

Feasibility of sentinel lymph node dissection using Tc-99m phytate in papillary thyroid carcinoma

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Purpose: Various methods of sentinel lymph node (SLN) biopsy in thyroid cancer have been introduced. Tc-99m phytate as a radiotracer has been successfully utilized for SLN biopsy in breast, cervix, and endometrial cancer. We assessed the feasibility of SLN dissection using Tc-99m phytate in papillary thyroid carcinoma (PTC).

Methods: Seventeen patients with PTC were prospectively enrolled. Ultrasound-guided peritumoral injection of 55.5 MBq Tc-99m phytate in 0.25-mL normal saline was performed. Preoperative single-photon emission-computed tomography (SPECT) and intraoperative gamma-probe were used for SLN detection during operation.

Results: Identification rate of SLNs was 70.6% (12 of 17) with SPECT, and 88.2% (15 of 17) with gamma-probe. Combined SPECT and gamma-probe had identification rates of 88.2% (15 of 17). Identification rates of SLNs in central LN compartments were 82.4% (14 of 17) and 41.2% (7 of 17) in lateral LN compartments. Overall sensitivity, specificity, positive predictive value, and negative predictive value of the results of SLN biopsy were 91.6%, 100%, 88.4%, and 100%, respectively. Eight patients (47.1%) had metastasis in SLNs; all patients had SLN metastasis in the central compartment and 2 patients had SLN metastasis in both the central and lateral compartments.

Conclusion: Combined SPECT and gamma-probe could detect SLNs with an 88.2% identification rate in PTC. SLN biopsy using Tc-99m phytate is technically feasible. Further investigation is warranted for clinical application of Tc-99m phytate in PTC.

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Key Words: Sentinel lymph node biopsy, Papillary thyroid cancer, Phytate, Gamma-probe, Single-photon emission-computed tomography

INTRODUCTION

Papillary thyroid carcinoma (PTC) predominantly metastasizes into regional lymph nodes (LNs) [1]. In cases with clinically

or radiographically apparent LN involvement, the prognostic benefit of neck dissection in addition to total thyroidectomy is unequivocal [1,2]. However, management of nodal negative tumors is still controversial. To date, there is no evidence in

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the literature proving any general benefit of prophylactic neck dissection for PTC, though some studies suggest a decrease of regional recurrence and improvement of survival for high-risk patients [2-6]. With the inconvenience for patients and the potential risks of this procedure (e.g., recurrent laryngeal nerve damage during dissection of the central compartment and postoperative hypoparathyroidism) many centers still favor a conservative policy [7,8]. Therefore, it is very important to determine the LN involvement of tumors preoperatively. Currently, ultrasound and CT are used to reveal the LN status preoperatively. However, the accuracy of those studies still does not reach 60% [9,10].

The sentinel lymph node (SLN) concept has been successfully attempted for malignant melanoma, breast cancer, oral squamous cell carcinoma, and other tumors with predominant nodal spread and high-risk for occult disease [11-13]. It allows the histological staging of the lymphatic drainage without excising the whole lymphatic basin [14]. By doing this, patients who would benefit from extended lymphatic dissection can be selected, and the others can be spared the risks and costs of this procedure [14]. SLN biopsy in thyroid carcinoma also has the potential to identify and stage regional LN status without performing a prophylactic neck dissection [15]. Its accuracy and safety has been reported in many previous studies by the use of a blue dye or a radioisotope as a tracer [15-17].

Meanwhile, Tc-99m phytate, as a radiotracer, has been successfully utilized to investigate LN metastasis patterns in breast, cervix, and endometrial cancer [18-21]. But there have been few attempts with Tc-99m phytate for LN detection in thyroid cancer patients. We conducted this study to assess the feasibility of Tc-99m phytate and to detect possible technical pitfalls of preoperative lymphatic mapping by single-photon emission-computed tomography (SPECT) and SLN biopsy guided by the intraoperative use of a gamma-probe in patients with PTC (Fig. 1).

