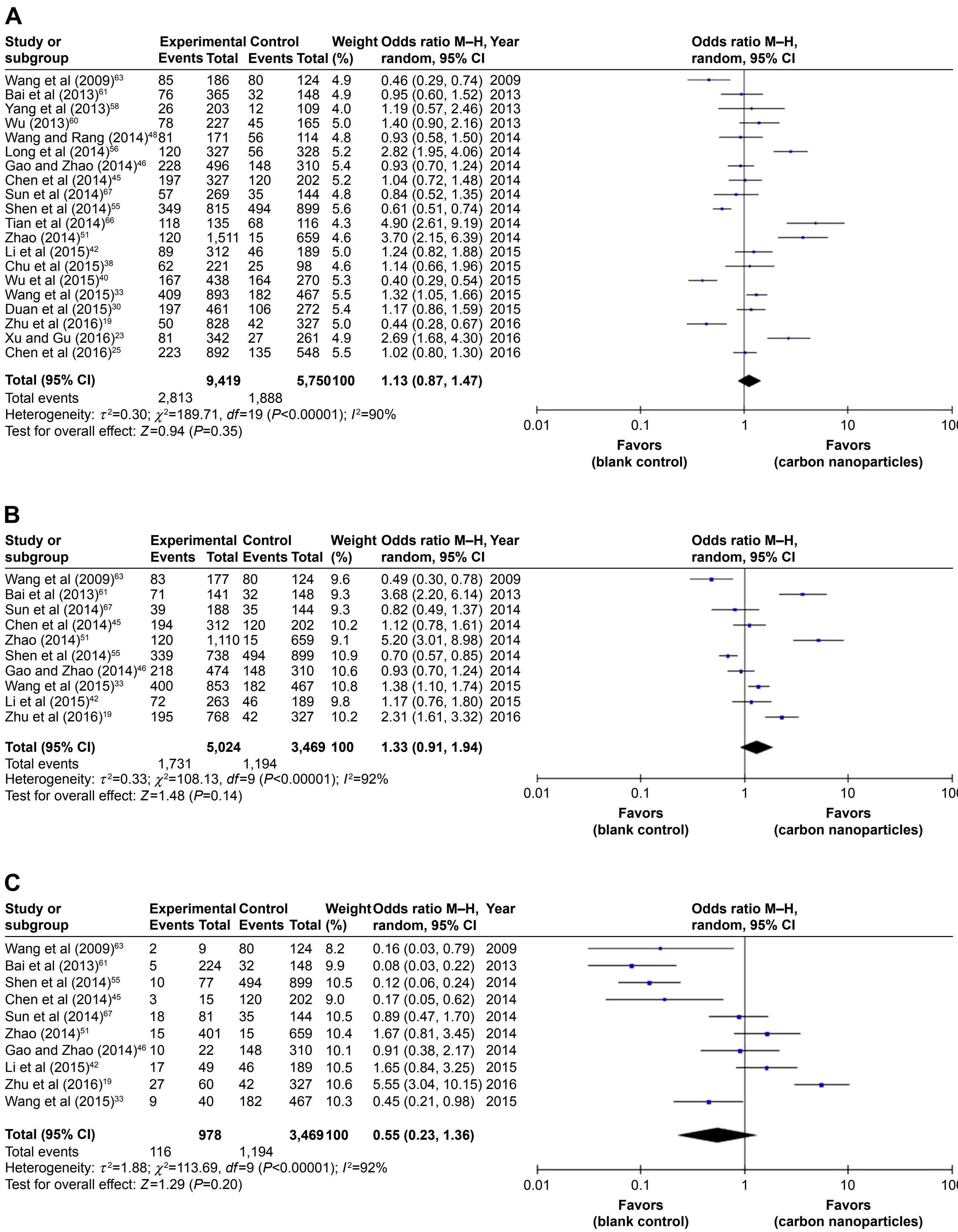

**Figure 4** Forest plot showing the association of CNs with retrieved lymph nodes and metastatic lymph nodes.
**Notes:** (**A**) Number of retrieved lymph nodes per patient in the CN and blank control groups. (**B**) Number of retrieved metastatic lymph nodes per patient.
**Abbreviations:** CN, carbon nanoparticle; SD, standard deviation; IV, interval variable; CI, confidence interval; random, random effect; *df*, degrees of freedom.

(OR =0.33, 95% CI =0.04–3.03, *P*=0.33; RD =–0.01, 95% CI =–0.03 to –0.01, *P*=0.35; Figure 8B).

