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Evaluation of the Clinical Outcome of Carbon Nanoparticles on Thyroid Cancer: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: An evaluation of the clinical outcome of thyroid cancer using carbon nanoparticles was conducted in this study.

Material and methods: PubMed, Scopus, Science Direct, ISI Web of Knowledge, and Embase were examined for all articles published in international databases. A keyword search was conducted until January 2023 based on the objectives of study. The current study was conducted based on the PRISMA 2020 checklist, and related articles were also found using Google Scholar. The fixed effect model calculated the 95% confidence interval risk ratio and mean differences. Stata/MP v.17 software was used to conduct the meta-analysis.

Results: A meta-analysis of 17 articles was conducted after reviewing the abstracts of 333 articles; 49 articles were selected for full-text review. The mean difference of lymph nodes harvested between the carbon nanoparticles and control groups was 1.31 (MD, 1.31 95% CI 1.20, 1.42; p<0.001). The odds ratio of parathyroid glands removed unintentionally between the carbon nanoparticles and control groups was -0.84 (OR, -0.84 95% CI -1.21, -0.47; p<0.001).

Conclusions: Based on the present meta-analysis, the administration of carbon nanoparticles during surgery can perform better in identifying and harvesting lymph nodes. Using carbon nanoparticles can reduce the chance of accidental parathyroid gland removal during surgery.

1. Introduction

One of the most common endocrine cancers is thyroid,[1] the fifth most common cancer in women.[2] Its incidence has increased significantly in the last two decades, and the ratio of its incidence is reported to be 1:3 male-to-female.[3] According to the available evidence, thyroid cancer generally occurs at a younger age (51 years); Studies have shown that new cases of this disease are in the age range of 45 to 64 years. The incidence rate of this cancer has been 300% globally; however, reports indicate that the death rate from this cancer has decreased or remained the same.[4] The five-year survival rate is reported as 98.1%, and in local cases, the survival rate reaches 99.9 %.[3] The origin of thyroid malignancies is from two cells (follicular epithelial cells and parafollicular C cells); there are several types of thyroid cancer, but papillary thyroid cancer is the most common.[5] The recurrence rate for this type of cancer is estimated at 25-35%, which is a relatively good prognosis. Generally, this cancer metastasizes in cervical lymph nodes.[6] Identifying and removing metastatic lymph nodes during surgery can help achieve desired results. Nanotechnology has been widely used in cancer diagnosis and management in recent years. Nanoparticles are very important due to the size of the particles because they can pass through lymphatic vessels with diameters between 120 and 500 nm and be absorbed by lymphatic nodes; however, they cannot pass through the blood vessels. For this reason, lymph nodes are colored black and are easily identified. Studies have shown that carbon nanoparticles act as carriers of various types of drugs and can be of great help in the early detection of cancer cells; Anti-inflammatory and antibacterial properties have also been reported for nanoparticles.[7-9] Based on the results of previous studies, carbon nanoparticles have been highly successful in tracking lymph nodes in endometrial, stomach, colorectal, breast, and thyroid cancer.[10-12] According to the results of the studies, carbon nanoparticles are a suitable option for identifying and protecting the parathyroid glands during thyroid surgery.[13] Although many studies have been conducted on using carbon nanoparticles in thyroid surgery, this issue is still controversial and needs more comprehensive studies. Some studies have reported that carbon nanoparticles do not have any benefit in protecting the parathyroid gland and only prolong the operation time;[14] Other studies have reported contrary results.[13] Also, studies have stated that carbon nanoparticles cannot improve long-term results after thyroid cancer surgery.[15] A study also reported that carbon nanoparticles could lead to more

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extensive lymph node dissection.[16] The differences in the findings of the studies make it doubly important to conduct a more comprehensive study. Therefore, in the present study, an attempt has been made to provide strong evidence through a comprehensive review of studies. An evaluation of the clinical outcome of thyroid cancer treatment with carbon nanoparticles was conducted in the present study.

