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ORIGINAL ARTICLE

Added Value of Postoperative Radioiodine Scan for Staging and Risk Stratification in Papillary Thyroid Microcarcinoma

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Abstract

Objective. The complete staging and risk stratification of Papillary thyroid microcarcinoma (PTMC) is usually not done due to its theoretically low recurrence rates. This study aimed to determine the value of postoperative radioiodine diagnostic scan and SPECT/CT for the accurate staging and risk stratification in PTMC patients.

Methodology. This study was a retrospective review of PTMC patients from January 2014 to May 2017 who underwent I-131 scans. All PTMC patients were initially staged by the 8th edition AJCC/TNM staging system and risk-stratified, based on clinical information, histopathology and stimulated thyroglobulin (sTg). After I-131 scan, staging and risk stratification were re-assessed. The proportion of patients who ended up with a higher stage and risk stratification were reported.

Results and Conclusion. Fifty-two patients were included. The overall upgrading of cancer stage was 7.7 %. The overall higher risk stratification was 19.2% with radioiodine-avid lymph node, lung, and bone metastases. Neck and paratracheal node metastases were found in 37.3% of the initial low-risk patients with sTg less than 5 ng/mL. Lung metastasis was found in the initial intermediate-risk patient. The I-131 scan helps to localize metastatic lesions and results in a higher stage in 50% of the initial high-risk patients. This study provides some evidence showing the value of postoperative radioiodine WBS for accurate staging and risk stratification in PTMC patients. Larger studies with analytical design should be further performed to prove its significant utility.

Key words: papillary thyroid microcarcinoma, postoperative radioiodine scan

INTRODUCTION

Papillary thyroid microcarcinoma (PTMC) is a differentiated cancer of the thyroid gland in which tumor size does not exceed 1 cm in maximum diameter.[1] The incidence of PTMC has increased over the last 20 years.[2-4] PTMC without extrathyroidal extension or lymph node metastasis has an excellent prognosis with a low recurrent rate (less than 2%) and mortality rate (less than 1%).[5,6] Although PTMC has a low risk of recurrence, the previous retrospective studies revealed that cervical lymph node metastases and distant metastasis in PTMC were found 12.4-30% and 0.4%, respectively.[7,8]

For disease staging and risk stratification after surgery, postoperative serum-stimulated thyroglobulin (sTg), neck ultrasonography (US), and postoperative radioiodine whole-body scan (WBS) are commonly performed.[9,10] The sTg level has a high sensitivity to detect distant metastasis, but serum thyroglobulin antibody (Tg-Ab) can interfere with its measurement.[11] Neck US has a high sensitivity in detecting gross residual disease and cervical lymph node metastasis,[12] but it is unable to detect micrometastasis and, occasionally, is limited in distinguishing post-operative changes and residual disease. Postoperative radioiodine WBS has an added value in the staging by improving the detection of occult functional locoregional disease and distant metastasis, however, its benefit is still debatable for complete staging in differentiated thyroid cancer patients.[13-16]

Accurate staging and risk stratification are necessary for decision-making and guidance for proper subsequent I-131 treatment. Evidence of locoregional or distant metastasis strongly increases disease recurrence risk, leading to poorer disease-free survival.[17-19] This study aims to determine the incremental value of postoperative radioiodine scan and SPECT/CT for the accurate staging and risk stratification in PTMC patients.

METHODOLOGY

This retrospective study protocol was approved by the Research Ethics Committee of the Faculty of Medicine of Chiang Mai University. Informed consent was not required. We consecutively reviewed 343 patients with

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Table 1. Initial risk stratification categories[9,21]

Initial low risk	Initial intermediate risk	Initial high risk
No local or distant metastasis	Microscopic invasion to perithyroidal soft tissue	Known distant metastasis
Complete resection of macroscopic tumor	Presence of vascular invasion	Macroscopic tumor invasion to surrounding soft tissue
No evidence of locoregional invasion	Clinical or pathologic N1	Pathologic N1 with any metastatic lymph node size ≥3 cm in a greatest dimension
No vascular invasion	Multifocal PTMC with ETE	
Clinical N0 or pathologic N0		sTg >30 ng/mL

PTMC = papillary thyroid microcarcinoma; ETE = extrathyroid extention; sTg = stimulated thyroglobulin

pathologically proven differentiated thyroid cancer from January 2014 to May 2017 who underwent near-total or total thyroidectomy. During this period, 60 patients were identified with the PTMC diagnosis. PTMC is defined as thyroid cancer with a primary tumor size equal to or less than 1.0 cm.[1] All 60 patients underwent postoperative radioiodine WBS. Eight patients were excluded from this study due to the presence of Tg-Ab, which leads to unreliable sTg. Thus, the remaining 52 patients met the study criteria.