In terms of the protection of the parathyroid, some previous studies showed that the usage of CNs was not beneficial;[18,24] however, our study demonstrated that the rates of accidental parathyroid removal (Figure 6), postoperative transient or permanent hypoparathyroidism (Figure 7), and transient hypocalcemia (Figure 8A) were lower in the CN group. This finding suggests that the usage of CNs will help distinguish and preserve the parathyroid glands. However, there was no significant difference in the rate of permanent hypocalcemia. This might have resulted from the quantitative restrictions of the RCTs included. In addition, Yang et al reported that the use of CNs resulted in a decreased rate of parathyroid auto-transplantation.[47]

## Publication bias and limitations

A funnel plot analysis of all RCTs was performed as part of the present meta-analysis. The findings indicated that the publication bias was low (Figure 9). But considering the difficulties in publishing studies with negative findings, many studies likely remain unpublished, and these were not available for analysis. In addition, the quality of assessment scores of the 47 RCTs included was relatively low, owing largely to a lack




**A**

| Study or subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight (%) | Odds ratio M–H, random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Wang et al (2009)[63] | 85 | 186 | 80 | 124 | 4.9 | 0.46 (0.29, 0.74) | 2009 |
| Bai et al (2013)[61] | 76 | 365 | 32 | 148 | 4.9 | 0.95 (0.60, 1.52) | 2013 |
| Yang et al (2013)[58] | 26 | 203 | 12 | 109 | 4.0 | 1.19 (0.57, 2.46) | 2013 |
| Wu (2013)[60] | 78 | 227 | 45 | 165 | 5.0 | 1.40 (0.90, 2.16) | 2013 |
| Wang and Rang (2014)[48] | 81 | 171 | 56 | 114 | 4.8 | 0.93 (0.58, 1.50) | 2014 |
| Long et al (2014)[56] | 120 | 327 | 56 | 328 | 5.2 | 2.82 (1.95, 4.06) | 2014 |
| Gao and Zhao (2014)[46] | 228 | 496 | 148 | 310 | 5.4 | 0.93 (0.70, 1.24) | 2014 |
| Chen et al (2014)[45] | 197 | 327 | 120 | 202 | 5.2 | 1.04 (0.72, 1.48) | 2014 |
| Sun et al (2014)[67] | 57 | 269 | 35 | 144 | 4.8 | 0.84 (0.52, 1.35) | 2014 |
| Shen et al (2014)[55] | 349 | 815 | 494 | 899 | 5.6 | 0.61 (0.51, 0.74) | 2014 |
| Tian et al (2014)[66] | 118 | 135 | 68 | 116 | 4.3 | 4.90 (2.61, 9.19) | 2014 |
| Zhao (2014)[51] | 120 | 1,511 | 15 | 659 | 4.6 | 3.70 (2.15, 6.39) | 2014 |
| Li et al (2015)[42] | 89 | 312 | 46 | 189 | 5.0 | 1.24 (0.82, 1.88) | 2015 |
| Chu et al (2015)[38] | 62 | 221 | 25 | 98 | 4.6 | 1.14 (0.66, 1.96) | 2015 |
| Wu et al (2015)[40] | 167 | 438 | 164 | 270 | 5.3 | 0.40 (0.29, 0.54) | 2015 |
| Wang et al (2015)[33] | 409 | 893 | 182 | 467 | 5.5 | 1.32 (1.05, 1.66) | 2015 |
| Duan et al (2015)[30] | 197 | 461 | 106 | 272 | 5.4 | 1.17 (0.86, 1.59) | 2015 |
| Zhu et al (2016)[19] | 50 | 828 | 42 | 327 | 5.0 | 0.44 (0.28, 0.67) | 2016 |
| Xu and Gu (2016)[23] | 81 | 342 | 27 | 261 | 4.9 | 2.69 (1.68, 4.30) | 2016 |
| Chen et al (2016)[25] | 223 | 892 | 135 | 548 | 5.5 | 1.02 (0.80, 1.30) | 2016 |
| **Total (95% CI)** | | **9,419** | | **5,750** | **100** | **1.13 (0.87, 1.47)** | |
| Total events | 2,813 | | 1,888 | | | | |

Heterogeneity: $\tau^2=0.30$; $\chi^2=189.71$, $df=19$ ($P<0.00001$); $I^2=90\%$
Test for overall effect: $Z=0.94$ ($P=0.35$)

