



The potential role of carbon nanoparticles-assisted biopsy for sentinel lymph nodes of incidental thyroid carcinoma

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Background: Some thyroid cancers are found after thyroidectomy for benign lesions, implying additional surgery and treatments. This work aimed to investigate the role of intraoperative sentinel lymph node biopsy (SLNB) for diagnosis of incidental thyroid carcinoma.

Methods: This was a retrospective study of 541 consecutive patients who underwent thyroid surgery between 02/2012 and 02/2014 at the Hunan Provincial People's Hospital. All patients were diagnosed with thyroid benign lesions preoperatively and intraoperatively. Among them, 375 underwent successful intraoperative SLNB using carbon nanoparticles (CNs).

Results: The preoperative diagnoses were nodular goiter (n=472), Hashimoto's disease with nodules (n=24), hyperthyroidism with nodules (n=16), and thyroid cysts with obstructive symptoms (n=29). In the SLNB group, SLN metastasis of thyroid microcarcinoma was confirmed in 21/392 cases (5.4%). These 21 patients received radical surgical treatment for thyroid carcinoma during the initial operation. In the no-SLNB group (n=149), seven patients (4.7%) were finally diagnosed with thyroid microcarcinoma. Six patients had to undergo a second surgery.

Conclusions: Intraoperative SLNB could help diagnose differentiated thyroid microcarcinoma that may be missed preoperatively and intraoperatively. This could prevent the need for a second surgery since the intraoperative frozen section examination of the SLNs can reveal metastasis from thyroid cancer.

Keywords: Sentinel lymph node biopsy (SLNB); thyroid carcinoma; carbon nanoparticles (CNs); second surgery; diagnosis

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Introduction

Thyroid nodules are a common clinical finding and the increasing prevalence of differentiated thyroid carcinoma is a challenge for thyroid surgeons since they have to identify

malignant nodules, which represent 5–15% of thyroid nodules. Although the majority of malignant nodules can be diagnosed by fine needle biopsy (FNA) and ultrasound examination preoperatively, incidental thyroid carcinoma (i.e., malignant finding of a nodule that was initially thought

as benign) identified in specimens of thyroidectomy performed for benign nodules is quite frequent (1). Thyroid microcarcinoma represents most of the incidental carcinoma since they are difficult to be sampled adequately by FNA. Hence, the diagnosis of differentiated thyroid cancer may be missed. The majority of follicular variants of thyroid papillary carcinoma are encapsulated and the neoplastic cells do not show the nuclear features of papillary carcinoma. As a result, the diagnoses of these tumors may be missed even by experienced pathologists (2).

In this situation, the presence of lymph nodes metastasis provides additional information and may help diagnose thyroid carcinoma intraoperatively. As reported, papillary thyroid carcinoma involves cervical lymph nodes in 20–50% of the cases (3). The spread of tumors usually begins in the perithyroidal lymph nodes and progresses to the lateral neck compartments (4,5). Given that 'skip' metastases occur rarely, especially when the primary tumor located in upper thyroid pole, perithyroidal lymph nodes are considered to be the first metastases station, i.e., sentinel lymph node (SLN) (6). Nevertheless, preoperative investigation of perithyroidal lymph nodes is technically difficult and unreliable by ultrasound and only half of lymph nodes metastasis in central neck compartment can be observed by the naked eye during the operation (7).

Ito *et al.* (8) suggest that for small incidental thyroid cancer <1 cm, observation is appropriate in the absence of unfavorable features. Nevertheless, incidental carcinoma may behave aggressively in some cases, particularly in those with unfavorable histopathological features (9). Nevertheless, some cancers are found in the surgical specimens after thyroidectomy for benign lesions, and the correct management of these patients is still unknown. This finding not only inflicts additional suffering and financial burden on the patients, but also implies the possible need for further treatments and surgeries. Kr *et al.* (10) suggested that incidental lymph node metastasis from thyroid cancer found during head and neck should prompt the search for the primary lesion.

