



# Carbon nanoparticles beneficial for prophylactic central compartment lymph node dissection in cN0 papillary thyroid carcinoma

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## ABSTRACT

**Objective:** This study explored prophylactic central compartment lymph node dissection (pCCLND) for patients with cN0 papillary thyroid carcinoma (PTC) and the effect of carbon nanoparticles (CNP) on surgical outcomes.

**Methods:** This retrospective study reviewed PTC cases treated at our tertiary medical institution between January 2019 and December 2022. Only patients with indications for total thyroidectomy and cN0 disease were included. CNP has been associated with a higher number of harvested lymph nodes and a lower rate of accidental parathyroid gland (PTG) removal. Patients who used CNP in this study were classified as group 1, while those who denied its use were classified as group 2.

**Results:** In total, 116 cases were included, with 80 patients in group 1 and 36 in group 2. Most patients were in stage T1, with 68 (85.0 %) patients in group 1 and 31 (86.1 %) in group 2. Postoperative hoarseness occurred in 3 (3.8 %) patients in group 1 and 1 (2.8 %) in group 2, which recovered within two months. In group 2, 250 nodes were harvested, 72 (28.8 %) of which were metastatic; in group 1, 889 nodes were harvested, 316 (35.5 %) of which were metastatic; the difference regarding the rates of metastatic lymph nodes between the 2 groups was statistically significant ( $P = 0.047$ ). Differences in postoperative blood calcium and parathyroid hormone levels between the two groups were statistically significant ( $P = 0.035$  and  $P = 0.034$ , respectively). There were symptoms of hypocalcemia in 6 (16.7 %) patients in group 2 but in only 2 (2.5 %) in group 1, all of which recovered within three months; the difference was statistically significant ( $p = 0.017$ ).

**Conclusion:** pCCLND is worth undertaking for cN0 PTC. CNP is beneficial for achieving more thorough dissection and reducing temporary hypoparathyroidism.

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## 1. Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma, and a significant rise in the frequency of PTC diagnosis has been observed, which is mainly attributed to the more frequent and widespread use of imaging techniques for the head and neck region, with the unanticipated discovery of these incidental cancers [1]. Currently, total thyroidectomy (TT) is the most efficient procedure for treating thyroid cancers [2,3]. In addition, TT with central compartment lymph node dissection (CCLND) could decrease locoregional recurrence (LRR) in patients with PTC [4,5].

However, according to the literature, this approach has numerous adverse effects, including temporary and permanent hypoparathyroidism and temporary recurrent laryngeal nerve (RLN) injury [5,6]. Carbon nanoparticles (CNP) have been introduced in recent years, which are associated with a higher number of harvested lymph nodes and a lower rate of accidental parathyroid gland (PTG) removal [7–9]. Hence, CNP has been suggested in thyroid cancer surgery on a broader scale [7].

However, the role of prophylactic CCLND (pCCLND) is still uncertain in patients with cN0 PTC [10,11]. In light of this, our department has applied CNP in thyroid surgeries, especially in patients with cN0 PTC. Based on our findings, CNP is significantly beneficial in achieving more thorough dissection and reducing temporary hypoparathyroidism in pCCLND without increasing RLN injury, as reported here.