METHODS

Patient selection

From April 2012 to December 2013, a total of 17 patients with PTC underwent SLN biopsy. Patients with Bethesda category VI PTC on fine needle aspiration biopsy, were eligible for the study.

The protocol of this study was approved by the relevant Institutional Review Board of Seoul National University Hospital (SNUH 1109-105-379) and patients were enrolled after they had given written informed consent.

All patients underwent an ultrasound and CT evaluation of the neck prior to operation. Cases with PTC with/without suspicious central or lateral neck node metastasis were included: eight patients with suspicious LN metastasis and nine patients without suspicious LN metastasis, respectively. Exclusion criteria were prior radiotherapy or surgery in the neck, pregnancy or lactation, and thyroiditis.

SLN mapping

LN mapping was performed by preoperative SPECT and intraoperative use of a hand-held gamma-probe (Neo 2000, Neoprobe Corp., Dublin, OH, USA). Tc-99m phytate (Techne Phytate Kit, FUJIFILM RI Pharma Co., Tokyo, Japan) was used as a radiotracer. Under ultrasound guidance, peritumoral injection of 55.5 MBq Tc-99m phytate in 0.25-mL normal saline using disposable syringes with a 25-G needle was administered cautiously to prevent spillage of the radiotracer outside the thyroid. Preoperative SPECT was performed 3 hours after Tc-99m phytate injection time.

Operative procedure

In the operating room, total thyroidectomy with routine ipsilateral prophylactic central neck dissection was performed. After formal hemithyroidectomy of the tumoral side through a low collar incision, the central compartment and the lateral compartment SLNs were searched for hot spots with the aid of the gamma-probe. Both radioactive nodes as well

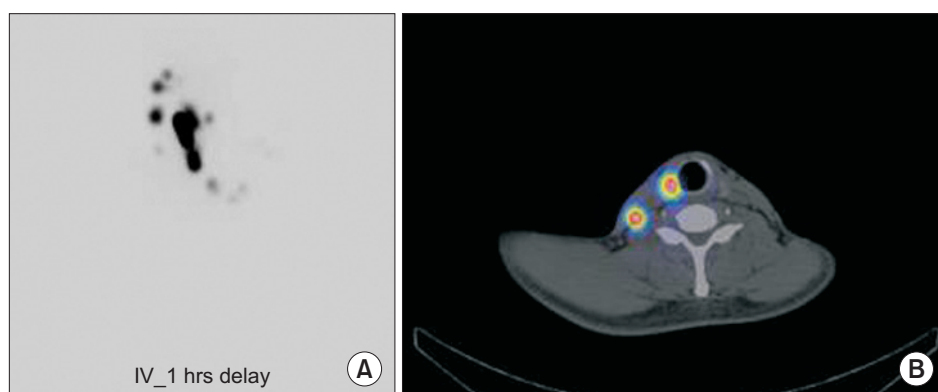


Fig. 1. Preoperative lymphatic mapping by single-photon emission-computed tomography. IV, intravenous injection.

Table 1. Clinicopathologic feature of the patients

Characteristic	Value
Age (yr), mean (range)	47.9 (32–63)
Sex, male:female	2:15
Extent of thyroidectomy	
Total thyroidectomy	14
Total thyroidectomy with MRND	3
Sentinel lymph nodes	
No. of SLNs	104
No. of lateral SLNs	21
No. of lymph node metastasis	
Central compartment	33
Lateral compartment	14
Tumor size (cm), mean ± SD (range)	0.65 ± 0.80 (0.4–1.0)
Tumor location, right:left	8:9
Extrathyroidal extension, n (%)	10 (58.9)
Gross	10
Microscopic	0
Lymph node metastasis, n (%)	9 (52.9)
N1a	5
N1b	4
<i>BRAF</i> mutation, n (%)	13 (76.5)
Transient hypoparathyroidism, n (%)	4 (23.5)
Permanent hypoparathyroidism	0
Vocal cord palsy	0
Chyle leakage	0

