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Predictors of impaired effectiveness of carbon nanoparticle-based central lymph node tracing in patients who underwent surgery for papillary thyroid cancer

A retrospective cohort study

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Abstract

Carbon nanoparticles (CNs) are used in papillary thyroid cancer (PTC) surgery to facilitate central lymph node dissection (CLND) and protect the parathyroid glands (PGs). However, some cases develop hypoparathyroidism after using CNs. This cohort study was undertaken to explore the predictors of the reduced effectiveness of CNs. Data on patients with PTC who underwent surgery wherein CNs were used during CLND were reviewed retrospectively. Patients who did not develop hypoparathyroidism and developed hypoparathyroidism were classified into Group A and B, respectively. Demographic and clinical characteristics were compared between the 2 groups. Univariate and multivariate logistic regression analysis were performed on related variables. The receiver operating characteristic curve was used to evaluate the predictors of the binary logistic model and the cutoff value of each predictor was obtained. A total of 265 patients were included. Compared with Group A, the patients in Group B had a higher body mass index (BMI) ($P = .003$), were more frequently associated with Hashimoto thyroiditis (HT) ($P = .001$), and tumors were larger in size ($P = .026$). Multivariate logistic regression analyses were performed on these variables and showed that HT ($P = .001$) and tumor size ($P = .001$) predicted the impaired role of CNs. CNs are not always useful in protecting PG function in patients who undergo CLND for PTC. In patients with coexisting HT (blood thyroid peroxidase antibody [TPOAb] level higher than 44.0 IU/mL or blood anti-thyroglobulin antibody [ATG] level higher than 125.0 IU/mL) or a tumor size exceeding 1.1 cm in diameter, the protective role of CNs may be impaired.

Abbreviations: ATG = anti-thyroglobulin antibody, BMI = body mass index, CLND = central lymph node dissection, CNs = carbon nanoparticles, HT = Hashimoto thyroiditis, PGs = parathyroid glands, PTC = papillary thyroid cancer, TPOAb = thyroid peroxidase antibody.

Keywords: carbon nanoparticles, central lymph node, Hashimoto thyroiditis, papillary thyroid cancer, parathyroid glands

1. Introduction

Papillary thyroid cancer (PTC) is the most common malignant tumor of the endocrine system affecting more than 50,000 patients annually in the USA.[1] A rapid increase in PTC incidence and heavy disease burden has been observed in the past decade.[2] The clinical treatment of PTC is mainly surgical, but the extent of thyroidectomy and indication for lymph node dissection in the central compartment remain matters of debate.[3–5] Owing to the difficulties in assessing the central neck nodal status preoperatively and intraoperatively and the limited accessibility to radioactive iodine ablation, prophylactic central lymph node dissection (CLND) is a routine procedure for PTC patients in China.[6–8]

However, CLND tends to cause postoperative hypoparathyroidism.[9] Incidental injury to the parathyroid glands (PGs) can lead to hypoparathyroidism and hypocalcemia. The patients will present with hand and foot numbness and even tetany. Most cases are transient, but once permanent hypoparathyroidism occurs, it significantly affects the patient's quality of life. Therefore, finding an approach to effectively distinguish PGs from other tissues during surgery is a major issue in thyroid surgery.

In recent years, a suspension of carbon nanoparticles (CNs) is being used in China as a novel tracer for intra-glandular injection to blacken lymph nodes but not stain the PGs. Using this technique, the lymph nodes can be better identified, and PGs can be well protected.[10–12] The incidence of postoperative hypoparathyroidism has reduced after adoption of this method.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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However, in the real world, we have found that the lymph nodes are not always stained well with CNs, and hypoparathyroidism cannot be completely avoided in some patients with PTC, indicating that the role of CNs is impaired in some cases. Furthermore, to the best of our knowledge, this issue has never been investigated in previous studies. In this study, we aimed to explore the predictors of the impaired effectiveness of CNs in PTC surgery.