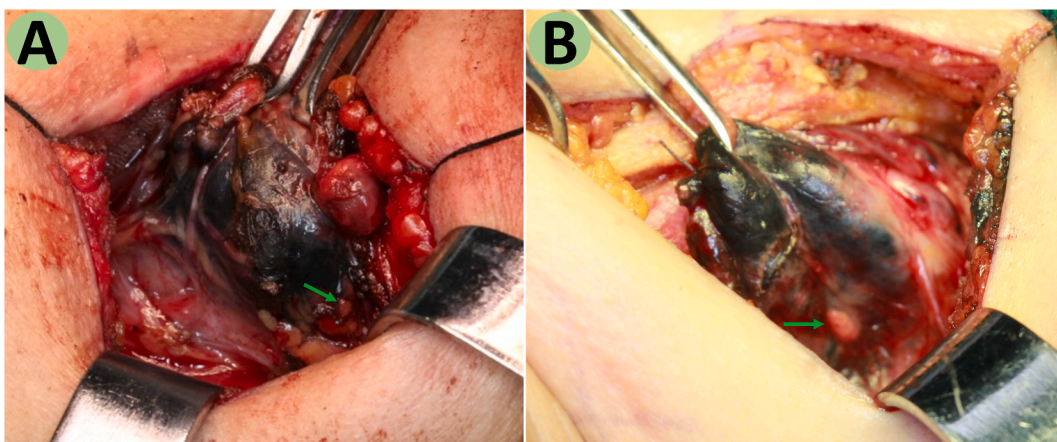
## 2. Materials and methods

We conducted a retrospective review of PTC cases treated at our tertiary medical institution between January 2019 and December 2022. The clinical and demographic data were retrieved from case notes. The protocol of the research project was approved by the institutional review board, and it conformed to the provisions of the Declaration of Helsinki. A written consent form was obtained from the patients.

The CNP (carbon nanoparticle suspension injection) is manufactured by Chongqing Lummy Pharmaceutical Co, Ltd (Chongqing, China). The diameter of the gaps between capillary endothelial cells is 20–50 nm, while that of the lymphatic ducts is 120–500 nm. Since the average diameter of CNP is 150 nm, CNP can enter lymphatic ducts through the gaps between lymphatic endothelial cells but cannot penetrate capillaries. After CNP is injected into tissues, it can be recognized as a foreign body by macrophages and phagocytized. When such macrophages enter lymph nodes, they are stained black [12]. Hence, when CNP is injected into the thyroid gland, the gland itself and its draining lymph nodes are stained black, but not PTGs, because they do not share a lymphatic network with the thyroid gland. This difference makes PTGs easily identified, which can be referred to as “negative development” [13].

### 2.1. Inclusion criteria

Only patients with indications for TT and cN0 disease were included in this study. And for cN0 patients, according to the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, TT was indicated in the following conditions: the primary tumor (pathologically diagnosed by preoperative fine needle aspiration or intraoperative frozen section) was  $\geq 1.0$  cm in diameter; there is an extra-thyroidal extension (ETE) of the tumor; indeterminate nodules that are cytologically suspicious for malignancy, positive for known mutations specific for carcinoma, sonographically suspicious, or large ( $>4$  cm), or in patients with familial thyroid carcinoma or history of radiation exposure, or bilateral nodular disease, or those with significant medical comorbidities, or those who prefer to undergo bilateral thyroidectomy to avoid the possibility of requiring a future surgery on the contralateral lobe [3,11].



**Fig. 1.** The negative development of parathyroid gland (PTG) by carbon nanoparticles (CNP). **A.** Approximately 10 min after injection of CNP into thyroid tissue, the thyroid gland and its draining lymphatic system would be stained black, but not PTGs, making PTGs easily identifiable (green arrow). **B.** The negative development of PTG in another case (green arrow).

## 2.2. Grouping

Since CNP is a relatively expensive agent and is not covered by medical insurance yet, grouping was based on patients' choice and ability to use CNP intraoperatively. All the included patients were informed of the benefits of using CNP intraoperatively during preoperative consultation. Patients who decided to use CNP were classified as group 1, while those who did not accept it were classified as group 2.

## 2.3. Surgical procedure

Experienced surgeons performed the surgical procedures in all the patients under  $\times 2.5$  loupe magnification, following the same protocol. After a cervical Kocher incision and elevating subplatysmal flaps, strap muscles were divided along the midline and retracted laterally. In group 1 patients, CNP would be injected into the exposed thyroid gland at multiple sites (especially near the superior and inferior poles, 0.1 mL per site). Several minutes later, the thyroid gland and its draining central compartment lymph nodes would be blackened, without blackening PTGs, making them more easily identifiable [Fig. 1(A and B)]. This step was not performed in patients in group 2. Further procedures from this step on were the same, and RLN monitoring was routinely performed. After identifying the external branch of the superior laryngeal nerve, superior thyroid vessels were ligated and divided, and superior PTGs were identified and preserved in situ. Then, meticulous capsular dissection was performed, RLNs were identified and preserved, and en bloc thyroid gland resection was achieved. Then, pCCLND was performed bilaterally: RLNs were mobilized along their whole course, and dissection was carried out extending superiorly to the hyoid bone, inferiorly to the innominate artery, laterally to the carotid sheaths, and dorsally to the prevertebral fascia. When inferior PTGs could not be identified and preserved in situ, dissection specimens were examined carefully to find them, and auto-transplantation into muscles was performed [14]. Blackened lymph nodes were conspicuous and could be harvested during dissection, some of which might have been left out if they were not stained black.