2. Material and methods

Search strategy

The study searched all international databases using keywords related to the study objectives, including PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase, until January 2023. The current study was conducted based on the PRISMA 2020 checklist,[17] and in order to answer the research questions, we used the Google Scholar search engine and the PICO strategy (Table 1). Keywords and the MeSH terms:

((((((("Neoplasms"[Mesh]) OR ("Neoplasms/diagnosis"[Mesh] OR "Neoplasms/surgery"[Mesh] OR "Neoplasms/therapy"[Mesh])) OR ("Thyroid (USP)"[Mesh] OR "Thyroid Gland"[Mesh])) AND "Nanoparticles"[Mesh]) OR ("Nanoparticles/adverse effects"[Mesh] OR "Nanoparticles/statistics and numerical data"[Mesh] OR "Nanoparticles/therapeutic use"[Mesh])) AND "Carbon"[Mesh]) AND "Lymph Nodes"[Mesh]) AND "Parathyroid Glands"[Mesh].

Table1. PICO strategy.

PICO Strategy	Description
P	Population: Thyroid Cancer
I	Intervention: Carbon Nanoparticles
C	Comparison: methylene blue or blank control
O	Outcome: number of lymph nodes harvested and the chance of accidental removal.

The selection process, data items, and data collection

The specifications of samples of the selected studies were extracted based on a checklist that included five items: author's name, publication year, study design, sample size, and sentinel lymph nodes. Also, the data required for the meta-analysis were extracted from the findings of the studies. Records were screened independently by two reviewers, and all reports were retrieved. Inclusion and exclusion criteria were used to select all studies.

Eligibility criteria

Inclusion criteria: Only articles published in English, randomized clinical trials, prospective and retrospective studies, Sample size above 10, age above 18, and complete data.

Exclusion criteria: Review papers, case studies, and case reports. Access to full-text is not available for these studies.

Risk assessment

The quality of studies was measured using the Risk of Bias in Non-Random Studies of Interventions (ROBINS-I).[18] The categories for risk of bias judgments are "Low risk," "Moderate risk," "Serious risk," and "Critical risk" of bias. Importantly, "Low risk" corresponds to the risk of bias in a high-quality randomized trial. The response options are: "Yes,"; "Probably yes,"; "Probably no,"; "No,"; and "No information". Responses of "Yes" are intended to have similar implications to responses of "Probably yes" (and similarly for "No" and "Probably no").

Cochrane Collaboration's tool evaluated the quality of randomized controlled clinical trials.[19] The scores of this tool are between 0 and 6, and a higher score shows the higher quality of the study; the scoring of each item is 1 for low risk and 0 for high and unclear risk.

Data analysis

Potential heterogeneity between studies was reported with the I^2 coefficient; low heterogeneity is indicated by values less than 50%, moderate heterogeneity by values between 50% and 75%, and high heterogeneity by values above 75%. Inverse-variance method and fixed-effect model were used to calculate the 95% confidence intervals for mean differences as well as odds ratios with a fixed-effect model and Mantel-Haenszel. The meta-analysis was performed using STATA/MP. V17.

3. Results

Study selection

In the initial search using keywords, 358 articles were found, and all references were entered into EndNote X8 software. Among these articles, 15 articles were duplicated, 5 articles were removed due to records marked as ineligible by automation tools, and 5 articles were removed for other reasons. Finally, the abstracts of 333 articles were reviewed, and 284 articles that did not meet the inclusion criteria were removed at this stage. Two blinded observers fully reviewed the full text of 49 articles. Incomplete articles without data and inconsistency with the objectives of the study were excluded (32 articles), and finally, 17 articles were selected (Fig. 1).

Study characteristics

Six randomized control studies, nine retrospective, and two prospective studies were selected and included in the present meta-analysis. A total of 2827 patients (Experimental: 1169; control: 1658); the mean ages of the experimental and control groups were 42.2 years and 37.12 years, respectively. Table 2 shows a summary of the data extracted.