Therefore, there is a need to find effective solutions to prevent thyroid microcarcinoma from being preoperatively and intraoperatively missed. Carbon nanoparticles (CNs) suspension has been widely used to assist to clean the lymph nodes by dyeing them during breast, gastric and thyroid surgery (11,12). Also it has been used to protect the function of parathyroid glands. We began in February 2012 to explore the differential and protective effects of CNs on parathyroid gland in thyroid surgery. With this

objective in view, we use CNs as a lymph node tracer to perform SLN biopsy (SLNB) during thyroid surgery to increase the possibility of detecting small aggressive thyroid cancers.

Methods

Study design and patients

This was a retrospective study of 541 consecutive patients who underwent thyroid surgery for benign thyroid tumors that were later determined as thyroid cancer, either during or after surgery. The surgeries were performed between February 2012 and February 2014 at the Thyroid Department of the Hunan Provincial People's Hospital. This study was approved by the Medical Ethics Committee of Hunan Provincial People's Hospital, Changsha, China (Ethic Number: 201612010). The need for individual consent was waived by the committee because of the retrospective nature of the study.

All patients were diagnosed with thyroid benign lesions both preoperatively by FNA and intraoperatively by frozen biopsy. The surgical indications for the benign tumors were (13): (I) presence of localized oppression symptoms that were significantly associated with nodules; (II) hyperthyroidism, which could not be alleviated with medical treatment; (III) tumor located behind the sternum or in the mediastinum; or (IV) the nodules were growing and could be considered as having a malignant tendency or were complicated with risk factors for thyroid cancer. Among the 541 patients, 392 underwent intraoperative SLNB while the other 149 did not. All tumor diagnoses were confirmed by two pathologists (deputy chief physician or above) using standard diagnostic criteria on pathological section (14). The nodules that were found incidentally during imaging examination were considered as incidental thyroid nodules (1). The incidental thyroid cancers were diagnosed according to the guidelines (15).

Surgical procedures

All surgeons were in the same team, and all of them were associate chief physician or above. General anesthesia was given to all patients. The patients were placed in the supine position. A cervical collar curved incision was made in the anterior cervical region to expose the prethyroid region including the paratracheal region and the isthmus of the thyroid gland. The injection of CNs in the central