The study data included the patients' age and sex, surgical procedures, histopathologic results, postoperative sTg and postoperative I-131 whole-body scan findings. Postoperative sTg was measured on the day of I-131 ingestion by electrochemiluminescence immunoassay (ECLIA) technique, using the Cobas e411 system, with the functional sensitivity is at 0.09 ng/mL (measuring range 0.04-5,000 ng/mL).

Before imaging, the disease staging and risk stratification in each patient was initially determined following the staging system of the 8th edition AJCC/TNM Cancer Staging[20] and the 2015 American Thyroid Association (ATA) Guidelines,[9] based on clinical and pathologic data. In addition to the ATA guidelines, a high level of sTg was defined as higher than 30 ng/mL.[21] The initial risk categories were shown in Table 1.

For the imaging technique, postoperative radioiodine WBS with additional spot planar images of anterior neck and chest as well as both lateral view of the neck were performed at 48 hours after the ingestion of I-131 37 MBq (1 mCi). All patients were prepared by thyroid hormone withdrawal at least four weeks before imaging to elevate serum TSH greater than 30 uIU/mL and dietary iodine restriction for two weeks. The images were acquired using a dual-head gamma camera (Symbia T, Siemens, USA) with high energy general-purpose (HEGP) collimator, a 20% energy window centered on a 364 keV photopeak, and the scan speed of 8 cm/min. The patients who showed radioiodine avidity outside the thyroid bed also received additional hybrid single-photon emission computed tomography/computed tomography (SPECT/CT) to localize the lesion. SPECT images were acquired by 128 × 128 matrices over 360° with 32 views (45 secs/view, step and shoot technique) using a 364 keV photopeak and 20% energy window, followed by a low dose CT scan for anatomical localization on the same instrument. SPECT images were reconstructed with filtered back projection and fused with CT images.

Postoperative radioiodine WBS of each patient was interpreted by two nuclear medicine physicians (20-year and 5-year experienced) with blinded consensus. After imaging, disease staging and the risk stratification were subsequently re-assessed in each patient.

The review data were shown in mean ± standard deviation (SD), range, and percentage. After WBS, the percentage of staging and risk stratification change were analyzed.

RESULTS

Of the 52 PTMC patients, 42 patients (80.8%) were females and 10 patients (18.2%) were males. The mean age of all patients was 45.7±14.0 years (age range 13-69 years). Patients underwent near-total (7.7%) or total (92.3%) thyroidectomy due to treatment of large multinodular goiter (38.4%), presence of thyroid nodules in both lobes on the pre-operative US (21.2%), suspected thyroid capsule invasion on US (25%) and the suspected metastatic cervical node on the pre-operative US (15.4%). Sixteen patients (30.8%) had cervical node dissection due to the suspected metastasis on the pre-operative US (8 patients) and intraoperative finding (8 patients). Postoperative radioiodine WBS was performed with a mean interval of 6.5±1.36 weeks after the surgery. All patients showed no clinical symptoms of distant metastasis before surgery. Demographic, pathologic data, and sTg level were shown in Table 2. Of the 52 patients, results of WBS changed the disease staging in four patients (7.7%) (Table 3) and risk stratification in ten patients (19.2%) (Table 4).

