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Sentinel lymph node biopsy for papillary thyroid cancer: the effect of dose, tracer and application of massage

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ABSTRACT

Objective(s): In patients with papillary thyroid cancer (PTC), sentinel lymph node (SLN) radio-guided biopsy is not routinely used for detection of involved neck lymph nodes (NLN); ^{99m}Tc- antimony sulfide colloid (^{99m}Tc- ASC) has been used for this purpose. In this study, besides ^{99m}Tc-ASC another radiotracer, ^{99m}Tc-phytate (^{99m}Tc-P) with different doses and injection methods were evaluated.

Methods: Twenty-two patients, scheduled to undergo thyroidectomy for PTC, were injected for radio-guided SLN biopsy in the morning of operation in 3 groups: intra tumoral injection of about 1 mCi ^{99m}Tc-P (group A; n=5); peritumoral injection of less than 3 mCi ^{99m}Tc-ASC (group B; n=6); and peritumoral injection of 3 to 5 mCi ^{99m}Tc-ASC with application of massage (group C; n=9). A patient refused to complete the study. A patient with follicular thyroid cancer was also excluded. No NLN was detected in the pre-operative ultra-sonographic examinations of all patients. Central neck dissection was done for all the participants. The presence of radio guided detected NLN and results of pathology were assessed.

Results: In group A and B, no SLN was detected. NLNs were resected in 4 patients in group A and B; 2 of them involved by the tumor. In group C, 6 out of 9 patients (66.7%) had between 1 to 6 SLNs; the procedure failed to detect NLN in a patient in group C with surgically resected reactive NLN (failure rate 1 out of 7).

Conclusion: The results underscored the significance of SLN radio guided biopsy in patients with PTC; the radiotracer, dose and method of injection may affect the detection rate.

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Introduction

Sentinel lymph node biopsy (SLNB) is the standard of care in many clinical scenarios including breast cancer and melanoma surgeries (1, 2). SLNB benefits for patients with thyroid cancer is not established yet. Lymph nodes (LN) are the major site for loco-regional metastasis in papillary thyroid cancer (PTC) (3-6). Usually, clinically significant LNs are detected by sonography before thyroidectomy and then therapeutic or prophylactic LN dissections are done. Neck dissection is an extensive and critical surgery which merits enough prior assessment and justifications (7, 8). ATA does not advocate prophylactic neck dissections (PND) in patients clinically negative for neck LN (cN0) (9). Although preoperative neck ultrasound identifies suspicious cervical lymphadenopathy in 20-30% of patients (10), a considerable portion of cN0 patients present with involved LNs in PND (11), or within post-therapeutic whole body iodine scans (12). Based on the

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results of SLNB, standard LN dissections are preserved in many patients with breast cancer, melanoma and vulvovaginal cancers (1, 13).The efficacy and value of SLNB is under study in many other malignant tumors including cervical and uterine cancers, neck squamous carcinomas, lung cancers and certain GI tract adenocarcinomas (14-17). There are a few reports concerning the application and efficacy of SLNB for PTC. Conflicting results are reported about the detection and failure rate by the frequently employed antimony sulfide colloid (18-23). For decades we have used, ^{99m}Tc-phytate (^{99m}Tc-P) routinely instead of ^{99m}Tc- antimony sulfide colloid (^{99m}Tc-ASC) (24); preparation of phytate is easier and the procedure is rapid without need for heating. However, the particle size differs between ^{99m}Tc-P and ^{99m}Tc ASC (25) (i.e. 1-30 nm vs. 3-30μm) (26), the detection rates for breast cancer and melanoma are perfect with ^{99m}Tc-P and comparable with ^{99m}Tc-ASC(27, 28). The particle in ^{99m}Tc-P is essentially formed within the body after stannous phytate enters the blood or LN and react with calcium (29). Due to small particles size there has been concerns about the retention in or washout from the LN, but the practice for breast cancer and melanoma proved its efficacy (30). ^{99m}Tc-P has recently been examined for SLNB in patients with PTC with a detection rate of 88.2% (31). Nevertheless, considering the above mentioned small particle size concern, (2) the use of ^{99m}Tc-phytate instead of ^{99m}Tc-ASC for PTC patients is not yet well established. In this article, we report our experience to use ^{99m}Tc-P for SLNB in patients with PTC, the possible difference between the above mentioned two tracers, and the importance of the site of injection and application of massage.