**B**

| Study or subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight (%) | Odds ratio M–H, random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Wang et al (2009)[63] | 83 | 177 | 80 | 124 | 9.6 | 0.49 (0.30, 0.78) | 2009 |
| Bai et al (2013)[61] | 71 | 141 | 32 | 148 | 9.3 | 3.68 (2.20, 6.14) | 2013 |
| Sun et al (2014)[67] | 39 | 188 | 35 | 144 | 9.3 | 0.82 (0.49, 1.37) | 2014 |
| Chen et al (2014)[45] | 194 | 312 | 120 | 202 | 10.2 | 1.12 (0.78, 1.61) | 2014 |
| Zhao (2014)[51] | 120 | 1,110 | 15 | 659 | 9.1 | 5.20 (3.01, 8.98) | 2014 |
| Shen et al (2014)[55] | 339 | 738 | 494 | 899 | 10.9 | 0.70 (0.57, 0.85) | 2014 |
| Gao and Zhao (2014)[46] | 218 | 474 | 148 | 310 | 10.6 | 0.93 (0.70, 1.24) | 2014 |
| Wang et al (2015)[33] | 400 | 853 | 182 | 467 | 10.8 | 1.38 (1.10, 1.74) | 2015 |
| Li et al (2015)[42] | 72 | 263 | 46 | 189 | 9.8 | 1.17 (0.76, 1.80) | 2015 |
| Zhu et al (2016)[19] | 195 | 768 | 42 | 327 | 10.2 | 2.31 (1.61, 3.32) | 2016 |
| **Total (95% CI)** | | **5,024** | | **3,469** | **100** | **1.33 (0.91, 1.94)** | |
| Total events | 1,731 | | 1,194 | | | | |

Heterogeneity: $\tau^2=0.33$; $\chi^2=108.13$, $df=9$ ($P<0.00001$); $I^2=92\%$
Test for overall effect: $Z=1.48$ ($P=0.14$)

**C**

| Study or subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight (%) | Odds ratio M–H, random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Wang et al (2009)[63] | 2 | 9 | 80 | 124 | 8.2 | 0.16 (0.03, 0.79) | 2009 |
| Bai et al (2013)[61] | 5 | 224 | 32 | 148 | 9.9 | 0.08 (0.03, 0.22) | 2013 |
| Shen et al (2014)[55] | 10 | 77 | 494 | 899 | 10.5 | 0.12 (0.06, 0.24) | 2014 |
| Chen et al (2014)[45] | 3 | 15 | 120 | 202 | 9.0 | 0.17 (0.05, 0.62) | 2014 |
| Sun et al (2014)[67] | 18 | 81 | 35 | 144 | 10.5 | 0.89 (0.47, 1.70) | 2014 |
| Zhao (2014)[51] | 15 | 401 | 15 | 659 | 10.4 | 1.67 (0.81, 3.45) | 2014 |
| Gao and Zhao (2014)[46] | 10 | 22 | 148 | 310 | 10.1 | 0.91 (0.38, 2.17) | 2014 |
| Li et al (2015)[42] | 17 | 49 | 46 | 189 | 10.5 | 1.65 (0.84, 3.25) | 2015 |
| Zhu et al (2016)[19] | 27 | 60 | 42 | 327 | 10.6 | 5.55 (3.04, 10.15) | 2016 |
| Wang et al (2015)[33] | 9 | 40 | 182 | 467 | 10.3 | 0.45 (0.21, 0.98) | 2015 |
| **Total (95% CI)** | | **978** | | **3,469** | **100** | **0.55 (0.23, 1.36)** | |
| Total events | 116 | | 1,194 | | | | |

Heterogeneity: $\tau^2=1.88$; $\chi^2=113.69$, $df=9$ ($P<0.00001$); $I^2=92\%$
Test for overall effect: $Z=1.29$ ($P=0.20$)

**Figure 5** Forest plot showing the relationship of CNs and different kinds of retrieved lymph nodes.
**Notes:** (**A**) Total metastatic rate of the retrieved lymph nodes. Metastatic rates of the (**B**) stained and (**C**) unstained lymph nodes in the CN and blank control groups.
**Abbreviations:** CN, carbon nanoparticle; M–H, Mantel–Haenszel; random, random effect; CI, confidence interval; *df*, degrees of freedom.

