

## Sentinel Lymph Node Biopsy in Papillary Thyroid Carcinoma

Dan-Gui Yan, Bin Zhang\*, Lin Liu, Li-Juan Niu, Chang-Ming An, Zheng-Jiang Li, Zhen-Gang Xu and Ping-Zhang Tang

Department of Head and Neck Surgery, Cancer Hospital & Institute, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100021, China

### Abstract

**Background:** The prognostic value of sentinel lymph node (SLN) biopsy mapping of tumor lymphatics for determining metastases in patients with papillary thyroid carcinoma (PTC) remains unconfirmed. Therefore, this study investigated the reliability and feasibility of the SLN biopsy to predict metastasis in PTC.

**Methods:** Fifty-one PTC patients without clinical evidence of lymph node involvement (cN0) underwent preoperative lymphoscintigraphy with Technetium-99m-labeled dextran. Total or near-total thyroidectomy was performed with SLN biopsy guided by intraoperative injection of methylene blue dye and scanning with a hand-held gamma probe. All patients received selective neck dissections.

**Results:** The SLN was identified by all three methods in all cases (100%). Identification rates for methylene blue dye and lymphoscintigraphy plus probe scanning were 90.2% and 96.1%, respectively. Metastases in SLNs were revealed in 31 and 38 cases by intraoperative frozen sectioning and final pathologic examination, respectively. Sensitivity, specificity, accuracy, and positive and negative predictive values of SLN biopsy were 97.4%, 100%, 98.0%, 100% and 92.3%, respectively.

**Conclusion:** SLN biopsy in patients with cN0 PTC detected occult metastasis with high accuracy and may have the potential to select patients who require selective neck dissection.

**Keywords:** Lymphatic metastases; Thyroid neoplasms; Carcinoma; Papillary; Sentinel node biopsy

### Introduction

The diagnosis of papillary thyroid carcinoma (PTC) is usually accompanied by elective modified radical neck dissection in addition to total thyroidectomy or near-total thyroidectomy. However, the benefit of this procedure for prognosis of metastasis remains to be established. Prognostic approaches range from the conservative “wait-and-see” to selective “node picking” lymphadenectomy and up to aggressive prophylactic neck dissection. The proactive approaches involve the identification and excision of a sentinel lymph node (SLN), specifically the first lymph node in a regional lymphatic basin that receives the lymph flow from a primary tumor. Since lymphatic drainage is presumed to occur in a step-wise fashion, the SLN should reflect the pathological status of the remaining lymph node compartment. From August 2007 and September 2010, we performed sentinel lymph node biopsy (SLNB) using various SLN identification techniques on 51 patients with PTC in order to detect cervical lymph node metastases.

### Materials and Methods

#### Subjects

Criteria for study inclusion were as follows: preoperative diagnosis of thyroid carcinoma by B-ultrasound or biopsy; determination of cervical lymph node metastases by B-ultrasound; and signed informed consent. Patients were excluded based upon: suspected thyroid carcinoma identified as *benign* neoplasm by frozen biopsy; history of neck and/or thyroid surgery; or the presence of systemic distant metastases.

During August 2007 and September 2010, 51 patients who met the study criteria and had thyroid carcinoma with lymph nodes clinically-negative for metastasis (cN0) were pathologically diagnosed as papillary thyroid carcinoma at the Department of Head and Neck Surgical Oncology the Carcinoma Institute and Hospital, Chinese Academy of Medical Sciences (CAMS). All study participants received preoperative cervical B-ultrasound, chest X-ray, and thyroid function tests. Prior to

operation, 22 of the patients were diagnosed by fine-needle aspiration, 14 by core needle biopsy, and 15 by intraoperative biopsy. Four of the patients were male and 47 were female. Ages ranged from 18 to 67 years, and the median age was 43 years. The primary tumor diameter was  $\leq 1$  cm in 22 of the patients, and  $> 1$  cm in 29. Cervical B-ultrasound and/or computed tomography (CT) was used to determine cervical lymph node metastases. cN0 judgment was formulated by consulting standards for clinical evaluation of cervical lymph nodes proposed by Kowalski et al. [1] and in accordance with the following conditions: clinical palpation revealed no swollen lymph nodes, or maximum diameter of swollen lymph nodes was  $< 20$  mm and had soft texture; B-ultrasound or CT imaging examination revealed no swollen lymph nodes or maximum diameter of swollen lymph nodes was  $< 20$  mm and presented no central liquefaction necrosis, strengthened peripheral edge and disappearance of fat space adjacent to node. Patients who lacked imaging data were retained in the study and palpation results were relied upon.