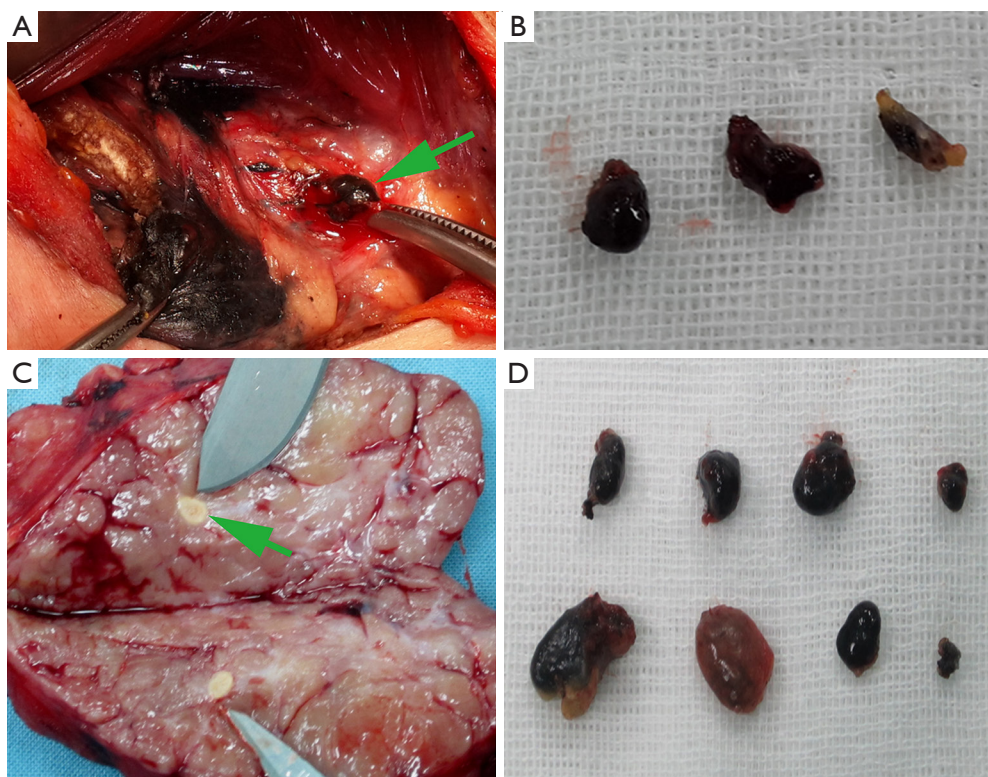


Figure 1 Sentinel lymph nodes (SLN) stained black using carbon nanoparticles (CNs) (A,B) are from patient 1 and (C,D) are from patient 2. Both patients were diagnosed with thyroid carcinoma intraoperatively using CNs-assisted SLN biopsy (SLNB). (A) Patient 1: lymphatic vessels stained black converge on SLNs (green arrow); (B) three removed SLNs stained black, as shown in (A), from which thyroid carcinoma was diagnosed due to lymph nodes metastasis; (C) patient 2: a thyroid microcarcinoma (green arrow) in a patient with Hashimoto's disease and nodules that were missed on intraoperative frozen section analysis but confirmed on postoperative paraffin sections; (D) SLNs stained black dissected from this patient. Intraoperative frozen section analysis of two lymph nodes from these black stained SLNs shows the metastases of thyroid carcinoma.

compartment lymph node was performed as previously described (16). At the previously chosen one to four sites on the thyroid surface, 0.1–0.3 mL of CNs was injected into the superficial thyroid gland 2–3 mm in depth. Prior to being injected, negative pressure was applied before administration to make sure there was no intravenous CNs injection. The flow of CNs inside the thyroid tissue and lymphatic vessels was observed. After 1–5 min, the lymph nodes stained black by CNs began to be sighted in the pretracheal region. We defined the first blacked lymph nodes as SLNs, including those in the prelaryngeal region, the region below the isthmus and on the tracheal surface, and the regions adjacent to the upper and lower poles of the thyroid, or those in the regions adjacent to the recurrent laryngeal nerves and/or in other parts of the central compartment. The first black stained SLNs were removed and submitted

for frozen section analysis (as shown in *Figure 1*). Meanwhile, thyroid surgery was performed and relevant specimens were submitted for frozen section analysis.

Statistical analysis

Only descriptive statistics were presented. Continuous variables were presented as mean \pm standard deviation. Categorical data were presented as frequencies.

Results

Characteristics of the patients

The demographic data are presented in *Table 1*. The patients' age ranged from 15 to 78 (mean, 39).

Preoperative diagnoses

As shown in *Table 1*, the preoperative diagnoses of the 541 patients were nodular goiter (n=472), Hashimoto's disease with nodules (n=24), hyperthyroidism with nodules (n=16), and thyroid cysts with obstructive symptoms (n=29).

SLN biopsy (SLNB)

Of 392 SLN biopsies conducted during operation, SLNs could be sampled in 375 cases (95.7%). SLNs failed to be

detected in 17 patients who only presented with thyroid nodules. *Table 2* presents the rates of SLNB according to the preoperative diagnosis.

Among the 375 successful biopsies, SLN metastasis of thyroid microcarcinoma was confirmed in 21 cases without intraoperatively detected thyroid microcarcinoma in the corresponding thyroid tissue and/or tumor/nodules by frozen section biopsy. All incidental nodes with thyroid carcinoma were microcarcinoma. The mean tumor size is 5.6 ± 2.4 mm. Accordingly, these 21 patients received radical surgical treatment for thyroid carcinoma during the initial operation and avoided undergoing a second one (*Table 2*).

Of the 149 patients who did not have intraoperative SLNB, seven were diagnosed with thyroid microcarcinoma by postoperative paraffin section analysis of thyroid nodules. The rate of incidental thyroid carcinoma was 4.7% (7/149, the mean tumor size is 5.9 ± 2.2 mm). One patient out of those seven had a near-total thyroidectomy during the first surgery and thus avoided undergoing a second surgery. The remaining six patients, however, had to undergo a second surgery later.