Blood calcium and parathyroid hormone (PTH) levels were examined on the first postoperative day, and hoarseness and numbness or spasms of extremities were documented.

Radioactive iodine (RAI) treatment would be recommended to patients with the American Thyroid Association (ATA) intermediate to high-risk group [11].

## 2.4. Follow-up

Patients were followed up every month after surgery for the first three months to observe postoperative complications and evaluate serum levels of calcium, thyroid hormone PTH, and thyroglobulin. Then, patients were followed up every three months for two years and then every six months for five years.

## 2.5. Statistical analysis

All statistical analyses were performed using SPSS 26.0 (IBM Corp, Armonk, NY) and GraphPad Prism 9.0 (GraphPad Software, Inc). The chi-squared test, Fisher's exact test, and continuity (Yates) correction were used to compare qualitative data. The two-tailed Student's t-test was used to compare differences in continuous variables at a significance threshold of  $P < 0.05$ .

## 3. Results

In total, 116 cases were included, with 80 patients in group 1 and 36 in group 2. There were 57 (71.2 %) female patients in group 1 and 25 (69.4 %) in group 2. The age range in group 1 was 19–80 (average and median ages were 47.1 and 48.5, respectively), with 28–74 in group 2 (average and median ages were 47.4 and 45.0, respectively). The majority of patients were in the T1 stage of the disease, with 68 (85.0 %) in group 1 and 31 (86.1 %) in group 2. The differences in these characteristics between the two groups were not significant (Table 1); therefore, the two groups were comparable.

Surgical procedures in all the patients were uneventful (intraoperative RLN monitoring showed good response for all RLNs). However, hoarseness occurred in three (3.8 %) patients in group 1 and one (2.8 %) patient in group 2, all of which resolved (confirmed

**Table 1**  
Clinical characteristics of patients in this series.

Patient characteristics	Group 1	Group 2	Statistical difference
Total No. of patients	80	36	–
Female sex (%)	57 (71.2 %)	25 (69.4 %)	$p = 0.843$
Male sex (%)	23 (28.8 %)	11 (30.6 %)	
Age range (average, median, y/o)	19-80 (47.1, 48.5)	28-74 (47.4, 45.0)	–
T Stage			
T1 (%)	68(85.0 %)	31(86.1 %)	$p = 0.876$
T2 (%)	7(8.7 %)	4(11.1 %)	$p = 0.953$
T3-T4 (%)	5(6.3 %)	1(2.8 %)	$p = 0.743$

No.: number; y/o: years old; -: not applicable.

by fiberoptic laryngoscope at the onset of symptoms and follow-up sessions) within two months after surgery. The difference between the two groups was not significant.

In group 2 patients, 250 lymph nodes were dissected from the central compartment, 72 (28.8 %) of which were metastatic on the pathologic report. Concerning group 1 patients, 889 lymph nodes were harvested with the help of CNP, 316 (35.5 %) of which were pathologically confirmed as metastatic (Table 2). The difference regarding rates of metastatic lymph nodes between the two groups was statistically significant ( $P = 0.047$ ). Hence, pCCLND was worthy of undertaking for cN0 PTC since 28.8 % of harvested lymph nodes were pathologically confirmed as metastatic. Moreover, CNP was beneficial in this procedure, as significantly more metastatic lymph nodes (35.5 %) could be harvested, and the central compartment dissection could be considered more thorough.