For disease staging, 36 patients younger than 55-year-old were all in Stage I. After postoperative WBS was performed, one of these (2.8%) was upgraded to Stage II

Table 2. Demographic, pathologic data, and laboratory results

Demographic data	N (%)
Gender	
Female	42 (80.8%)
Male	10 (19.2%)
Age	
<55 years	36 (69.2%)
≥55 years	16 (30.8%)
Pathology	
Cell type	
Papillary with classic variant	32 (61.5%)
Papillary with follicular variant	20 (38.5%)
Multiple tumor foci	20 (38.5%)
Presence of lymphovascular invasion	13 (25.0%)
Surgical margin involvement	8 (15.3%)
Extrathyroidal extension	
Microscopic	4 (7.7%)
Macroscopic	0
Pathological lymph node metastasis	
Absence (N0)	6 (11.6%)
Presence (N1)	10 (19.2%)
No neck node dissection (Nx)	36 (69.2%)
Serum thyroglobulin level	
<2.0 ng/mL	31 (59.7%)
2.0 to <30 ng/mL	13 (25.0%)
≥30 ng/mL	8 (15.3%)

Nx = unknown nodal metastasis status

Table 3. Changes in disease staging (AJCC/TNM 8th Edition) with postoperative WBS results

	Initial staging N (%)		After WBS N (%)
<55 years old (N = 36)			
Stage I	36 (100%)	Stage I	35 (97.2%)
		Stage II	1 (2.8%, lung)
≥55 years old (N = 16)			
Stage I	12 (75.0%)	Stage I	10 (62.5%)
		Stage II	1 (6.25%, node)
		Stage IV	1 (6.25%, lung)
Stage II	4 (25.0%, node)	Stage II	3 (18.75%)
		Stage IV	1 (6.25%, bone)

WBS = whole body scan

Table 4. Changes in risk stratification for disease recurrence with postoperative WBS results

Initial ATA risk stratification N (%)		Risk stratification after WBS N (%)	
Initial low	24 (46.2%)	Low	15 (28.8%)
		Intermediate	9 (17.4%)
Initial intermediate	20 (38.5%)	Intermediate	19 (36.5%)
		High	1 (2.0%)
Initial high	8 (15.3%)	High	8 (15.3%)

WBS = whole body scan

due to radioiodine-avid lung metastasis. For 16 patients ≥55 years, three patients changed to a higher stage due to the lymph node, lung, and bone metastases (Table 3).

Of the 24 patients initially defined as low risk, nine patients (37.3%) were grouped to intermediate-risk due to neck node metastases detected by WBS. The metastatic lymph nodes were central in 6 patients (67%), lateral in 2 patients (22%), and supraclavicular in 1 patient (11%). All metastatic nodes were equal or less than one cm in size. None of these patients had neck node dissection, and their postoperative sTg levels were low (undetectable to 4.9 ng/mL). Figure 1 showed that the planar image of postoperative I-131 scan (Figure 1A) of an initial low-risk patient with undetectable stimulated thyroglobulin revealed subcentimeter radioiodine-avid right upper cervical and right supraclavicular (SPC) lymph node metastases as demonstrated on SPECT/CT image (Figure 1B and 1C).

Of the 20 patients initially defined as intermediate risk, one patient (5%) with sTg of 23.2 ng/mL was re-grouped to high risk according to bilateral lung metastases detected on WBS (Figure 2A and 2B), corresponding with multiple tiny lung metastases on CT images (Figure 2C and 2D). In another six patients (30%), which remained grouped as intermediate risk, radioiodine-avid lymph nodes were found. The metastatic lymph nodes were central neck in 2 patients (10%), lateral neck in 2 patients (10%), and paratracheal in 2 patients (10%) region. All metastatic nodes were equal or less than one cm in size.

All eight patients, who were initially defined as high risk, had a high sTg >30 ng/mL. None of these had macroscopic tumor invasion or large neck node metastasis (>3 cm). Postoperative WBS assisted with detecting lymph node metastasis in two patients (25%, lateral and paratracheal lymph nodes). Distant metastases were found in two patients, with one patient in the lungs (12.5%) and another one (12.5%) in multiple levels of the spine, sacrum, and left proximal femur. No radioiodine-avid cervical neck node or distant metastasis was demonstrated in the remaining four initial high-risk patients.