2. Methods

2.1. Case selection

Consecutive patients from January 2015 to December 2020 were included in this retrospective study. All patients were diagnosed with PTC with preoperative fine needle aspiration pathology and the diagnosis was consistent with the postoperative pathology and immunohistochemistry results. The medical records of patients were reviewed. The inclusion criterion was that CNs (China Food and Drug Administration approval no. H20041829; Chongqing Lummy Pharmaceutical Co., Ltd., Chongqing, China) were used and CLND was performed during surgery. The exclusion criteria included surgery for lateral neck lymph node metastasis, prior cervical radiotherapy, preoperative parathyroid dysfunction, unidentified postoperative parathyroid hormone (PTH) level before discharge, and lost follow-up 6 months after surgery. Patients were divided into 2 groups according to the PTH level 24 hours postoperatively: Group A (without hypoparathyroidism) and Group B (with hypoparathyroidism). This study was approved by the Clinical Ethics Committee of the Affiliated People's Hospital of Ningbo University (No. 030,107-*P*-066, August 18, 2021) and the study was conducted in accordance with the tenets of the 1995 Declaration of Helsinki. All participants were provided informed consent.

2.2. Surgical procedure

All patients underwent general anesthesia and the surgeries were performed by experienced thyroid surgeons using an open approach. After the cervical strap muscles were pulled apart and the affected thyroid lobe was exposed, a 0.1 to 0.2 mL suspension of CNs was injected into the lobe with a 1 mL syringe. The depth of injection was 0.5 cm. Injection into blood vessels and tumors was avoided. The puncture hole was cauterized instantly upon withdrawing the needle to prevent leakage to the surrounding operation field. The surgeons waited for 3 minutes to allow the CNs to spread and stain the lymph nodes. Thereafter, lobectomy or total thyroidectomy plus CLND were performed. All black-stained lymph nodes in the central compartment were harvested. During the process, efforts were made to locate the unstained PGs and preserve them. If the staining of lymph nodes did not meet the expectation, all adipose and lymphoid tissues in the central compartment were resected. Autotransplantation was performed only if the PGs were incidentally removed or if blood supply to the PGs was impaired. Any identified excised PGs were re-planted into the ipsilateral sternocleidomastoid muscle during surgery.

2.3. Perioperative management

PTH and serum calcium levels were tested preoperatively and 24 hours postoperatively. When the PTH level was <15 pg/mL (normal range, 15–65 pg/mL), it was defined as postoperative hypoparathyroidism. Postoperative hypocalcemia was defined as serum calcium levels below 2.11 mmol/L (normal range, 2.11–2.52 mmol/L). If hypoparathyroidism or hypocalcemia occurred, both PTH and serum calcium were re-measured 7 days, 30 days, 3 months, and 6 months after the operation until it returned to normal. Intravenous infusion of calcium gluconate or oral calcium carbonate tablets and calcitriol capsules was administered to patients with hypocalcemia. PTH was measured 6 months postoperatively in patients with persistently low PTH levels. If the level did not reach the normal range, it was defined as permanent hypoparathyroidism. Otherwise, it was regarded as transient hypoparathyroidism.

2.4. Follow-up of patients

Long term postoperative follow-up was performed during outpatient visits. All patients who developed hypoparathyroidism or hypocalcemia were continuously monitored for symptoms, PTH levels, and serum calcium levels within 6 months after discharge.

2.5. Data collection

Patient data including age, sex, body mass index (BMI), tumor size, surgical approach, tumor side, and comorbidity were collected. Information about combined incidence of thyroid disorders such as Hashimoto thyroiditis (HT), nodular goiter, hyperthyroidism, and hypothyroidism was also recorded. Intra- and postoperative variables including surgical time, blood loss, postoperative drainage, hoarseness, number of harvested lymph nodes, and number of metastatic lymph nodes were also collected.

2.6. Statistical analysis

Mean values ± standard deviation for continuous normally distributed variables were compared using independent samples *t* tests (parametric). Pearson's chi-square test or Fisher's exact test were used for categorical data. Unadjusted and adjusted logistic regression analyses were performed. To determine the clinical cause leading to the failure in protection of hypoparathyroid function, each predictor was analyzed in the univariate logistic regression model, and variables with $P < .10$ were included in the multivariate logistic regression analysis. The receiver operating characteristic curve was used to evaluate the predictor of the binary logistic model and the cutoff value of each predictor was obtained. Statistical significance was set at $P < .05$. SPSS (version 17.0; SPSS, Inc., Chicago, IL) was used to perform the statistical analyses.