Differences in preoperative blood calcium and PTH levels between the two groups were not significant (Table 2). However, the differences in postoperative serum calcium and PTH levels between the two groups were significant ( $P = 0.035$  and  $P = 0.034$ , respectively). Concerning the clinical symptoms of hypocalcemia or hypoparathyroidism, including numbness or spasm of extremities, only 2 (2.5 %) patients in group 1 exhibited such symptoms, compared with 6 (16.7 %) in group 2, and the difference between the two groups was significant ( $P = 0.017$ ). All these patients received oral calcitriol and calcium carbonate tablets, and hypoparathyroidism was relieved within three months of follow-up (confirmed by serum PTH levels). Hence, CNP was beneficial for reducing postoperative hypocalcemia and hypoparathyroidism because PTGs were more easily identified and could be better preserved in situ or more easily retrieved from dissection specimens for auto-transplantation.

#### 4. Discussion

In this series of patients, only temporary hypoparathyroidism and vocal cord paralysis were documented, without any permanent occurrence, which could be attributed to the fact that experienced senior surgeons performed all the procedures. Moreover, pCCLND could be considered for patients with cN0 PTC, especially with the help of CNP, as this procedure could be considered relatively safe [15], and more than a quarter of lymph nodes harvested from the central compartment were metastatic. In fact, central compartment lymph node metastases (CCLNM) are common (20 %–90 %) and are related to a poor prognosis (including recurrence, distant metastases, reduced survival, and higher morbidity), even for patients with cN0 micro-PTC, despite negative preoperative imaging evaluation [15]. Unfortunately, the sensitivity of both ultrasound and CT imaging for CCLNM is reported to be 42–47 % [16]; therefore, more than half of patients might only present cN0, but they are not.

A more thorough dissection of the central compartment could lead to RAI treatment for more patients in need, which would otherwise not be administered for not meeting ATA intermediate risk criteria (>5 pathologic N1) [11], and this could potentially result in a better prognosis of such patients. So far, male sex, low age, sub-capsular carcinoma localization, multifocality, and ETE have been reported as independent predictive factors for CCLNM in pT1a PTC [15,17]. Hence, pCCLND should be considered at least for patients with cN0 PTC. In addition, when CCLNM did occur after TT without CCLND, revision CCLND can be a challenging procedure with increased complication rates [18].

A significantly higher rate of metastatic lymph nodes harvest could be achieved with the help of CNP (35.5 % Vs 28.8 %,  $p = 0.047$ ), which could be associated with less chance of recurrence in the central neck. Furthermore, CNP could not only facilitate achieving more thorough dissection, but also help in reducing hypocalcemia and hypoparathyroidism, which was consistent with the literature [9]. The median incidence of temporary and permanent hypocalcemia after TT was reported to be 27 % (19–38 %) and 1 % (0–3%), respectively, by a meta-analysis of 115 studies [19]. Additionally, the position of inferior PTGs could be quite variable, and it is often difficult to distinguish them from lymph nodes, adipose tissue, and PTGs in the surgical field of CCLND. Furthermore, blood vessels supplying PTGs are small and fragile and vulnerable to surgical manipulation, possibly causing ischemia or even necrosis of PTGs [9]. It is our assumption that although CNP would cost a little more than \$ 200, its potential benefit could compensate.

Indeed, both ipsilateral and bilateral pCCLND after TT were reported to be associated with a higher rate of transient hypoparathyroidism (36.1 % and 51.9 %, respectively) in a series of 1087 patients [20]. Hence, the findings in group 2 after TT and pCCLND (16.7 % and 0 % of temporary and permanent hypocalcemia, respectively) indicated that our surgical techniques were adequate. Moreover, CNP further reduced temporary hypocalcemia to as low as 2.5 % in group 1, which could be considered significant. It was our assumption that when PTGs were more easily identified, their vasculature could be preserved better, and hence led to better

**Table 2**

Effect of carbon nanoparticle in total thyroidectomy with prophylactic central compartment lymph node dissection.