| Study or subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight (%) | Odds ratio M–H, fixed, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Wang et al (2009)[63] | 7 | 18 | 8 | 18 | 2.1 | 0.80 (0.21, 3.00) | 2009 |
| Yang et al (2013)[58] | 2 | 21 | 10 | 22 | 3.9 | 0.13 (0.02, 0.68) | 2013 |
| Wu (2013)[60] | 0 | 26 | 7 | 29 | 3.1 | 0.06 (0.00, 1.05) | 2013 |
| Tian et al (2014)[66] | 1 | 50 | 8 | 50 | 3.4 | 0.11 (0.01, 0.89) | 2014 |
| Chen et al (2014)[45] | 5 | 36 | 13 | 36 | 4.9 | 0.29 (0.09, 0.91) | 2014 |
| Zhang et al (2014)[54] | 0 | 36 | 7 | 36 | 3.2 | 0.05 (0.00, 0.98) | 2014 |
| Sun et al (2014)[67] | 0 | 40 | 3 | 40 | 1.5 | 0.13 (0.01, 2.65) | 2014 |
| Liu et al (2014)[44] | 0 | 23 | 7 | 24 | 3.2 | 0.05 (0.00, 0.93) | 2014 |
| Shao et al (2014)[57] | 0 | 9 | 5 | 20 | 1.5 | 0.15 (0.01, 3.00) | 2014 |
| Shen et al (2014)[55] | 5 | 45 | 11 | 64 | 3.5 | 0.60 (0.19, 1.87) | 2014 |
| Liu et al (2014)[49] | 0 | 26 | 7 | 29 | 3.1 | 0.06 (0.00, 1.05) | 2014 |
| Gao and Zhao (2014)[46] | 0 | 50 | 4 | 50 | 2.0 | 0.10 (0.01, 1.95) | 2014 |
| Du (2014)[50] | 1 | 20 | 7 | 20 | 2.9 | 0.10 (0.01, 0.89) | 2014 |
| Wang and Rang (2014)[48] | 0 | 35 | 3 | 35 | 1.5 | 0.13 (0.01, 2.63) | 2014 |
| Liu and Qing (2015)[34] | 2 | 33 | 7 | 33 | 2.9 | 0.24 (0.05, 1.25) | 2015 |
| Duan et al (2015)[30] | 0 | 40 | 5 | 40 | 2.4 | 0.08 (0.00, 1.49) | 2015 |
| Li et al (2015)[42] | 0 | 36 | 0 | 36 | | Not estimable | 2015 |
| Du et al (2015)[32] | 1 | 60 | 3 | 58 | 1.3 | 0.31 (0.03, 3.08) | 2015 |
| Wang et al (2015)[64] | 0 | 28 | 5 | 27 | 2.4 | 0.07 (0.00, 1.37) | 2015 |
| Zhu et al (2016)[19] | 4 | 81 | 14 | 81 | 5.8 | 0.25 (0.08, 0.79) | 2016 |
| Wang et al (2015)[39] | 0 | 44 | 9 | 44 | 4.1 | 0.04 (0.00, 0.75) | 2015 |
| Li et al (2015)[37] | 1 | 26 | 5 | 26 | 2.1 | 0.17 (0.02, 1.55) | 2015 |
| Wu et al (2015)[36] | 4 | 90 | 20 | 155 | 6.1 | 0.31 (0.10, 0.95) | 2015 |
| Yin et al (2015)[41] | 0 | 40 | 6 | 40 | 2.8 | 0.07 (0.00, 1.21) | 2015 |
| Li (2015)[27] | 1 | 20 | 7 | 20 | 2.9 | 0.10 (0.01, 0.89) | 2015 |
| Feng and He (2015)[28] | 0 | 30 | 7 | 30 | 3.2 | 0.05 (0.00, 0.95) | 2015 |
| Chu et al (2015)[38] | 8 | 28 | 2 | 29 | 0.6 | 5.40 (1.03, 28.23) | 2015 |
| Gu et al (2015)[65] | 3 | 50 | 13 | 50 | 5.4 | 0.18 (0.05, 0.68) | 2015 |
| Chen et al (2016)[25] | 6 | 87 | 23 | 86 | 9.4 | 0.20 (0.08, 0.53) | 2016 |
| Xu and Gu (2016)[23] | 2 | 57 | 7 | 57 | 3.0 | 0.26 (0.05, 1.31) | 2016 |
| Liu et al (2016)[18] | 0 | 78 | 0 | 78 | | Not estimable | 2016 |
| **Total (95% CI)** | | **1,263** | | **1,363** | **100** | **0.22 (0.16, 0.30)** | |
| Total events | 53 | | 233 | | | | |

Heterogeneity: $\chi^2$=31.83, *df*=28 (*P*=0.28); $I^2$=12%
Test for overall effect: *Z*=9.73 (*P*<0.00001)