MRND, modified radical neck dissection; SLN, sentinel lymph node; SD, standard deviation.

as nonradioactive nodes in the central compartment were removed. Then hot nodes were selectively excised to compare on the permanent section. When SLN(s) were detected in the lateral compartment, frozen biopsies of lateral hot nodes were performed to determine whether to do modified radical neck dissection (MRND) according to the result of the frozen section. The activity of the lymphatic bed had to drop to background levels after excision of the SLN(s). All step-sections were stained for hematoxylin and eosin (H&E) and cytokeratin. As to procedure-related complications, no intraoperative or postoperative complications occurred.

RESULTS

Characteristics of patients

The mean age of the 17 patients who met the inclusion criteria was 47.9 years (range, 32–63 years). Of the 17 patients, 2 were men and the others were women. Primary tumor locations, tumor size, tumor extent, the thyroid procedures performed, and other characteristics of these patients are shown in Table 1.

Table 2. Location of sentinel lymph nodes (SLNs)

SLN level	Detected number of SLNs	No. of metastatic SLNs
Ipsilateral		
Central	67	16
Lateral	19	7
Contralateral		
Central	16	1
Lateral	2	0
Total	104	24

Accuracy of SLN biopsy

Identification of SLNs was possible in 12 of 17 cases (70.6%) with SPECT and in 15 of 17 cases (88.2%) with the gamma-probe. Combined SPECT and gamma probe identified 15 patients with SLNs in 17 patients (88.2%). Identification rates of SLNs in central LN compartments were 82.4% (14 of 17) and 41.2% (7 of 17) in lateral LN compartments. Sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of the results of SLN biopsy were 91.6%, 100%, 88.4%, and 100%, respectively.

Eight patients (47.1%) had metastasis in SLNs; all patients in the central compartment and two patients in both central and lateral compartments. In one female patient, SLN metastasis was revealed on lateral LN frozen sections, she thus underwent immediate MRND. Histologic work-up of the thyroid specimens revealed all patients with PTC.

Distribution of SLNs

Distribution of SLNs is shown in Table 2. A total of 104 SLNs were identified and 24 SLNs were metastatic LN. Sixteen and 7 SLNs were located in the ipsilateral central and lateral neck compartments, respectively. Eighteen SLNs in 5 patients were located at the contralateral level. The patients with contralateral lateral neck SLNs had no metastatic SLNs.

DISCUSSION

SLN biopsy has achieved consensus as a staging procedure in breast cancer and melanoma patients [12,13]. It allows the histological staging of lymphatic drainage without excising the whole lymphatic basin. By doing this, patients who benefit from extended lymphatic dissection can be selected while the others can be spared the risks and costs of this procedure [14].

Since its introduction in 1988 [22], many authors have described the usefulness of SLN biopsy in thyroid carcinoma patients [14-17]. SLN biopsy for PTCs has the potential to identify and stage regional LN status without performing a prophylactic neck dissection [14]. Its accuracy and safety has been addressed in many studies by the use of a blue dye as a tracer, as well as

trials using a radioisotope.

Most previous studies used the intraoperative injection of a blue dye to trace the lymphatics to the SLN. However, there are several disadvantages of this technique [14]. First, lymphatics that run out of the central compartment cannot be followed through the collar incision for thyroidectomy. Second, dissection of the thyroid node for injection may interrupt important lymphatic vessels. Finally, recognizing a blue node is not always easy. To overcome these problems we used the preoperative ultrasound guided injection of a radiotracer: Tc-99m phytate, instead of a blue dye. Tc-99m phytate has more advantages in lateral compartment SLN detection. Moreover, preoperative SPECT and intraoperative gamma-probe can aid in detecting SLNs which may not be easily recognized by the blue dye injection method.