#### Drugs, reagents and equipment

Radiopharmaceutical Technetium-99 labeled dextran ( $^{99m}\text{Tc}$ -DX) was purchased from Beijing Suncor Pharmaceutical Company (China). The labeled rate was  $> 95\%$ , and the volume used was 0.4 ml/74 MBq (2mCi) per patient. Methylene blue (Jiangsu Ji Chuan Pharmaceutical Co., Ltd., Jiang Su, China) was administered as 20 mg/2 ml injection.

**\*Corresponding author:** Bin Zhang, Department of Head and Neck Surgery, Cancer Hospital & Institute, Chinese Academy of Medical Sciences, Peking Union Medical College, No. 17 Panjiayuananli, Chaoyang District, Beijing 100021, P.R. China, Tel: +86-10-87787190; Fax: +86-10-87787190; E-mail: [docbinzhang@hotmail.com](mailto:docbinzhang@hotmail.com)

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Radionuclide scintigraphic lymphatic imaging was conducted 30-90 minutes after injection of  $^{99m}\text{Tc}$ -DX using single photon emission computed tomography (SPECT). The Millennium VG nuclear imager and Hawkeye system (GE Healthcare, Waukesha, WI, USA) was equipped with a low-energy high-resolution parallel-hole collimator. Images were collected for 40 minutes ( $5 \times 10^5$  counts per frame) on a  $256 \times 256$  matrix at a magnification of 1.5. A hand-held r-finder (Gamma Finder; World of Medicine Co., Berlin, Germany) was used in surgery for SLN localization.

### Cervical partitioning

Cervical lymph node partition was performed according to the classifications established by the United States Institute of Otolaryngology Head and Neck Surgery Foundation in 1991 [2]. Specifically, classifications were made among level I (submental and submandibular lymph nodes), level II (the upper group of internal jugular vein lymph nodes), level III (the middle group of internal jugular vein lymph nodes), level IV (the lower group of internal jugular vein lymph nodes), level V (spinal accessory nerve lymph node chain and supraclavicular lymph nodes), level VI (juxta visceral nodes or anterior cervical lymph nodes), and level VII (anterior mediastinal lymph nodes). For narrative convenience, levels VI and VII were collectively designated as cervical central area, and levels II-V as cervical lateral area.

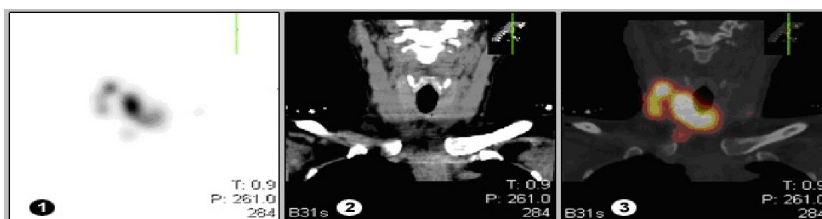
### Surgical procedure

One-and-a-half to eight hours prior to surgery, 0.4 ml (74 MBq) of  $^{99m}\text{Tc}$ -DX was injected under the guidance of B ultrasound into the primary thyroid tumor while patients were in the supine position. Thirty to 90 minutes after injection, lymph scintigraphic imaging was carried out on the anterior or lateral of the primary thyroid tumor to identify the SLN. One-and-a-half to eight hours later, while patients were under general anesthesia, the anterior cervical scalp flap and