3. Results

A total of 265 patients (36 men [13.6%] and 229 women [86.4%]) were included in this study, and the mean age was 56.2 ± 12.1 years. There were 234 and 31 patients in Groups A and B, respectively. Three patients (1.1%) in Group B developed permanent hypoparathyroidism. The patients in Group B had higher BMI (22.7 ± 2.6 vs 21.0 ± 4.1) ($P = .003$) and bigger tumor size (0.9 ± 0.5 vs 1.4 ± 1.0) than Group A patients did ($P = .026$). No significant differences were found in other variables, such as age, sex, tumor side, reoperation, surgical approach, surgical time, and comorbidity, between the 2 groups ($P > .05$) (Table 1). There were more patients with HT in Group B than in Group A (32.3% vs 10.3%). There were no significant differences in the number of patients with nodular goiter, hyperthyroidism, or hypothyroidism between the 2 groups ($P > .05$) (Table 2). Regarding surgical outcomes, there were no significant differences in blood loss, postoperative drainage, voice hoarseness, number of harvested lymph nodes, or number of metastatic lymph nodes in the 2 groups ($P > .05$) (Table 3). Univariate logistic regression for variables showed BMI, tumor size, reoperation rate, incidences of HT and nodular goiter with $P < .10$ (Table 4). These variables were further analyzed

Table 1

Demographic and clinical characteristics of patients in 2 groups.

	Group A (n = 234)	Group B (n = 31)	t/χ^2	P value
Age, yrs	56.7 ± 12.1	53.0 ± 12.1	1.601	.111
Sex			0.996	.318
Male	30 (12.8%)	6 (19.4%)		
Female	204 (87.2%)	25 (80.6%)		
Body mass index	21.0 ± 4.1	22.7 ± 2.6	−3.106	.003
Tumor side			0.192	.661
Unilateral	196 (83.8%)	25 (80.6%)		
Bilateral	38 (16.2%)	6 (19.4%)		
Tumor size, cm	0.9 ± 0.5	1.4 ± 1.0	−2.338	.026
Reoperation			0.370	.066
Yes	7 (3.0%)	3 (9.7%)		
No	227 (97.0%)	28 (90.3%)		
Surgical approach			1.975	.372
LI + UCLND	185 (79.1%)	22 (71.0%)		
TT + UCLND	39 (16.7%)	6 (19.4%)		
TT + BCLND	10 (4.3%)	3 (9.7%)		
Surgical time, min	6.2 ± 10.2	80.0 ± 12.6	−1.918	.056
Comorbidity			0.097	.756
Yes	51 (21.8%)	6 (19.4%)		
No	183 (78.2%)	25 (80.6%)		

CLND = central lymph nodes dissection, LI + UCLND = lobectomy + isthmectomy + unilateral central lymph nodes dissection, TT + BCLND = total thyroidectomy + bilateral central lymph nodes dissection, TT + UCLND = total throidectomy + unilateral central lymph nodes dissection.

Table 2

Comparison of coexisting disorders in 2 groups.

	Group A (n = 234)	Group B (n = 31)	χ^2	P value
Hashimoto thyroiditis			11.848	.001
Yes	24 (10.3%)	10 (32.3%)		
No	210 (89.7%)	21 (67.7%)		
Nodular goiter			2.984	.084
Yes	27 (11.5%)	7 (22.6%)		
No	207 (88.5%)	24 (77.4%)		
Hyperthyroidism			0.693	.405
Yes	8 (3.4%)	2 (6.5%)		
No	226 (96.6%)	29 (93.5%)		
Hypothyroidism			0.001	.979
Yes	23 (9.8%)	3 (9.7%)		
No	211 (90.2%)	28 (90.3%)		

Table 3

Comparison of outcomes of patients in 2 groups.

	Group A (n = 234)	Group B (n = 31)	t/χ^2	P value
Blood loss, mL	12.8 ± 4.5	13.2 ± 4.8	−0.519	.604
Postoperative drainage, mL	46.4 ± 9.8	45.5 ± 7.2	0.508	.612
Hoarseness			0.010	.920
Yes	24 (10.3%)	3 (9.7%)		
No	210 (89.7%)	28 (90.7%)		
Number of harvested lymph nodes	3.3 ± 1.1	2.9 ± 0.9	1.941	.053
Number of metastatic lymph nodes	0.9 ± 0.8	0.8 ± 0.7	0.195	.846

using a multivariate logistic regression model. We found that tumor size (OR, 1.949, CI: 1.069–3.554; $P = .029$) and HT (OR, 6.649; 95% CI: 1.627–27.178; $P = .008$), were associated with impaired effectiveness of CNs (Fig. 1). Receiver operating characteristic curves were made for tumor size, blood thyroid peroxidase antibody (TPOAb) level, and anti-thyroglobulin antibody (ATG) level. The area under curve was 0.8150, 0.7310, and 0.7383, respectively (Fig. 2). Furthermore, the cut-off value was analyzed for each variable. As a result, the predictors were as follows: tumor size larger than 1.1 cm, blood TPOAb level higher than 44.0 IU/mL, and blood ATG level higher than 125.0 IU/mL.