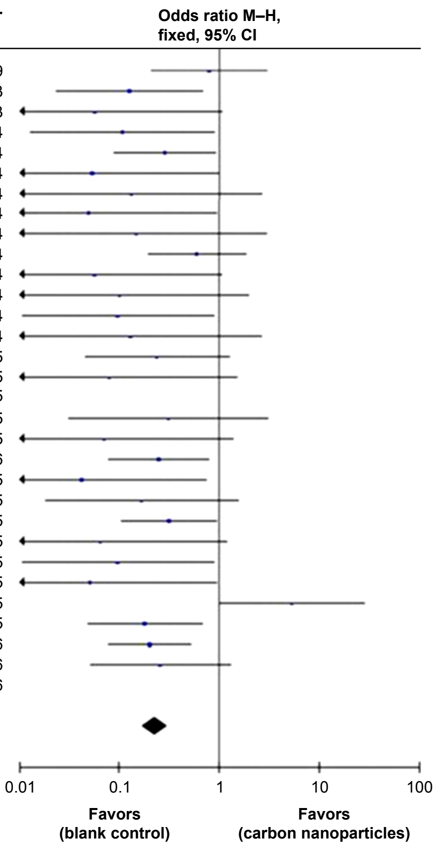



**Figure 6** Accidental parathyroid removal rate in the CN and blank control groups.
**Abbreviations:** CN, carbon nanoparticle; M–H, Mantel–Haenszel; CI, confidence interval; *df*, degrees of freedom.

**A**

| Study or subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight (%) | Odds ratio M–H, fixed, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Wu (2013)[60] | 1 | 26 | 1 | 29 | 0.3 | 1.12 (0.07, 18.86) | 2013 |
| Tian et al (2014)[66] | 1 | 50 | 7 | 50 | 2.3 | 0.13 (0.01, 1.06) | 2014 |
| Shao et al (2014)[57] | 2 | 9 | 11 | 20 | 1.8 | 0.23 (0.04, 1.42) | 2014 |
| Long et al (2014)[56] | 26 | 75 | 45 | 75 | 9.8 | 0.35 (0.18, 0.69) | 2014 |
| Du (2014)[50] | 3 | 20 | 8 | 20 | 2.3 | 0.26 (0.06, 1.21) | 2014 |
| Liu et al (2014)[49] | 1 | 26 | 1 | 29 | 0.3 | 1.12 (0.07, 18.86) | 2014 |
| Wang and Rang (2014)[48] | 0 | 35 | 5 | 35 | 1.8 | 0.08 (0.00, 1.47) | 2014 |
| Zhang et al (2014)[54] | 1 | 36 | 5 | 36 | 1.6 | 0.18 (0.02, 1.60) | 2014 |
| Liu et al (2014)[44] | 0 | 23 | 2 | 24 | 0.8 | 0.19 (0.01, 4.21) | 2014 |
| Liu (2014)[53] | 7 | 76 | 36 | 108 | 9.0 | 0.20 (0.08, 0.49) | 2014 |
| Wu et al (2015)[36] | 10 | 90 | 48 | 155 | 10.4 | 0.28 (0.13, 0.58) | 2015 |
| Li et al (2015)[37] | 5 | 26 | 10 | 26 | 2.7 | 0.38 (0.11, 1.34) | 2015 |
| Liu and Qing (2015)[34] | 2 | 33 | 10 | 33 | 3.1 | 0.15 (0.03, 0.74) | 2015 |
| Guo et al (2015)[29] | 4 | 30 | 15 | 29 | 4.4 | 0.14 (0.04, 0.52) | 2015 |
| Shao et al (2015)[35] | 2 | 30 | 9 | 30 | 2.8 | 0.17 (0.03, 0.85) | 2015 |
| Gu et al (2015)[65] | 24 | 50 | 28 | 50 | 4.9 | 0.73 (0.33, 1.59) | 2015 |
| Wang et al (2015)[33] | 5 | 60 | 12 | 60 | 3.7 | 0.36 (0.12, 1.11) | 2015 |
| Du et al (2015)[32] | 2 | 60 | 7 | 58 | 2.3 | 0.25 (0.05, 1.26) | 2015 |
| Wang et al (2015)[64] | 3 | 28 | 6 | 27 | 1.8 | 0.42 (0.09, 1.89) | 2015 |
| Li et al (2015)[42] | 1 | 36 | 8 | 36 | 2.6 | 0.10 (0.01, 0.85) | 2015 |
| Zhu et al (2016)[19] | 8 | 81 | 20 | 81 | 6.0 | 0.33 (0.14, 0.81) | 2016 |
| Wu et al (2015)[40] | 4 | 43 | 4 | 43 | 1.2 | 1.00 (0.23, 4.29) | 2015 |
| Feng and He (2015)[28] | 1 | 30 | 8 | 30 | 2.6 | 0.09 (0.01, 0.82) | 2015 |
| Yin et al (2015)[41] | 5 | 40 | 14 | 40 | 4.1 | 0.27 (0.08, 0.83) | 2015 |
| Chen and Wu (2015)[31] | 7 | 48 | 10 | 48 | 2.8 | 0.65 (0.22, 1.88) | 2015 |
| Chen et al (2016)[25] | 0 | 87 | 3 | 86 | 1.2 | 0.14 (0.01, 2.68) | 2016 |
| Yang et al (2014)[47] | 18 | 178 | 48 | 201 | 13.5 | 0.36 (0.20, 0.64) | 2014 |
| **Total (95% CI)** | | **1,326** | | **1,459** | **100** | **0.31 (0.25, 0.39)** | |
| Total events | 143 | | 381 | | | | |