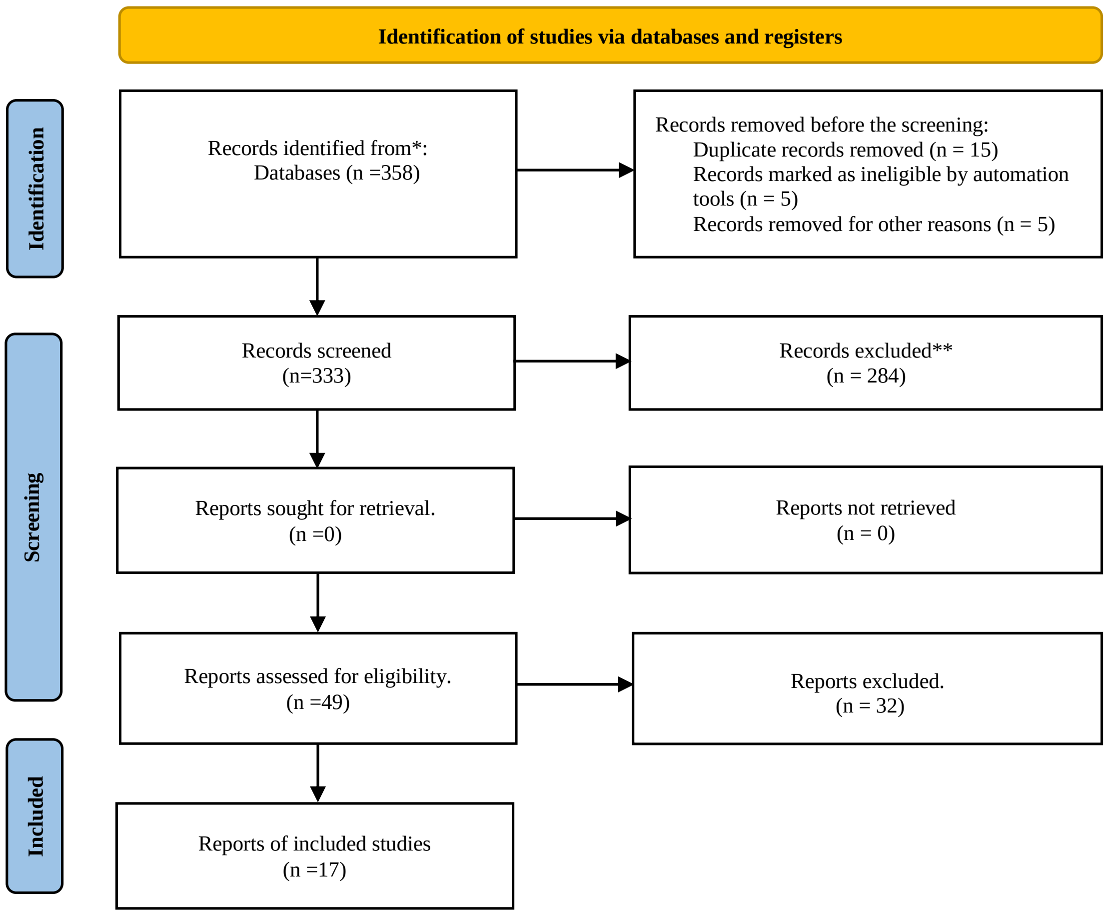

Fig. 1. PRISMA 2020 Checklist.

Table 2. Demographic information was extracted from the full text of the selected studies.