Discussion

Some thyroid cancers are found after thyroidectomy for benign lesions, implying additional surgery and treatments. There is a need to find effective solutions to prevent thyroid microcarcinoma from being preoperatively and intraoperatively missed. Therefore, the present study aimed to investigate the role of intraoperative SLNB for diagnosis of incidental thyroid carcinoma. The results suggest that intraoperative SLNB could help diagnose differentiated thyroid microcarcinoma that may be missed both preoperatively and intraoperatively. This approach could prevent the patients from having to undergo a second surgery since the intraoperative frozen section examination

Table 1 Patient demographics and clinical data

Demographics and clinical data	Patients with SLNB (n=392)	Patients without SLNB (n=149)
Gender		
Male	59	25
Female	333	124
Age (mean \pm SD)	51.3 \pm 14.2	47.4 \pm 12.7
Type of benign thyroid disease		
Multinodular goiter (n=472)	366	106
Hashimoto's disease with6 nodule (n=24)		18
Hyperthyroidism with nodules (n=16)	11	5
Thyroid cysts (n=29)	9	20
Prevalence of incidental thyroid cancer	21 (5.36%)	7 (4.70%)
Number of completion thyroidectomy	0	6

SLNB, sentinel lymph node biopsy.

Table 2 Results of intraoperative SLN biopsy during thyroid surgery

Primary disease	Case number of SLNB	Case number with detected SLNs, n (%)	Positive rate of SLNs
Multinodular goiter	366	349 (95.4)	4.4% (16/366)
Hashimoto's disease with nodules	6	6 (100.0)	33.3% (2/6)
Hyperthyroidism with nodules	11	11 (100.0)	18.2% (2/11)
Thyroid cysts	9	9 (100.0)	11.1% (1/9)
Total	392	375 (95.7)	5.4% (21/392)

SLNB, sentinel lymph node biopsy.

of the SLNs can reveal metastasis from thyroid cancer.

According to reported literature, incidental thyroid carcinoma has an incidence of about 5–15% in patients treated operatively for benign thyroid diseases (1,17,18) and the diagnosis of differentiated thyroid cancer may be missed, even by experienced pathologists (2). In this situation, the presence of lymph nodes metastasis provides additional information and may help diagnose thyroid carcinoma intraoperatively (3). Preoperative investigation of perithyroidal lymph nodes is technically difficult and unreliable by ultrasound and only half of lymph nodes metastasis in central neck compartment can be observed by the naked eye during the operation (7). Therefore, SLNB could be an appropriate approach and can be performed with low-risk techniques such as CNs.

As reported in the literature, 18–87% of those missed well-differentiated thyroid carcinomas were diagnosed as multifocal thyroid carcinoma by postsurgical pathologic analyses, and the ratio reported by Li *et al.* (19) and Park *et al.* (20) was around 37% (20). According to the NCCN guidelines, incidentally discovered papillary thyroid carcinomas of 1–4 cm in size may warrant a completion thyroidectomy for lymphovascular invasion, although observation is another option for some patients (21). In addition, ATA guidelines suggest that completion thyroidectomy may be required when the diagnosis of malignancy is confirmed following lobectomy to ensure of complete resection of multicentric disease and allow for efficient radioactive iodine therapy (22). Nevertheless, reoperation not only inflicts additional pain and financial burden on these patients but also challenge surgeons for increased risk of possible complications. Thus, the key to avoid the aforesaid unfavorable situations and consequences brought by a second surgery is to effectively prevent missing diagnosis of thyroid carcinoma prior to or during the initial thyroid surgery. In the present study, SLNs were detected in 375 (95.7%) of the 392 with intraoperative SLNB and 21 were confirmed to be with lymph node metastasis of thyroid carcinoma. On the other hand, seven out of 149 patients (4.7%) who did not receive intraoperative SLNB were diagnosed with thyroid cancer by postoperative paraffin section analysis. All incidental nodes with thyroid carcinoma were microcarcinoma. This may be related to the uncertainty of Thyroid Imaging, Reporting and Data System (TIRADS) and FNA results, and the uncertainty of these methods is mainly concentrated in microcarcinoma evaluation (23,24). Completion surgeries had to be performed in six patients due to insufficient extent of initial

surgical operation.