DISCUSSION

This study was performed to address the lack of clinical data regarding the clinical benefit of postoperative radioiodine WBS, which is not routinely performed in PTMC patients. In our study, WBS added the value of accurate staging and risk stratification by identifying radioiodine-avid lymph nodes and distant metastasis, which resulted in the required subsequent postoperative I-131 treatment. As we found subclinical regional lymph node and distant metastases by WBS, these PTMC patients had a potential for the disease recurrence. In our study, the change of the risk stratification of recurrence is more pronounced than that of the staging because the detection of unexpected lymph node metastasis did not change the staging or mortality in patients younger than 55 years.

The changes in staging and risk stratification in PTMC patients in our study were concordant with prior studies[13,22-25] that showed the benefits of WBS by changing the staging and the recurrent risk in overall DTC patients. For the curative intent, the WBS findings can improve disease-free mortality rate and recurrence rate by identifying unexpected regional lymph node or distant metastasis leading to higher dose I-131 treatment with 5,550–7,400 MBq (150-200 mCi). Low-risk patients without aggressive features or metastasis are not routinely recommended for radioiodine ablation with 1,110 MBq (30 mCi).[9,26] Detection of metastasis also impacts the selection of potential surgical candidates in the case who presented with large metastatic lesions before I-131 treatment to improve treatment outcomes and optimize long-term follow-up.

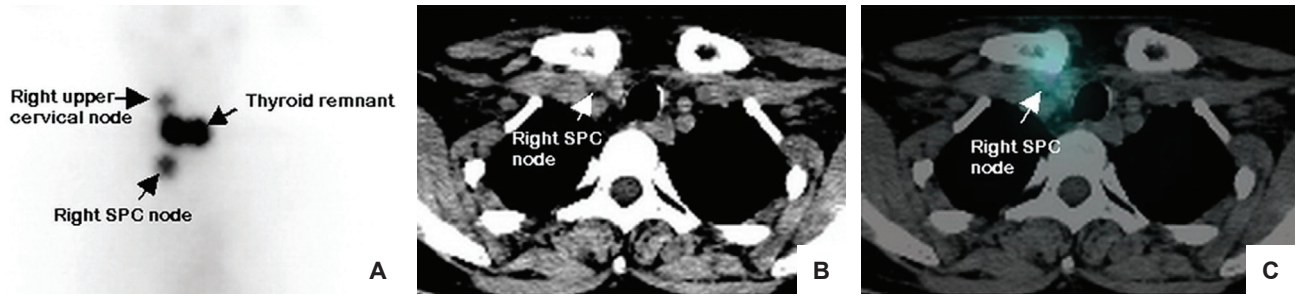

Figure 1. (A) Postoperative I-131 scan revealed two radioiodine-avid right upper cervical and supraclavicular (SPC) node metastases. The right SPC node was demonstrated in these **(B)** CT scan and **(C)** SPECT images.