Methods

We studied 22 patients scheduled, dated April 2015 to April 2017, for total thyroidectomy by a surgeon in a teaching university hospital. The study protocol was in accordance with international and national ethical guidelines and written informed consents were collected. Patients comprised those with high suspicion for PTC based on the results of fine needle aspiration and ultrasonography who had no neck LNs (NLN) detected in their preoperative sonography. Two patients were excluded, 1 because the pathology was revealed to be follicular thyroid cancer and the other patient refused to share the researchers her pathology report. Preoperative reports of neck sonography were collected. Under the guide of sonography (Digital Color Doppler SSI-6000, Sonoscape, Shenzhen, China), 1 or 2 intra-thyroidal injections of 0.1 to 0.2 ml radioisotope were done in the morning of surgery with different methods in 3 groups. In group A, about 1 mCi ^{99m}Tc-P was intratumorally injected (n=5). In group B, peritumoral injections of less than 3 mCi ^{99m}Tc-ASC were done (n=6). In group C, peritumoral injections of 3 to 5 mCi ^{99m}Tc-ASC were done (n=9). In the latter group, post injection massage was applied for 30 seconds on the injection site. For preparations of ^{99m}Tc-ASC and ^{99m}Tc-P, ^{99}Mo-^{99m}Tc generators (Pars Isotope Co, Tehran, Iran), and phytate and antimony sulfide colloid kits (Pars Isotope Co, Tehran, Iran) were employed. The manufacturer instructions were followed; particularly in contrast to ^{99m}Tc-P, ^{99m}Tc-ASC was boiled for 30 minutes which equals to roughly about 40 minute longer preparation time. The patients were sent to operation room where the neck was searched for the presence of active LN by gamma probe (Surgeoguide, Partonegarpersia Co, Tehran, Iran). The suspected LNs were excised and labeled for pathological examination. Then total thyroidectomy and central neck dissection were done in all patients preserving the recurrent laryngeal nerves. The results of the pathologic examination were collected after two weeks. Data was analyzed using IBM SPSS (V22.0) and cross tabulation with significance of $p<0.05$ was employed.

Results

The disease related data of the participants are presented in table 1. T staging was as: T1, 10 patients (50%); T2, 8 (40%); T3, 1 (5%); and T4, 1 (5%). In group A and B no sentinel lymph node (SLN) was detected. In group C, 1 or 2 SLNs were detected in 6 (66.7%) patients. In 3 other patients in group C with no detected SLN, one had surgically resected LN, which was reactive (failure rate 1 out of 7; false negative rate of 0). Out of 6 patients with SLNB, a patient had pathologically involved LN. In a patient from group A and in 3 patients of group B, LNs were resected surgically out of which 2 patients had pathologically involved LNs. The results of pathologic examination of the patients are summarized in table 2. Among vascular/ lymphatic, capsular, and extra-thyroidal invasion, the only variable correlated with involvement of central NLNs was vascular/ lymphatic invasion (Fisher exact test P value=0.03). Neither detection of SLN nor the involvement of NLN was correlated with any other characteristics collected by sonography or pathology. The central neck dissection had the potential to affect decision for radioiodine ablation or the dose of radioiodine in 8 patients. The dose of radioiodine was increased to 150 mCi in 2 patients with involved NLNs. Also the idea to

leave T1b tumors untreated was strongly fostered confirming pathologically negative NLN (6 patients in this study). Overall, 8 patients out of 20 patients (40%) might have encountered decision change considering the results of central neck dissections.

Table 1. Characteristics of the participants in pre-operative ultrasonography

Sex	Female	16 (80)
Age		36.7 (11.1)
Lobe (Larger nodule/ Injection site)	Right	10 (50)
	Left	10 (50)
Size		19.5 (11.6)
Micro-calcification	Yes	19 (95)
Vascularity	Increased/Abnormal	12 (60)
Echogenicity	Hypoechoic	20 (100)
Simultaneous nodule	Yes	5 (25)
Suspicions LN in sonography		0 (0)

Data are mean (standard deviation) or number (percentage)
LN, lymph node

Table 2. Sentinel lymph node detection and the pathologic characteristics of the patients in 3 groups; 1 mCi ^{99m}Tc-phytate; less than 3 mCi ^{99m}Tc- ASC(low dose); and 3 to 5 mCi ^{99m}Tc- ASC with post injection massage (high dose)

	^{99m}Tc-phytate n= 5	**Low dose ^{99m}Tc-Antimony n =6**	**High dose ^{99m}Tc-Antimony n =9**	**Total**
LN involvement	1 (20)	1 (17)	1 (11)	3 (15)
Surgical resected LN	1 (20)	3 (50)	7 (78)	11 (55)
Radio guided detected SLN	0 (0)	0 (0)	6 (67)	6 (30)
Node detection†	4 (80)	3 (50)	8 (88)	15 (75)
False negative rate ‡	1(20)	1(17)	0(0)	10%
Vascular invasion	2 (22)	2 (33)	0 (0)	4 (20)
Capsular invasion	1 (20)	1 (17)	1 (11)	3 (15)
Extra-thyroid extension	0 (0)	1 (17)	0 (0)	1 (5)

Data are number (percentage)
LN, lymph node; SLN, sentinel LN
†True positive and true negative lymph node detection†
‡ Sentinel lymph node