	No. of Patients	No. of dissected lymph nodes	No. of metastatic lymph nodes (%)	Pre-op. blood calcium (mmol/L)	Post-op. blood calcium (mmol/L)	Pre-op. blood PTH (pg/ml)	Post-op. blood PTH (pg/ml)	No. of patients with symptoms of post-op. hypocalcemia (%)	No. of patients with temporary vocal cord paralysis (%)
Group 1	80	889	316 (35.5 %)	2.35 ± 0.54	2.17 ± 0.19	47.68 ± 12.35	20.76 ± 5.73	2(2.5 %)	3 (3.8 %)
Group 2	36	250	72 (28.8 %)	2.33 ± 0.37	2.07 ± 0.31	47.34 ± 13.96	18.34 ± 5.31	6 (16.7 %)	1 (2.8 %)
SD	–	–	$p = 0.047^*$	$p = 0.841$	$p = 0.035$	$p = 0.896$	$p = 0.034$	$p = 0.017$	$p = 1.000$

No.: number; op.: operative; PTH: parathyroid hormone; SD: Statistical difference; -: not applicable; \*: comparison was made regarding the rates of metastatic lymph node between the 2 groups.

preservation of PTG function. Since numbness or spasms of extremities were actually quite painful, avoiding such symptoms could surely give patients a better experience. In addition, every effort must be made to avoid permanent hypoparathyroidism due to the potential negative aspects of prolonged administration of calcium and vitamin D (calcification of extra-skeletal soft tissues, basal ganglia, and kidney when higher doses were required) and the unavailability of a replacement hormone [21]. Furthermore, comorbidities (e.g. renal/cardiovascular diseases) associated with permanent hypoparathyroidism played a key role in hospitalizations and deaths [22].

One limitation of this study was that long-term outcomes, especially LRR, regional or distant metastasis, and mortality, could not be evaluated since CNP is a recent treatment option. Another limitation of this study was that the number of included patients was relatively small, necessitating further validation by future studies. Criteria for grouping is another great limitation in this study. Notably, all included patients agreed to TT and pCCLND. Based on recent development of the technique of intraoperative CNP usage, we tried to explore whether such patients would benefit from it. The results could be more easily interpreted and convincing if such patients were randomly grouped. In contrast, the approach adopted herein was more considerate for patients' economic concern (not significant enough to mean social status difference, or otherwise biased). All included patients complied well to their treatment and the only comparing factor was the choice of CNP usage, which was the essence of a controlled study. As such, we believe that the conclusion of this study was well founded, statistically sound, and might contribute to the literature.

## 5. Conclusion

Since more than a quarter of lymph nodes harvested from the central compartment were metastatic in patients with cN0 PTC, pCCLND is worth undertaking and might not increase surgical complications in the hands of experienced senior surgeons. Additionally, CNP was beneficial in achieving more thorough dissection (harvesting significantly more lymph nodes, which were stained black) and reducing temporary hypoparathyroidism (PTGs more easily identifiable, which could not be stained black) for patients undergoing TT with pCCLND.

## Ethics statement

This study was reviewed and approved by Bioethics Committee of Beijing Friendship Hospital, Capital Medical University, with the approval number: [2022-P2-411-01]. All participants/patients (or their proxies/legal guardians) provided informed consent to participate in the study. All participants/patients (or their proxies/legal guardians) provided informed consent for the publication of their anonymised case details and images.

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## Availability of data and materials

Data associated with this study has not been deposited into a publicly available repository. However, data will be made available on request.

## CRedit authorship contribution statement

**Ya-Qing Ren:** Writing - original draft, Resources, Investigation, Formal analysis, Data curation. **Kai-Xuan He:** Writing - original draft, Investigation, Formal analysis, Data curation. **Yan-Bo Dong:** Writing - original draft, Software, Resources, Project administration, Methodology, Funding acquisition. **Yu-He Liu:** Writing - review & editing, Supervision, Methodology, Funding acquisition. **Cheng Lu:** Writing - review & editing, Validation, Supervision, Methodology. **Wan-Xin Li:** Writing - review & editing, Writing - original draft, Validation, Supervision, Project administration, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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