Heterogeneity: $\chi^2$=19.55, *df*=26 (*P*=0.81); $I^2$=0%
Test for overall effect: *Z*=10.23 (*P*<0.00001)

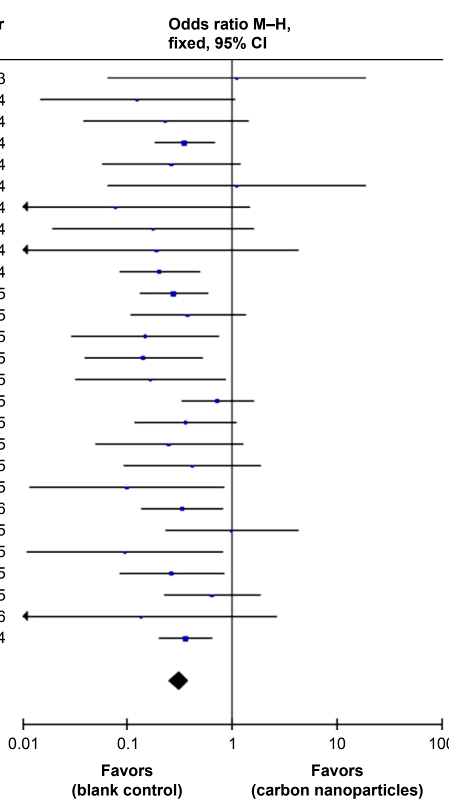



**Figure 7** (*Continued*)

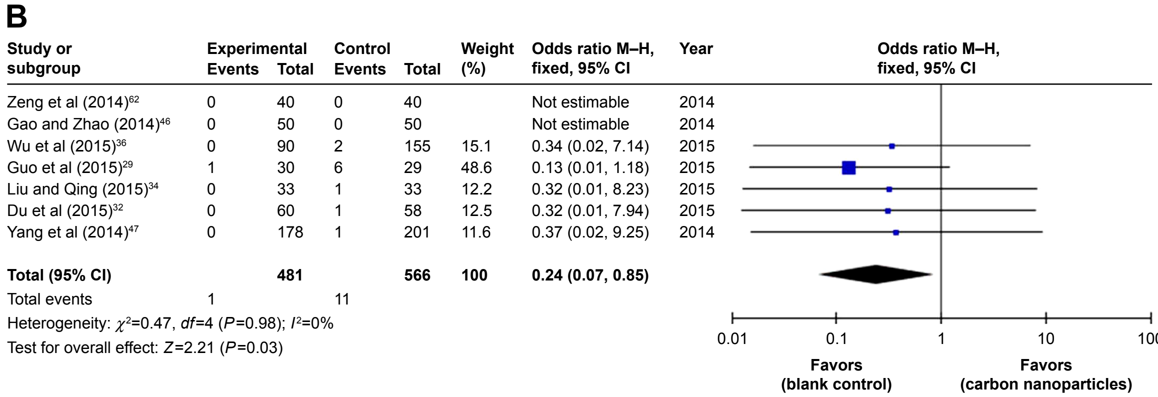



**Figure 7** (**A**) Postoperative transient and (**B**) permanent hypoparathyroidism rates in the CN and blank control groups.
**Abbreviations:** CN, carbon nanoparticle; M–H, Mantel–Haenszel; CI, confidence interval; *df*, degrees of freedom.