No	Study. Years	Study Design	Number of Patients		Mean of Age	
			Carbon	Control	Carbon	Control
1	Tao et al., 2023[20]	RCT	18	18	52.5	50.5
2	Chen et al., 2022[21]	Retrospective	234	31	56.7	53
3	Ouyang et al., 2021[22]	Retrospective	64	50	34.7	37.2
4	Li et al., 2021[23]	Retrospective	96	98	42.5	43.8
5	Chen et al., 2021[24]	RCT	103	88	48.5	45.4
6	Rao et al., 2021[25]	RCT	50	58	46.8	44
7	He et al., 2021[26]	Retrospective	54	72	34.7	35
8	Ma et al., 2020[27]	RCT	51	42	31	30
9	Liu et al., 2020[13]	Retrospective	334	52	44	46.6
10	Min et al., 2020[28]	Retrospective	120	86	45	39.6
11	Xu et al., 2020[29]	Retrospective	38	34	30	32
12	Zhang et al., 2020[30]	RCT	152	150	33	34

13	Liu et al., 2018[31]	Prospective	45	47	46	45
14	Xu et al., 2017[32]	RCT	57	57	42	45
15	Shi et al., 2016[33]	Retrospective	52	45	45	42
16	Wang et al.,2016[34]	Prospective	90	141	44	44
17	Hao et al., 2012[35]	Retrospective	100	100	41	44

Risk assessment

The Cochrane Collaboration's tool identified six randomized clinical trials with a low risk of bias (high quality). According to the ROBINS-I tool, the risk of bias for eight studies was low, while the risk of bias for three of the studies was middle (Tables 3 and 4).

Lymph nodes harvested

The mean differences of lymph nodes harvested between the carbon nanoparticles group and control group were 1.31 (MD, 1.31 95% CI 1.20, 1.42; $p<0.001$) with high heterogeneity ($I^2=75.35\%$; P =0.00) (Fig. 2). There was a significant difference between the carbon nanoparticles group and the control group regarding lymph nodes harvested (p=0.00). This significant difference favored the carbon nanoparticles group, indicating the intervention's effectiveness.

Metastatic lymph nodes harvested

The odds ratio of metastatic lymph nodes harvested between the carbon nanoparticles group and control group was 0.13 (OR, 0.13 95% CI 0.03, 0.24; $p<0.001$) with high heterogeneity ($I^2=70.19\%$; P =0.00) (Fig. 3). There was a significant difference between the carbon nanoparticles group and the control group in terms of metastatic lymph nodes harvested (p=0.01). This significant difference favored the carbon nanoparticles group, indicating the intervention's effectiveness.

Table 3. Risk of bias assessment (Cochrane Collaboration's tool).

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome data	Selective Reporting	Total Score
Tao et al., 2023[20]	+	+	?	+	+	+	5
Chen et al., 2021[24]	+	+	?	+	+	+	5
Rao et al., 2021[25]	+	+	?	+	+	+	5
Ma et al., 2020[27]	+	+	?	+	+	+	5
Zhang et al., 2020[30]	+	+	?	+	+	+	5
Xu et al., 2017[32]	+	+	?	+	+	+	5

(Low (+), unclear (?), high (-)).

Table 4. Bias assessment (ROBINS-I).

Study. Years	Bias due to Confounding	Bias in the Selection of Participants Into the Study	Bias in Classification of Interventions	Bias due to Deviations from Intended Interventions	Bias due to Missing data	Bias in Measurement of Outcomes	Bias in the Selection of the Reported result	Overall
Chen et al., 2022[21]	Low	Low	Low	Low	Low	Low	Low	Low
Ouyang et al., 2021[22]	Low	Low	Low	Low	Low	Low	Low	Low
Li et al., 2021[23]	Low	Low	Low	Low	Low	Low	Low	Low
He et al., 2021[26]	Low	Low	Low	Low	Low	Low	Low	Low
Liu et al., 2020[13]	Low	Low	Low	Low	Low	Low	Low	Low
Min et al., 2020[28]	Low	Low	Low	Low	Low	Middle	Low	Middle
Xu et al., 2020[29]	Low	Low	Low	Low	Low	Low	Middle	Middle
Liu et al., 2018[31]	Low	Low	Low	Low	Low	Low	Low	Low
Shi et al., 2016[33]	Low	Low	Low	Low	Low	Middle	Low	Middle
Wang et al.,2016[34]	Low	Low	Low	Low	Low	Low	Low	Low
Hao et al., 2012[35]	Low	Low	Low	Low	Low	Low	Low	Low