Table 4

Univariate logistic regression for predictors of impaired effectiveness of carbon nanoparticles.

	B	S.E.	Wals	OR	95%CI	P value
Age, yrs	−0.025	0.016	2.527	0.975	0.945–1.006	.112
Sex	0.490	0.495	0.980	1.632	0.619–4.305	.322
Body mass index	0.092	0.043	4.691	1.097	1.009–1.192	.030
Tumor side	−0.213	0.488	0.191	0.808	0.310–2.102	.662
Tumor size	0.790	0.244	10.504	2.204	1.367–3.556	.001
Reoperation	1.245	0.719	3.004	3.474	0.850–14.208	.083
Surgical approach	−1.024	0.658	1.876	0.300	0.101–1.550	.391
Comorbidity	−0.149	0.481	0.096	0.861	0.335–2.212	.756
Hashimoto thyroiditis	1.427	0.441	10.496	4.167	1.757–9.880	.001
Nodular goiter	0.805	0.476	2.861	2.236	0.880–5.682	.09
Hyperthyroidism	0.667	0.815	0.670	1.948	0.395–9.621	.413
Hypothyroidism	−0.017	0.646	0.001	0.983	0.277–3.486	.979
Surgical time	0.030	0.016	3.529	1.030	0.999–1.063	.060

4. Discussion

PTC is the most common type of thyroid cancer.[13] Overall survival in patients with PTC is high, and lymph node metastasis is a significant risk factor for recurrence.[14] The central neck nodal is most commonly involved in PTC patients, with a reported rate of metastases as high as 50% to 70%.[15] Regional lymph node metastases may occur even when the PTC is small and intrathyroidal.[16] Prophylactic CLND may prevent recurrence and improve overall survival and has been recommended in some studies.[4,17] The number of lymph nodes removed is an important indicator of the quality of surgery is and helps determine the prognosis. However, up to 80% of positive lymph nodes

	OR	95%CI	*P* value
Body mass index	1.043	0.925-1.175	0.495
Tumor size	1.949	1.069-3.554	0.029
Reoperation	3.405	0.363-31.918	0.283
Hashimoto thyroiditis	6.649	1.627- 27.178	0.008
Nodular goiter	0.978	0.945-1.012	0.210
Surgical time	1.022	0.960-1.088	0.490

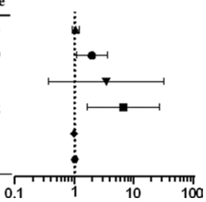

Figure 1. Multivariate logistic regression model.

are undetectable because some metastatic lymph nodes in the central cervical region are small, hidden, and difficult to identify on preoperative imaging. In addition, surgeons may mistake the lymph nodes for fat, and thus, fail to extract them.[18] Therefore, metastatic lymph nodes in the central neck compartment are easily missed during intraoperative dissection.

The incidence of permanent hypoparathyroidism after surgery was 1.1% in our cohort; this is lower than previously reported rates of approximately 2% to 16%.[19] Nonetheless, post-thyroidectomy hypoparathyroidism is a serious but common complication of thyroid cancer surgery.[20] Postoperative hypoparathyroidism due to inadvertent damage to PGs during CLND is a transient to permanent complication among patients with PTC.[21] It may occur secondarily to devascularization, surgical trauma, and unintentional removal of PGs, particularly in patients who undergo reoperation or total thyroidectomy. Twitching and numbness of the limbs caused by permanent postoperative hypoparathyroidism seriously affect the quality of life of patients and usually require prolonged hospitalization. Properly identifying PGs is the best way to preserve their functions. However, the similarity of PGs to the surrounding tissues makes their identification and protection a challenge during thyroid surgery. It is common to mistake PGs for lymph nodes, or vice versa.