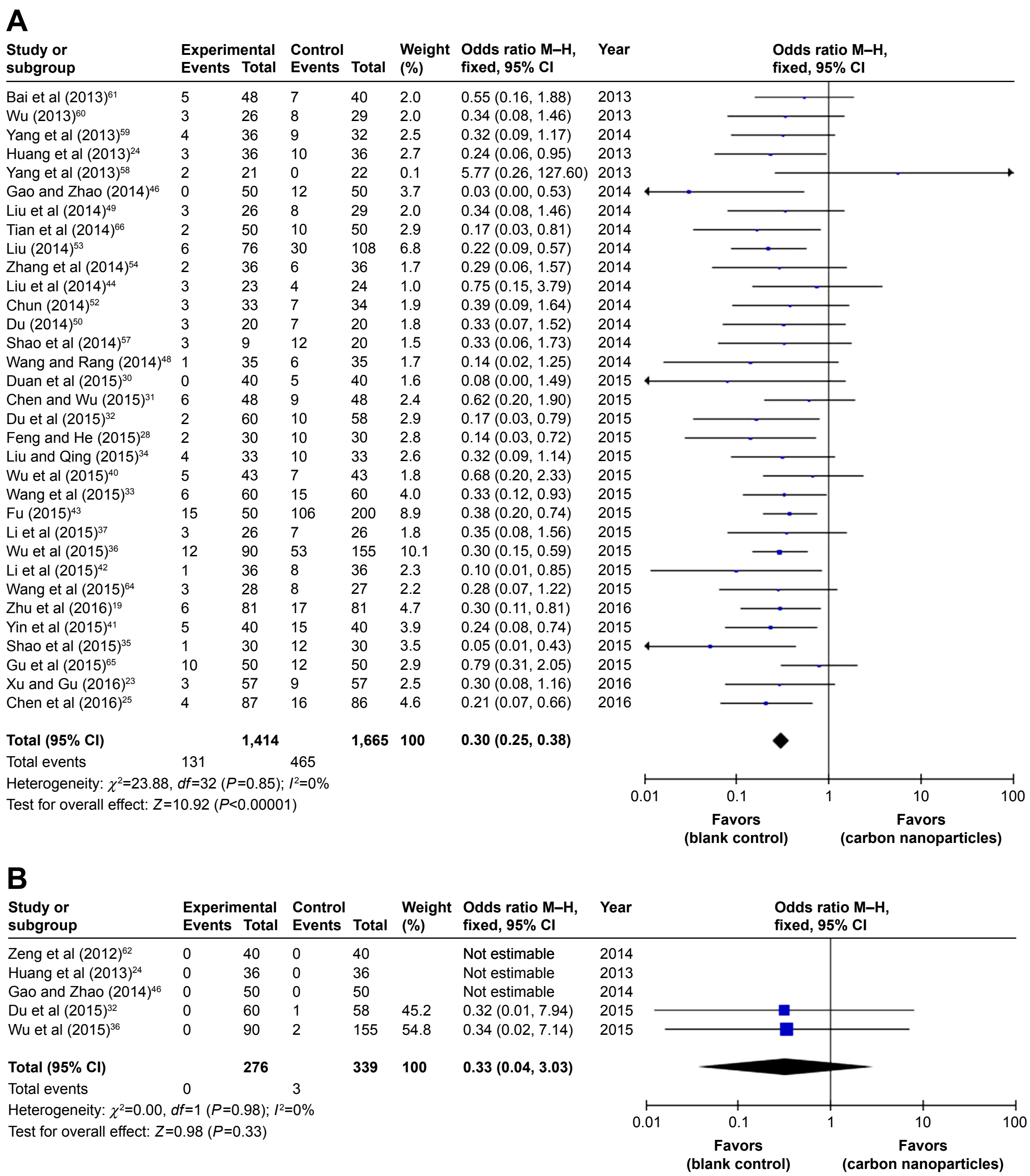



**Figure 8** (**A**) Postoperative transient and (**B**) permanent hypocalcemia rates in the CN and blank control groups.
**Abbreviations:** CN, carbon nanoparticle; M–H, Mantel–Haenszel; CI, confidence interval; *df*, degrees of freedom.