These results are important in terms of patient management. Indeed, finding a positive SLN intraoperatively not only leads to total thyroidectomy and prevents a second procedure, but it is also an ideal surgical treatment during the initial surgery, which is therapeutic central neck dissection and leading to accurate staging and risk stratification of these patients. This is just as important if not more significant than preventing a second procedure. Finding metastatic disease may lead to radioactive iodine treatment instead of total thyroidectomy alone, potentially decreasing recurrence. Such cancers were detected at rates of 5.6% and 4.7% in the excised thyroids from patients with and without a SLNB, respectively. That is in fact lower than some reported estimates (1,9,16–18). The fact is, there is no consensus about treatment of microcancers and consider that if not for the benign lesion indicating surgery, none of these patients would have been discovered and the longer-term clinical course of these cancers is unknown. Some of them could have progressed rapidly, but it is also probable that many of them were relatively indolent disease that progressed over many years. Additional studies will have to be performed to determine the long-term natural course of this disease. Nevertheless, Ito *et al.* (8) suggests that small thyroid cancers <1 cm could be simply observed. This point warrants further investigation.

SLNB is a routine procedure in cancers such as breast cancer (25). Moreover, occult breast cancers may be diagnosed through the sampling of suspicious SLNs in the axilla (26,27). In light of these facts and inspired by our previous successful experience in using CNs as lymph node tracer in differentiated thyroid carcinoma requiring reoperation, we investigated potential role of CNs-assisted SLNB in the diagnosis of incidental thyroid carcinoma intraoperatively (16). Numerous studies have demonstrated the role of SLNB in cervical neck dissection using patent blue and radiotracers with dynamic lymphoscintigraphy (28,29). CNs have recently been used to identify lymph nodes and protect parathyroid gland during thyroid cancer surgeries (19) and cervix cancer (30). NC suspension, with a particle diameter of 150 nm and a high tropism for the lymphatic system, can quickly enter the lymphatic circulation after being uptaken by macrophages and without entering the blood vessels when injected into the thyroid tissue (31). As the CNs gather and deposit in the lymph nodes, the thyroid lymph drainage area will be dyed black and the perithyroidal lymph nodes will be their first stop (32).

In the present study, 392 SLN biopsies were performed

to detect 21 microcancers and prevent a second operation compared to six patients requiring reoperation for microcancers. It is extremely likely that lymph node metastases occur in patients with macrocancers, but lymph node biopsy is not a routine practice in macrocancers and we do not know the significance of lymph node metastases in well-differentiated thyroid carcinoma (33-35). Sampling lymph nodes in well-differentiated thyroid carcinoma is controversial and could be beneficial only in selected patients (33,34,36,37).

As SLNB in thyroid cancer management is still under study at the present time, no criteria have been established for SLNs biopsy for thyroid carcinoma. Although application of costly CNs undoubtedly increases the healthcare costs, the identification rate of SLNs was up to 95.7% and 21 patients may have derived benefits from it. Studies suggested that SLNB may help guide neck dissection, patient surveillance, and radioactive iodine therapy in thyroid carcinoma (6,38).

The present study is not without limitations. The sample size was small and from a single center. Because of the retrospective nature of the study, we could not perform predictive analyses of the presence of positive SLNs based on the clinical features of the patients. Finally, follow-up data were unavailable for many patients. Additional studies are necessary to overcome these issues.

In conclusion, we should bear in mind that patients with benign thyroid tumors have a certain combination rate of malignant nodes. Intraoperative SLNB could help diagnose differentiated thyroid microcarcinoma that may be missed both preoperatively and intraoperatively. This approach may prevent patients from having to undergo a second surgery since the intraoperative frozen section examination of the SLNs can reveal metastasis from thyroid cancer. However, the indication of specific conditions rather than routine use of CNs in surgery of benign thyroid tumors has yet to be studied.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Medical Ethics Committee of Hunan Provincial People's Hospital, Changsha, China (Ethic Number: 201612010). The need for individual consent was waived by the committee because of the retrospective nature of the study.

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