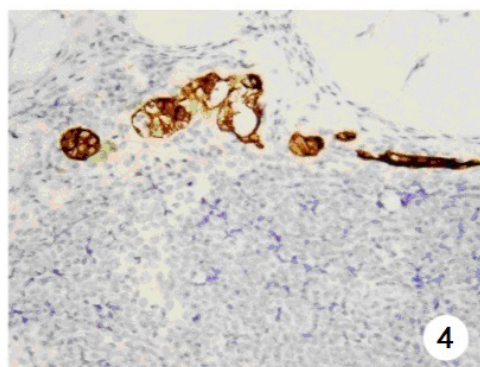
cervical midline were separated, and a low collar (2 cm above the sternal notch) dermatoglyphic incision was made in the anterior neck. The thyroid surface was exposed and the location of the primary tumor(s) was determined. Then, 0.2-0.8 ml of methylene blue was injected at four points (1-2 mm) around the tumor, with careful intent to maintain the thyroid gland in the original anatomical position; two to four minutes later the affected side's lobe and isthmus were removed and sent for frozen section analysis. The r-finder was used to probe the distribution of radiopharmaceutical hot spots around the thyroid and in levels II-VII of bilateral neck. Lymph nodes with maximum spot count were excised and collected (Figure 1). Lymph nodes in which more than 10 times background gamma count was detected were determined to be SLN, and were used for subsequent comparisons with the results of preoperative lymph scintigraphic imaging. The amount of SLN lymph nodes that took up the blue-dye were recorded and considered for their capability to serve as visual indicators to identify SLN. The SLN was harvested and a total or near-total thyroidectomy was carried out, which included dissection of the lymph nodes from the ipsilateral central compartment. The intraoperative exploration was focused on SLN within the lateral cervical area in order to make a judgment for a modified dissection.

### Cervical treatment after SLN identification

Modified dissections were performed on those SLNs in the cervical lateral area outside the central area at levels II-V of the ipsilateral neck, and were found to be positive by frozen-section analysis. The internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle were carefully kept intact. Cases who are SLNs from the central area were frozen biopsy-positive, and all-negative SLNs were subject to ipsilateral selective lymph node dissection under original low collar incision in the anterior neck at levels III and IV. Cases with negative SLNs were subsequently processed for cytokeratin-7 (CK-7) immunohistochemical staining (Figure 2) (Beijing Zhongshan



**Figure 1:** Lymphoscintigraphy acquired at 1.5 h after 74 MBq  $^{99m}\text{Tc}$ -DX injections. The SPECT image with invasive PTC located in the right lobe shows three SLNs. Three SLNs are seen in the right lateral compartment (level III and IV). All three SLNs were excised intraoperatively with the help of a gamma probe.



**Figure 2:** Epithelial neoplastic cells infiltrating the subcapsular sinus of an SLN. CK-7 immunoreactivity is shown in brown. Magnification: 400x.

Goldenbridge Biotechnology Co., Ltd., Beijing, China). The diagnosis of micrometastasis was made when small groups of neoplastic epithelial cells (<0.5 mm) with cytoplasmic and membrane signals were identified (Figure 2). Cervical lymph node dissection specimens were sent for routine biopsy after *partition* pruning, and the results were compared with frozen biopsy.

### Tumor staging

The American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification was carried out [3]. T1 was defined as <2 cm, T2 as 2-4 cm, T3 as 4 cm and limited to the thyroid, T4a as minimal extra thyroid extension, and T4b as more extensive unresectable invasion. N0 was defined as no regional lymph node metastasis, with N1a as metastasis to Level VI, and N1b as metastasis to unilateral, bilateral, or contralateral cervical or retropharyngeal or superior mediastinal lymph nodes. M0 was defined as no distant metastasis, and M1 as distant metastasis.

### Statistical methods

Fisher's exact test on a four-fold table was carried out using SPSS v13.0 software (Chicago, IL, USA). Following the criteria for the SLN biopsy technique established by the University of Louisville in the United States, [4] the following definitions were applied to analysis: true-positive, SLN shows metastases; true-negative, both SLN and non-SLN show no metastases; false-negative: non-SLN shows metastases, while SLN shows no metastases. Sensitivity was calculated as: (SLN-positive case number/cervical lymph node metastases case number). Accuracy was calculated as: [(true-positive case number+true-negative case number)/SLN identification case number]×100%. Negative predictive value was calculated as: [true-negative/(false-negative+true-negative)]×100%. Positive predictive value was calculated as: [true-positive/(false-positive + true-positive)]×100%.