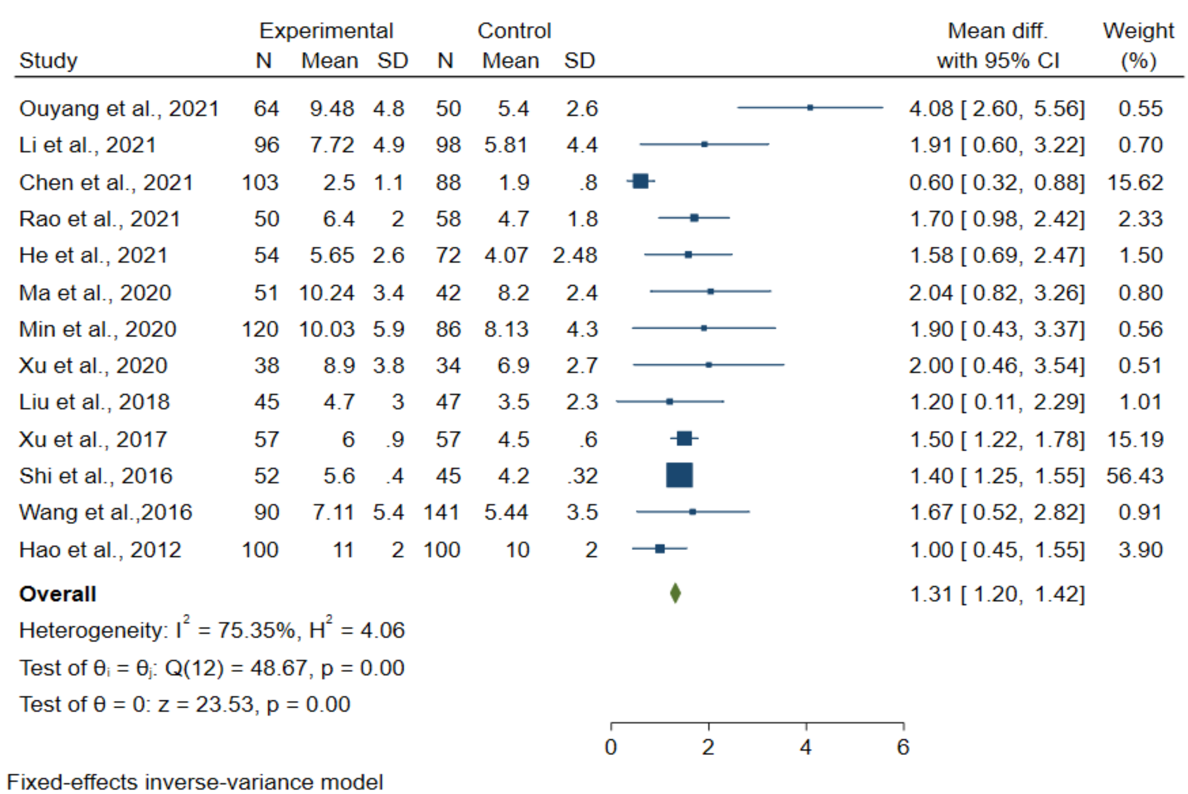

Fig. 2. The forest plot showed mean differences in lymph nodes harvested between the two groups.