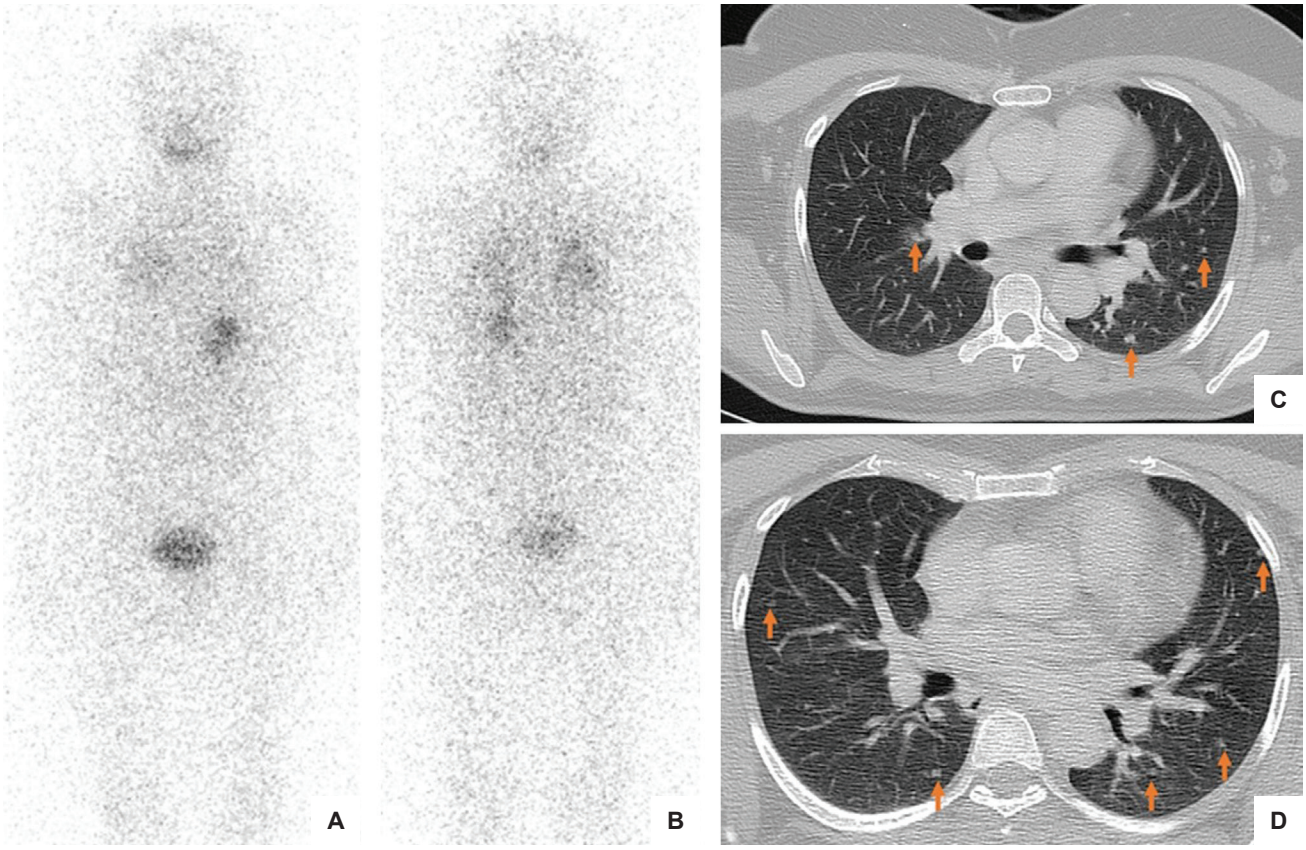

Figure 2. (A,B) Post-operative I-131 scan reveals diffuse radioiodine uptake in the bilateral lungs, corresponding with multiple tiny pulmonary metastases as seen on **(C,D)** CT images (orange arrows).

Radioiodine WBS helps demonstrate occult lymph node metastasis, mainly in the central compartment, that is difficult to detect by other investigation methods. Moreover, sTg in these patients (<5 ng/mL) did not show any clue of metastasis. These metastatic patients with low measurable sTg are possibly due to too small tumor volume to synthesize Tg and partial loss of Tg secretory function from the tumor cells into the blood.[27] Thus, complementary imaging is necessary for long-term follow-up or detecting suspected recurrence in these undetectable sTg patients. The neck US has a high specificity to detect cervical lymph node metastasis, however, the small size of the central lymph node is difficult to detect by US.[28,29] Among the high-risk patients, who had high sTg levels suspected for distant metastasis, radioiodine WBS demonstrates metastatic location in about 50% of the cases in our study. In undetectable metastasis cases by WBS, re-evaluation on post-treatment I-131 WBS and follow-up sTg is necessary. Correlative anatomical imaging will be considered in the patients with persistent or progressively rising sTg levels without radioiodine-avid metastasis, and these patients are unlikely to respond to I-131 treatment.

Our study had some limitations. First, a small sample size as we focused on PTMC patients who generally had a good prognosis. Second, as a retrospective study, there might be some bias in clinical profile or investigations leading to treating these PTMC patients with near-total or total thyroidectomy, which guidelines recommend mostly can be treated by lobectomy.

CONCLUSION

The study provides some evidence showing the value of postoperative radioiodine WBS for accurate staging and recurrent risk stratification by detecting metastatic lesions in PTMC patients, particularly those with initial low risk with low sTg. Larger studies that are able to test for statistical significance should be done to further prove its added utility in the diagnosis and management of papillary thyroid microcarcinoma.

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