## Results

### SLN identification rate and distribution

The identification rate of sentinel lymph nodes was 100% (51/51). The blue dye technique was able to identify SLN in 90.2% (46/51) of patients, while the radionuclide technique (lymphoscintigraphy + probe scanning) was successful in 96.1% (49/51) of the patients. The number of sentinel lymph nodes identified in each patient was between one and six, with an average of 3.1. A total of 159 SLNs were identified in all 51 patients, of which 10 were in level II, 59 in level III, 30 in level IV, 59 in level VI, and one in level VII.

### Pathological results

Routine pathological examination after primary tumor surgery confirmed the diagnosis of PTC in all patients. UICC/AJCC TNM staging [3] indicated that there were seven cases of T1N0, four cases of T1N1b, one case of T2N1a, four cases of T3N0, seven cases of T3N1a, 22 cases of T3N1b, one case of T4N0, one case of T4N1a, and four cases of T4N1b. In the 51 patients, the intraoperative frozen biopsy indicated that 31 patients were experiencing SLN metastases, while post-operative routine pathological examination, as well as immunohistochemical staining with CK-7 antibody, was able to diagnose seven additional patients with lymph node micrometastases. Of these seven patients, five presented with additional metastases: two in the central and three in the lateral compartment. These five patients represent the five false-negative SLNs stained with H-E. Figure 2 shows the microscopic view of a representative micrometastasis. Routine pathological

Parameters of success	Number	Percentage
Identification rate	51/51	100.0
Sensitivity	38/39	97.4
Specificity	11/11	100
Negative predictive value	12/13	92.3
Positive predictive value	38/38	100.0
Accuracy	50/51	98

**Table 1:** Assessment of the combined technique to identify SLNs and metastasis.

examination has long been considered the gold standard to determine metastatic events; however, in one patient, SLN frozen-section biopsy and routine pathological examination showed no metastases, but postoperative pathological biopsy revealed that three nodes in level VI were experiencing non-SLN metastases. In the 39 total patients who were eventually diagnosed with metastasis, 38 were SLN-positive and non-SLN-negative, while the remaining one was SLN-negative and non-SLN-positive. Therefore, the combined identification showed the sensitivity of SLN was 97.4%. Specificity was 100%, negative predictive value was 92.3%, positive predictive value was 100%, and accuracy was 98% (Table 1). Routine biopsy of 38 patients indicated SLN metastases in a total of 72 nodes, of which 30 were level VI, 13 were level IV, 25 were level III, and four were level II.

Twenty patients underwent modified neck lymph node dissection in level II-VI of ipsilateral neck, while another 29 underwent ipsilateral neck selective dissection (level II, III, or IV). In one case out of 16 multifocal papillary carcinomas, intraoperative frozen biopsy showed positive SLN in bilateral jugulocarotid, and bilateral modified neck lymph node dissection was carried out after total thyroidectomy and dissection of the central compartment. In another case, the intraoperative frozen biopsy showed positive SLN in one lateral jugulocarotid, which was carried out by modified neck lymph node dissection. Negative SLN in another lateral was carried out by selective neck dissection. Overall, the occult metastases rate of PTC in this patient cohort of 51 individuals was 76.5% (39/51).

### Postoperative complications

No postoperative complications, such as wound fluid, wound bleeding, or incision infection, were experienced by any of the 51 treated individuals. In one patient, the recurrent laryngeal nerve located on the affected side had to be removed because of tumor invasion and wrap. Another patient experienced transient symptoms of numbness in the hands; the symptoms were relieved after consumption of calcium tablets (600 mg Ca<sup>2+</sup> and 125 IU vitamin D). No permanent hypocalcemia occurred. No patient experienced toxicity or allergic reactions due to injection of radionuclide tracer or methylene blue.