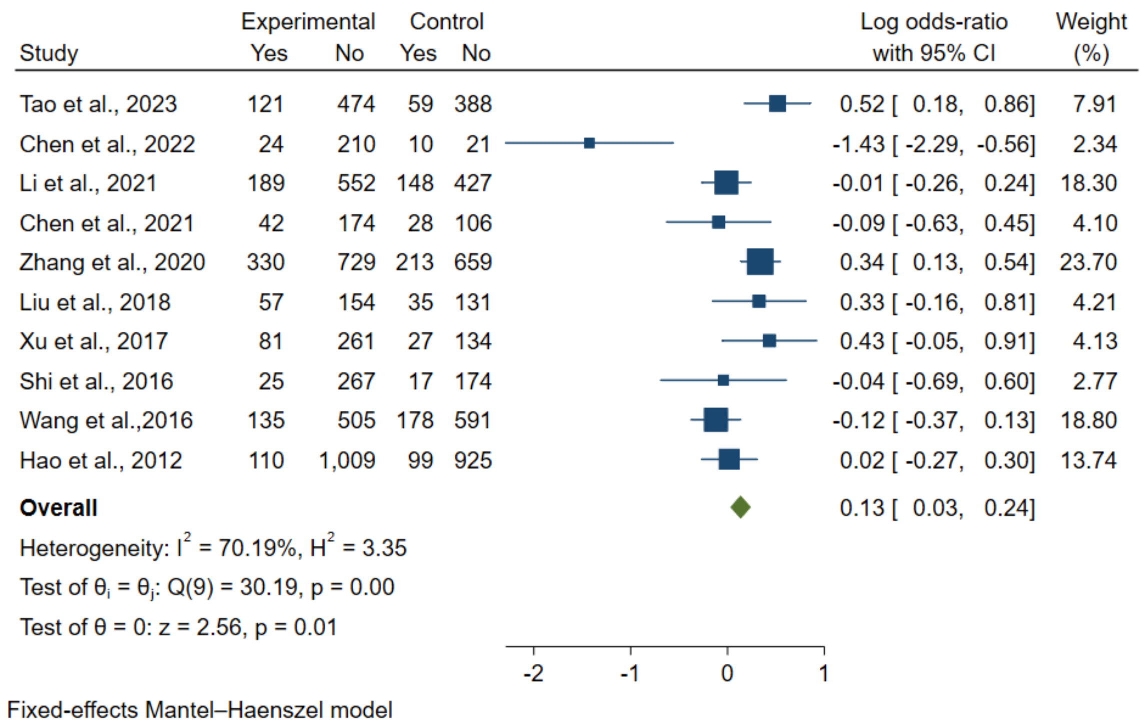

Fig. 3. The forest plot showed an odds ratio of metastatic lymph nodes harvested between the two groups.

Unintentional parathyroid gland removal

The odds ratio of parathyroid glands removed unintentionally between the carbon nanoparticles group and control group was -0.84 (OR, -0.84 95% CI -1.21, -0.47; p<0.001) with low heterogeneity (I^2=20.90%; P =0.26) (Fig. 4). There was a significant difference between the carbon nanoparticles group and the control group in terms of Parathyroid glands removed unintentionally (p=0.00). Administration of carbon nanoparticles can reduce Parathyroid glands removed unintentionally by 84%.