Therefore, simultaneous identification of PGs and precise CLND are vital for the success of PTC surgery. CNs are a new lymph node tracer and are approximately 150 nm in diameter. The endothelial gap of capillaries is 20 to 50 nm while that of capillary lymphatic vessels is 120 to 500 nm. Because of the difference in permeabilities, CNs cannot enter the blood vessels after being injected into the thyroid gland but can enter the lymphatic vessels rapidly and be captured by macrophages. CNs spread in the lymphatic vessels with the flow of lymph fluid and thus stain the lymph nodes black. Some studies have shown that the application of CNs in PTC surgery increases the detection rate of lymph nodes and reduces the injury of PGs in both conventional and endoscopic PTC surgeries.[10–12,16,22,23]

However, the effect of using CNs in some patients with PTC who underwent CLND does not necessarily meet expectations, even in experienced hands. HT is associated with a significantly higher risk of PTC and is an autoimmune disease caused by an overproduction of antithyroid antibodies that destroy thyroid tissue.[24] The inflammatory process includes lymphocyte infiltration, fibrosis, and atrophied follicular cells, which results in the thyroid gland tending to adhere more to its anatomic surroundings.[25] This pathological process can make thyroid surgery more difficult and leads to an increased risk of complications including hypoparathyroidism and recurrent laryngeal nerve injury. Moreover, the formation of fibrosis in patients with HT affects the diffusion of CNs, leading to poor staining of lymph nodes and difficulties in recognition of PGs. In our experience, we noted that the central lymph nodes were not stained black well in patients with HT. Furthermore, our study shows that patients with concurrent PTC and HT were more prone to develop postoperative hypoparathyroidism than PTC patients without HT, which indicates that the protective role of the CNs is limited in this population.

Our study showed that when the tumor was larger than 1 cm in diameter, the possibility of postoperative hypoparathyroidism was much higher even when CNs were used during the surgery. The underlying cause may be the disruption of normal lymphatic drainage within the thyroid gland due to the invasion of large tumors, which impacts the staining of lymph nodes. PGs cannot be differentiated from unstained lymph nodes. Therefore, incidental damage to PGs occurs more frequently. Another potential cause for the affected diffusion of CNs may be the blockage of the lymphatic drainage channels of the thyroid concerning the mechanism of CNs. Patients with tumors larger than 1 cm may have more impaired lymphatic drainage channels. Interestingly, we found that although the effectiveness of CNs was impacted in PTC patients with HT or large tumors, the number of harvested lymph nodes was not statistically significant. This may be because of the relatively small sample size in group B.

Our study has several limitations. First, it was a retrospective one. A selection bias in using CNs may exist in this cohort. Second, the sample was not sufficiently large. Third, the potential contributing variables were not included. Therefore, further randomized controlled studies are required to address this issue in the future.

In conclusion, the value of CNs should not be overstated in protecting PG function in patients who undergo CLND surgery for PTC. In patients with coexisting HT (blood TPOAb level higher than 44.0 IU/mL or blood ATG level higher than 125.0 IU/mL) or tumor size larger than 1.1 cm in diameter, the protective role of CNs may be limited.

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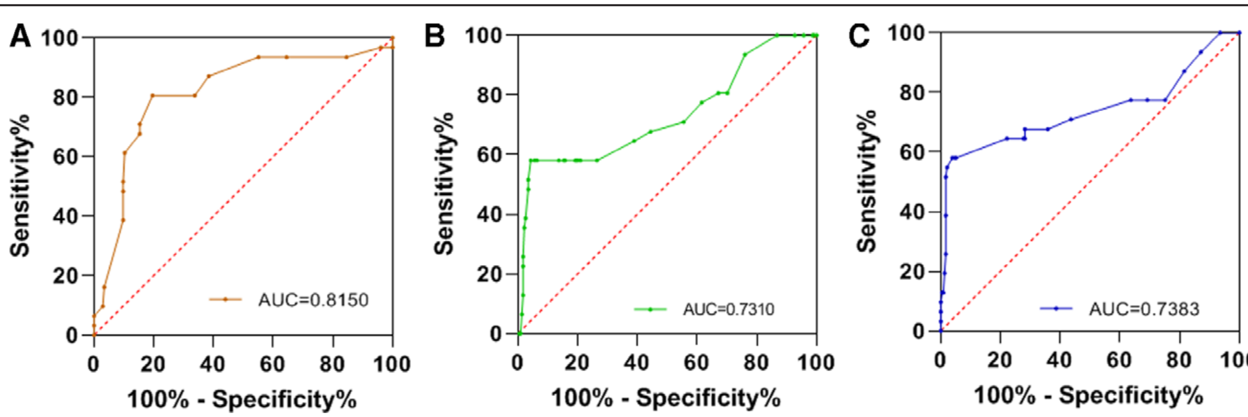

Figure 2. ROC curves of logistic model. ROC = receiver operating characteristic.

Author contributions

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