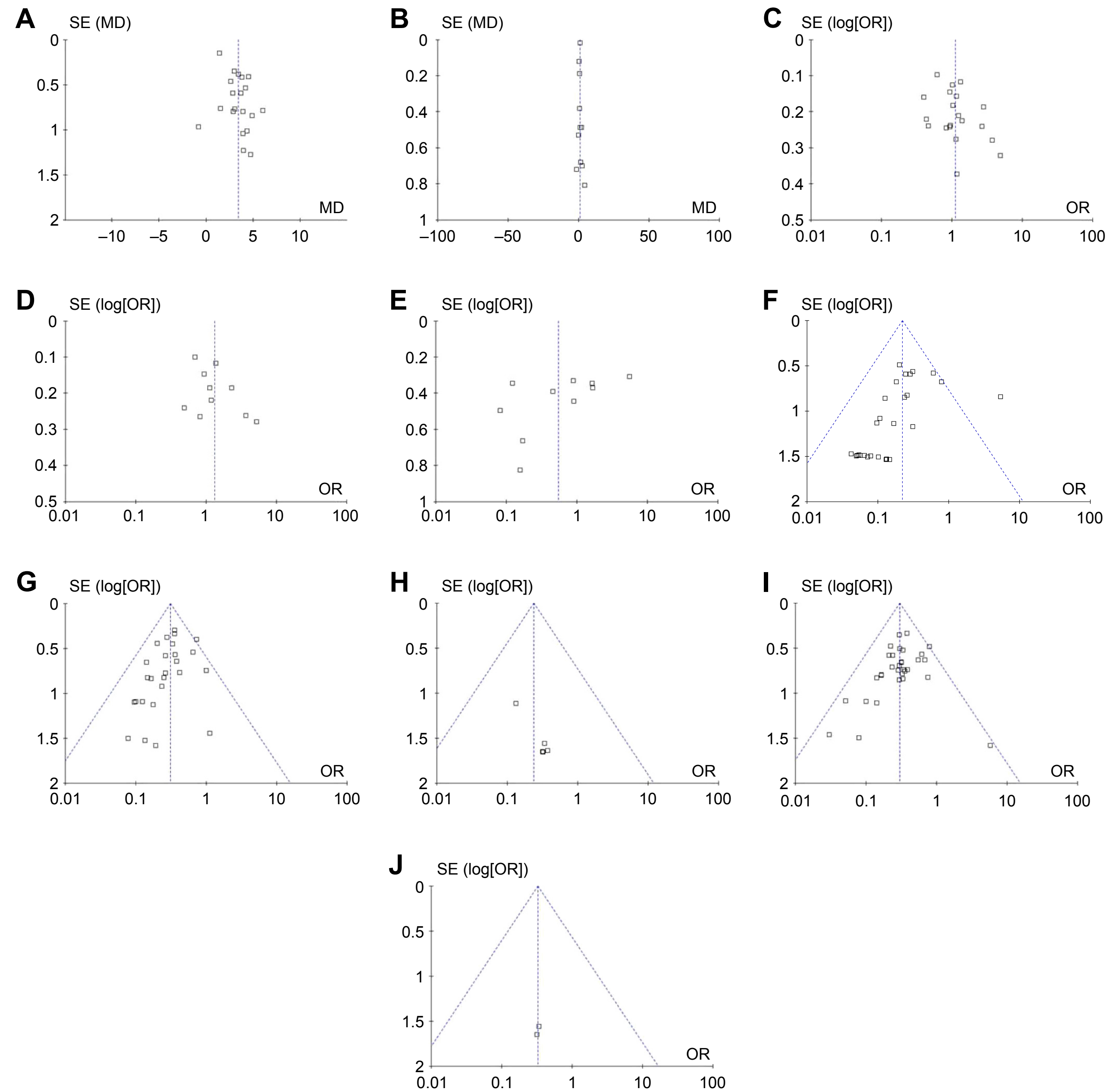



**Figure 9** Funnel plots for publication bias.

**Notes:** Publication bias for (**A**) the number of retrieved lymph nodes per patient, (**B**) number of retrieved metastatic lymph nodes per patient, (**C**) total metastatic rate of the retrieved lymph nodes, (**D**) metastatic rate of the stained lymph nodes, (**E**) metastatic rate of the unstained lymph nodes, (**F**) accidental parathyroid removal rate, (**G**) postoperative transient hypoparathyroidism rate, (**H**) postoperative permanent hypoparathyroidism rate, (**I**) postoperative transient hypocalcemia rate, and (**J**) postoperative permanent hypocalcemia rate in the CN and blank control groups. Each point represents a separate study for the indicated association.

**Abbreviations:** CN, carbon nanoparticle; SE, standard error; MD, mean difference; OR, odds ratio.

of blinding; however, it is difficult to apply double-blinding during surgery. Thus, further high-quality research is needed to verify the conclusions of the present study.

## Conclusion

This systematic review and meta-analysis demonstrated that the usage of CNs can improve the extent of neck dissection and preserve the normal anatomic structure and physiological function of the parathyroid. At the same time, the number of retrieved metastatic lymph nodes can also be improved during thyroid cancer surgery.

## Disclosure

The authors report no conflicts of interest in this work.

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