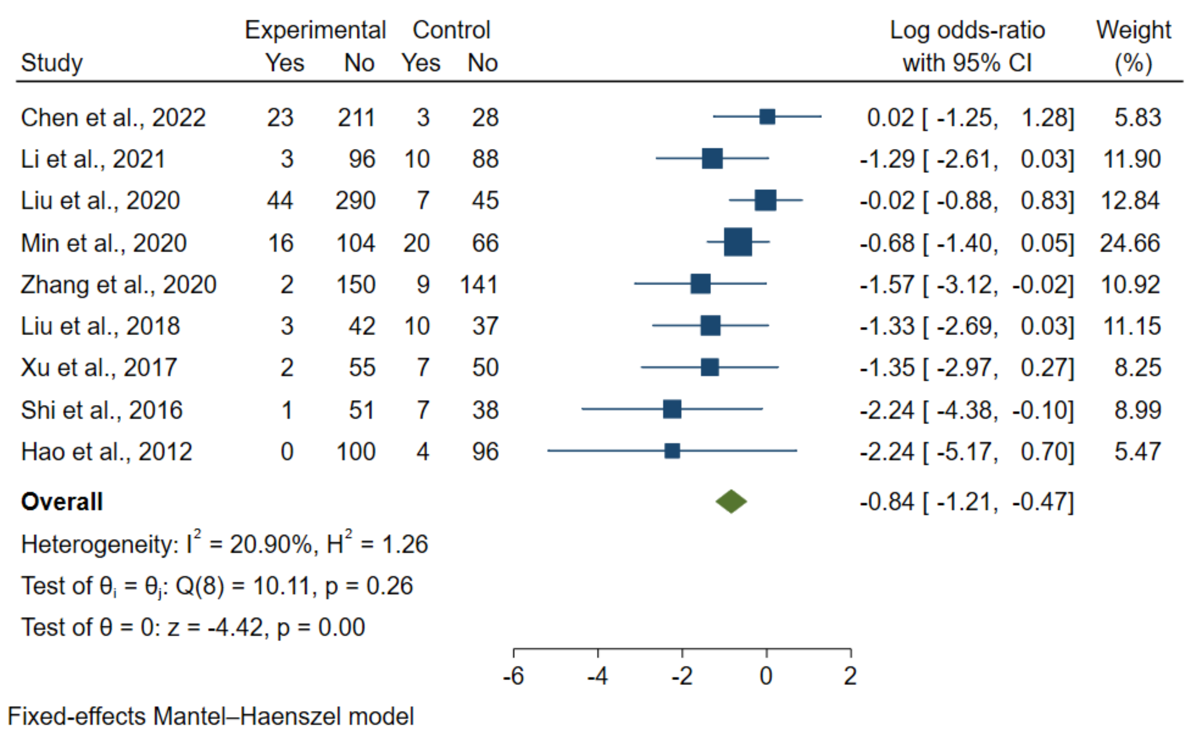

Fig. 4. The forest plot showed an odds ratio of Parathyroid glands removed unintentionally.

Galbraith plots give information about the study-specific effect sizes, their precisions, and the overall effect size, detecting potential outliers and assessing heterogeneity among the effect sizes (Fig. 5).