Discussion

Applying 1 mCi ^{99m}Tc-P intratumoral injection was not useful for radio-guided SLNB. Changing the tracer into ^{99m}Tc-ASC and shifting the injection site from intratumoral into peritumoral did not improve the result to detect any SLN while the surgeon found LNs in 4 out of 11 patients in group A and B. The increased radioactive dose (up to 5 mCi) and post injection massage showed remarkable changes in detection rate (66.7%). The participants were the patients that were not in need for central LN dissections because there was no suspicious LN in clinical or sonographic examinations. Out of 6 patients with detected SLNs, one patient had pathologically involved LNs (16.7%). Consequently, the surgical procedure for this patient changed by lymphoscintigraphy with the burden of 6 SLNBs. Because the main indicator to repeat surgery and iodine therapies are loco-regional surgical remnants, these results infer that the use of SLNB is plausible in the sonographically negative thyroidectomy candidates. It is noteworthy to consider that it is not yet confirmed that the pathological status of sentinel nodes is reliable for central lymph node status.

There are shreds of evidence that massage improves the results of SLNB in breast cancer and the detection rate for axillary LNs but this is the first time that similar notion about massage is reported for thyroid lymphoscintigraphy. The massage may improve the entrance of the tracer into the lymphatic vessels. The intratumoral injection was first adopted because it was employed for thyroid lymphoscintigraphy previously by stoeckli (32), pelizzo (33) and boschin et al (34); however, the intratumoral injection is not the routinely accepted method of injection in breast lymphoscintigraphy. The change of the injection site from intra to peritumoral site did not improve the detection ability while the tracer was simultaneously changed to more internationally employed tracer, ^{99m}Tc-ASC. ^{99m}Tc-P is used widely in our practice, in Iran, for SLNB of breast cancer and melanoma and also instead of ^{99m}Tc- sulfur colloid for GI bleeding scintigraphy and infrequent liver and spleen scans (35). Nevertheless, there have been always concerns about the comparability of the results for SLNB with ^{99m}Tc-P and ^{99m}Tc-ASC (2, 36). The performance of the two tracers are mutually similar for breast cancer and melanoma. The

main idea behind current study was to test ^{99m}Tc-P for thyroid lymphoscintigraphy for the first time. We cannot disregard the possibility that using higher doses and massage may lead to achieving similar results with ^{99m}Tc-P. This may be the topic for future studies as well as testing the idea of SPECT or SPECT/CT imaging the day before the surgery. Considering the prophylactic neck dissection performed in the current study which was done according to the routine practice of our surgeon (i.e. AA), there are remarkable inconsistency for its appropriateness. The rate of positive NLN involvement in clinically negative NLN (cN0) patients are rather high, and it is documented that unremoved involved NLN increases the recurrence rate and reduces the overall survival. However, there are documents indicating similar overall survival for T1-T2 cN0 patients treated with thyroidectomy alone and thyroidectomy with prophylactic central neck dissection (37) . Prophylactic dissection changes decisions for radioiodine ablation in about 1 out of 4 patients with T1-T2 cN0 PTC. The decision for prophylactic neck dissection could be "personalized" regarding surgeon's experience (38). In the current study, 10% of prophylactically resected central NLNs were involved by the tumor. Did the SLN detection enable the surgeons to reduce the uninvolved NLN resection, the prophylactic LN resections may be more reasonably supported to reduce recurrence rates .

The dose we used for detection of SLNs is rather high compared to lymphoscintigraphy of breast. We may use lower doses with the same results employing the post injection massage, this concept also should be further studied. The radiation dose to the body with 5 mCi ^{99m}Tc is similar to that from the Technetium thyroid scans and less than 2 mSv which is lower than the absorbed dose from natural sources annually (39). Hence the hazards of this radiation are seemingly acceptable in tradeoff with its benefit. For future studies, the addition of pre-operative SPECT imaging could be sought in order to provide the surgeon with additional information to improve surgery planning (40).

We did not perform lymphoscintigraphy mainly due to tight operation room schedule and that the thyroidectomy surgeries of the contributing surgeon were booked for the early morning. The operation team required patient present at their unit soon after radiotracer injection. Also, the detailed location of the dissected LN was not labeled by the surgeon. These weak points should be considered and addressed in future researches.

Conclusion

We may conclude intra-thyroid ^{99m}Tc-ASC injections employing post injection massage could be used for detection of central neck region LNs in thyroidectomy candidates with negative clinical and ultrasonography for suspicious LN before surgery. The detection rate for doses between 3 and 5 mCi was 66.7% with a failure rate of 14.3%. These figures are fairly acceptable in the population of our study, the patients with negative LNs at preoperative ultrasound examination. The low dose (1 mCi) ^{99m}Tc-P without massage cannot be used for SLN detection.

Compliance with Ethical Standards

Ethics approval and consent to participate

All human studies have been approved by the Tehran University of Medical Sciences ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions.

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Conflict of interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Authors contributions

MZ participated in developing the study idea, data gathering and interpretation, AA and MM performed the surgeries and conducted the radio-guided biopsies, SF and MA conceived the study and participated in radiotracer injection part and data gathering and interpretation, ME supervised the study and MN participated in data gathering and interpretation. All the authors contributed to draft the paper.

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