## Discussion

PTC is a common thyroid malignant tumor, accounting for 60-80% of the total thyroid malignant tumors diagnosed in clinic. Moreover, it is common to find multiple cervical lymph node metastases in these patients. The metastases rate has been estimated at between 15-50%, [5] and occult cervical lymph node metastases have been reported at 40-90% [6,7]. Unfortunately, the therapeutic value of neck surgery on patients with apparent cN0 PTC remains unconfirmed. Studies have suggested that cervical lymph node metastases do not affect the survival rate of patients with PTC, supporting the passive "wait-and-see" approach [8-10]. If and when cervical lymph node metastatic events occur lymph node dissection is undertaken, but the disease has advanced and precious treatment time has been lost. In contrast, a small

number of studies [11,12] have suggested that lymph node metastasis can reduce the survival rate. Modified radical neck dissection was shown to improve the survival rate in some subsets of patients [13]. To date, though, no reliable or effective clinical method has been established that will differentiate occult lymph node metastases in patients with cN0. Sentinel lymph node biopsy has been proposed as an alternative means of diagnosis and treatment for cN0 cases.

In 1998, Klemen et al. [14] first applied SLNB to the study of thyroid carcinoma; since then, several articles on the successful application of SLNB to PTC have appeared in the literature. The methods currently used for SLNB are most often blue dye and dye combined with radionuclide. Balasubramanian and Harrison [15] performed a retrospective meta-analysis of 24 thyroid carcinoma SLNB studies that appeared in the literature from January 1998 to November 2010. In these, 17 reports comprising a total of 832 cases of thyroid carcinoma used a single staining method to identify the SLN; the total SLN identification rate for this approach was determined to be 83.7%. Another four studies, composed of 129 cases, used single isotope  $^{99m}\text{Tc}$  labeled colloids to identify the SLN; the overall SLN identification rate for this approach was 98.4%. The other two studies, composed of 50 cases, used both methylene blue dye and radioisotope techniques to identify the SLN, and the overall SLN identification rate was 96%. Evidence from these studies has shown that the radioisotope technique and the combination of dye and radioisotope methods are superior to use of blue dye alone in the detection of SLNs. In our study, we obtained similar results in that the SLN identification rate of 51 patients using the blue dye technique was 90.2%, while the identification rate using the radionuclide method (lymph node scintigraphic imaging+probe scanning technique) was 96.1%.

The advantages of the blue dye technique are that there is no need for special equipment, the procedure is technically simple to perform, the reagents are low-cost, and there is no radioactive contamination resulting. In particular, the technique facilitates the unaided visualization of the targeted tissues, which can be helpful when combined with the radionuclide technique for the r-probe to locate the "hot" lymph nodes. The disadvantages of the dye technique are that it requires a low collar incision of the thyroid gland which may not fully expose the SLNs outside the central compartment (level VI) which may lead to omissions of SLNs in the lateral neck area, and that the blue pollution occurring upon lymph node rupture during subsequent anatomical analysis of the thyroid gland may make SLN identification more difficult. The above shortcomings are likely to contribute to the relatively low SLN identification rate which characterizes this staining method.

In a review by Rubello et al. [16] the outcomes associated with the SLN biopsy technique in differentiated thyroid carcinoma were summarized from among papers cited on PubMed/MEDLINE through June 2005. The authors noted that the vital blue dye technique has some disadvantages, such as risk of disruption of the lymphatic channels deriving from the thyroid carcinoma, difficulty in disclosing those SLN lying outside the central compartment, and the fact that parathyroid glands can take up the blue dye as well. Some of these disadvantages can be overcome by using the lymphoscintigraphy and intraoperative gamma probe technique. Moreover, a combination of the blue dye and gamma probe technique has been proposed and in our hands has yielded acceptable results. We used the combined nuclear medicine technique with lymphatic vital dye with the expectation of enhancing the identification rate of sentinel nodes in thyroid carcinoma. The SLN identification rate from using the vital blue dye technique was 90.2%,

while the identification rate from using the nuclear medicine technique (lymph node scintigraphic imaging + probe scanning technique) was 96.1%.