Tc-99m phytate was first used in 1973 for imaging of the reticuloendothelial system [23]. Since then, Tc-99m phytate has been used as a radiotracer to investigate the LN status in some cancer patients [18-21]. Tc-phytate has a diameter of 100–200 nm. Tc-phytate may overcome the limitations of the slow migration rate of larger particles and does not have the disadvantage of smaller particles diffusing quickly to the distal LN [18,24]. One study reported that in breast cancer and cervix cancer, NPV was 97.3% and 100%, respectively, with Tc-99m phytate use, and that in endometrial cancer, the sensitivity and specificity of Tc-99m phytate was 100%. Even Seok et al. [18] reported the SLN detection rate as superior for Tc-99m phytate compared to that with Tc-99m Tin-colloid in breast cancer patients.

When it comes to safety issues, Tc-99m has been already used widely in many clinical trials. SLN biopsy became the standard procedure in early breast cancer surgery. SLN biopsy using radioactive colloid is safe in terms of radiation safety, with the actual exposed doses being safe for the attending surgeon, operation nurse, pathology technologist, and nuclear medicine physician [25].

The identification rate of SLNs was 88.2%. Sensitivity, specificity, positive predictive value, and NPV of the results of SLN biopsy were 91.6%, 100%, 88.4%, and 100%, respectively. Though we enrolled a small number of cases, Tc-99m phytate showed good accuracy results compared to previous SLN biopsy study results [15]. The total of 104 SLNs in 17 cases was considered high. Slightly overdiagnosed SLNs might be due to the sentinel LNs in the lateral compartment as well as the central compartment, and contamination which is thought to be from spillage. Also, the size of the LN was so small that it might be difficult to distinguish the sentinel LNs from the non-sentinel LNs in early cases. It was possible to overcome these technical problems by repeating the study.

In one patient, SLN frozen biopsy results were all negative, but permanent biopsy results of all dissected LNs revealed some metastatic LNs. The false-negative rate (FNR) is one of the most

important issues for the SLN technique [26]. High FNR would render this technique unsuitable for routine practice. Novel methods for SLN detection such as MR lymphangiography and carbon dye labeling are currently under investigation [27]. Furthermore, more studies on the technical aspects of harvesting SLN such as serial sections, immunohistochemical stains, and molecular marker assays can also increase the detection rate of SLN metastases [28,29].

We performed SPECT 3 hours after Tc-99m phytate injection because we believed that it might take some time for sufficient lymphatic drainage. It is much easier to handle the gamma-probe when the surgeon has a rough idea of where to look for the SLN [14]. Distant SLNs (lateral compartment or lower central compartment) were more adequately revealed with SPECT.

In the operating room, we performed routine ipsilateral prophylactic central neck dissection in order to solve technical problems and ethical problems. Central hot nodes were separated and we reviewed their permanent biopsy results retrospectively. The use of the SLN biopsy technique in thyroid cancer as an alternative to prophylactic LN surgery in preoperatively node-negative patients is still controversial [26]. Therefore, we performed routine ipsilateral prophylactic central neck dissection. Additional subpopulation studies based on more cases are considered necessary in deciding on whether to skip central compartment dissection.

Our study is a pilot study and we enrolled 17 cases. Certainly, further investigation based on more cases is warranted for clinical application of Tc-99m phytate in PTC. However, it was possible to establish study protocol and to show satisfactory detection rates with 17 cases alone.

The impact of occult metastatic LN involvement on recurrence and survival has not yet been elucidated prospectively [30]. Therefore, we cannot verify benefits with regard to survival from disclosing occult metastatic neck disease by SLN biopsy in all patients [14,30]. The benefit of SLN biopsy in PTC could be hard to prove. Further investigations are needed.

In conclusion, SLN biopsy using Tc-99m phytate is safe and technically feasible. The combination of SPECT and gamma-probe reveals SLNs in the central and lateral compartments more easily. However, further investigation is warranted for clinical application of Tc-99m phytate in PTC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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