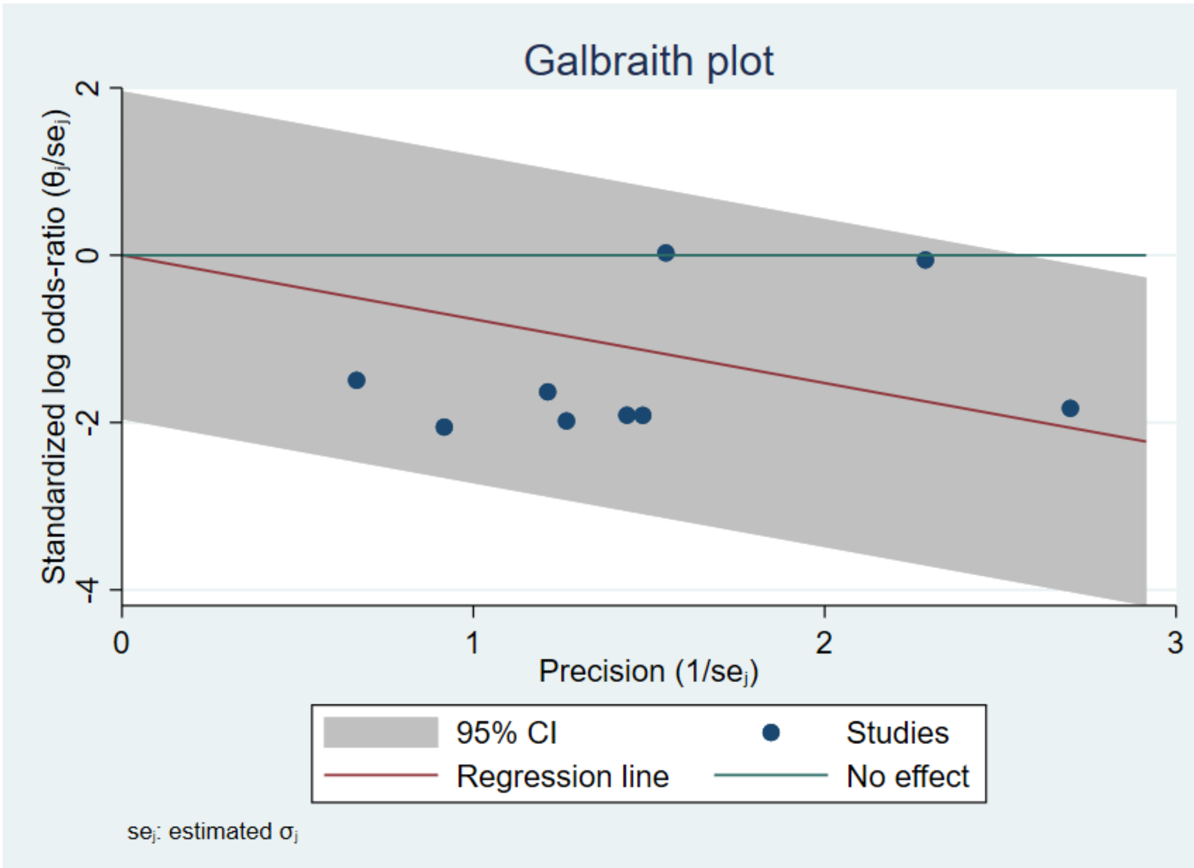

Fig. 5. Galbraith plot.

4. Discussion

The most basic treatment for papillary thyroid carcinoma is tumor removal and lymph node dissection.[35] The complications of thyroid surgery are very important. The most common are hypoparathyroidism and hypocalcemia, which have been reported in studies of the incidence rates for temporary hypoparathyroidism and permanent hypoparathyroidism to be 1.6% to 4.11%, respectively.[36] The cause of complications can be because the accidental removal of the glands occurs during thyroid surgery, caused by the anatomy of the parathyroid glands.[37] Identifying the location of these glands before surgery helps to preserve them during surgery. The use of new techniques can be of great help in this regard; The use of carbon nanoparticles has recently been introduced to facilitate the dissection of lymph nodes and identification of the parathyroid gland.[16] So far, no toxic side effects have been reported for carbon nanoparticles.[38] In the present study, lymph nodes harvested and metastatic lymph nodes harvested have been compared between two groups of carbon nanoparticles and the control group; In the search, 17 articles were found related to the topic of the present study. Meta-analysis showed a statistically significant difference between lymph nodes harvested and metastatic lymph nodes harvested between two groups of carbon nanoparticles and the control group. The carbon nanoparticles group performed better than the control group. The findings of the present study show that using carbon nanoparticles plays an important role in tracking lymph nodes and is effective in better identification of metastatic lymph nodes. However, due to the high heterogeneity between studies, the results of the present study should be interpreted with caution. This heterogeneity can be due to the difference in the cognitive methodology of the studies. It has been shown in a study that carbon nanoparticles do not have tumor tropism and can stain normal and pathological lymph nodes at the same time.[39] According to the meta-analysis, the chance of accidental parathyroid gland removal in the carbon nanoparticle group is 84% lower than in the control group. A study examining the staining of lymph nodes between two groups of carbon nanoparticles and methylene blue showed that carbon nanoparticles work better.[34] The current study had limitations; few RCT studies were found, the rest were retrospective cohort studies, and only two were prospective. More RCT studies need to be conducted; also, all studies were conducted in China, and similar studies need to be conducted in other countries to provide stronger evidence because different results may be observed in other countries. Another limitation of the current study was the high heterogeneity between studies, and studies with similar cognitive methods should be conducted in the future. However, the present meta-analysis provides good evidence. The long-term results of using carbon nanoparticles should also be discussed; more studies should be done to confirm the current evidence.

5. Conclusion

Based on the present meta-analysis, administration of carbon nanoparticles during surgery can perform better in identifying and harvesting lymph nodes and identifying and harvesting metastatic lymph nodes harvested compared to the control group. Also, using carbon nanoparticles can reduce the chance of accidental parathyroid gland removal during surgery.

Conflict of Interest

The authors declared that there is no conflict of interest.

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