The radionuclide imaging principle maintains that after intratumoral injection of tracer the tracer colloid enters into the lymphatic capillaries as a result of permeabilization of the lymphatic wall and pinocytosis of the endothelial cell. Local dynamic imaging observations have revealed that the lymph node presenting first in the imaging is the SLN. In addition, lymph nodes are further identified using an r-probe with high sensitivity during the surgical procedure; the lymph node with the maximum count, or more than 10 times more than the background count, is considered the SLN. In our patient cohort, the lymph node identification rate for the radionuclide method was 96.1%. The higher success rate is likely related to the fact that the preoperative B ultrasound-guided intratumoral injection of the tracer did not damage the lymphatic drainage system, and possibly that the highly sensitive r-probe was used to identify those sentinel lymph nodes that were invisible to our naked eyes, particularly those residing in the cervical lateral area.

Unfortunately, the radionuclide method is limited by some inherent disadvantages. Injection of radioisotope is necessary and may cause secondary damage. The hand-held r-probe is expensive, and the technique requires additional ultrasound diagnosis and cooperation of nuclear medicine physicians. Finally, the ability to differentiate SLN from non-SLN is not as straight-forward as the simple visualization obtained with the staining method. Nonetheless, the improved identification rate achieved through the combined use of the staining and radionuclide methods justifies their concomitant use [17].

In SLNB of thyroid carcinoma, isotopic tracer should be injected into the tumor under the guidance of B-ultrasound. During our initial attempts, we injected tracer into the thyroid tumors of three patients based only upon palpation, but the SLN was not able to be identified in any of these patients. This failure may have been due to inaccurate isotopic tracer injection. The tracer might have been injected into the proximal muscle outside the thyroid tissue and fascia tissue, resulting in a high background r count surrounding the thyroid and interfering with the hand-held r-probe detection abilities.

The metastases rate of lymph node is believed to be low in level II and V of cN0 PTC; specifically, the metastases rate has been reported as 9.3% in level II and as 5.7% in level V [18]. Our patients that were found to have negative SLN in the cervical lateral area (including levels II-V) were subjected to dissection in lateral levels III, IV and non-lateral level VI to determine the accuracy of SLN biopsy. The subsequent SLN identification rates for levels II and V were 15.7% (8/51) and 0%, respectively, and the metastases rates were 17.6% 9/51 and 0%, respectively.

The low collar incision technique of conventional thyroid surgery is routinely used in patients with negative SLN in the cervical lateral area; moreover, surgical incision is usually not extended to the level of III, IV and VI, in order to maintain important structures such as the cervical plexus nerve, internal jugular vein and carotid artery. Thus, the incision results in little to no impact on functions and appearance of the patients.

As stated above, thyroid carcinoma has a tendency to manifest as multiple primary lesions. Preoperative B ultrasound-guided biopsy is capable of identifying nodules with large diameter (presumed as those most likely to be malignant). These nodules are then the primary targets for tracer injection, creating the possibility that some affected

but smaller nodules may be excluded from the SLN analysis. In our study, the SLNB accuracy was 98%, the negative predictive value was 92.3%, the positive predictive value was 100%, specificity was 100%, and sensitivity was 97.4%. Thus, our results suggest that the use of SLNB is feasible for PTC prognosis.

We also determined that the accuracy of intraoperative frozen biopsy was 82.3%. The major factor negatively impacting this measurement was presumed to be the limited material collected for the intraoperative frozen biopsy which might not have accurately represented the whole specimen. SLNB showed a high success rate for patients with PTC and was technically feasible. The identification of lymph node metastases in patients with cN0 PTC through SLNB will facilitate the decision to conduct regional lymph node dissection or not, and could significantly reduce surgical complications by avoiding over-treatment. Moreover, the technique will contribute to the improvement of prognosis for PTC patients. Whether the approach is able to significantly enhance the long-term survival rate of patients with PTC and reduce neck recurrence rate remains to be confirmed by large-scale rand.

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