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Role of the ^{131}I whole body scan for initial follow-up in patients with intermediate-risk differentiated thyroid cancer

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KEYWORDS
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Intermediate risk;
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Whole body scan;
Neck Ultrasound.

ABSTRACT

A combination of diagnostic whole body scan (DxWBS), neck ultrasound, and serum stimulated thyroglobulin (stim-Tg) is now recommended for the initial follow-up in patients with intermediate-risk differentiated thyroid cancer (DTC). However, previous studies demonstrated the low additional value of DxWBS for the detection of persistent disease. This study aimed to determine the necessity of using DxWBS for the initial follow-up of these patients. This retrospective analytical study included 126 patients with intermediate-risk DTC (according to 2015 ATA guidelines) after total thyroidectomy and received the first ^{131}I treatment. All patients underwent stim-Tg, neck ultrasound, and DxWBS at about 6–12 months after ^{131}I treatment. Persistent disease was defined as uptake outside the thyroid bed from DxWBS, uptake within the thyroid bed from DxWBS, or an abnormal ultrasound finding with cytologically or pathologically proven persistent disease, positive for serum anti-thyroglobulin antibody (TgAb), or stim-Tg of 1 ng/mL or more. The percentage difference for detection of persistent disease when using only neck ultrasound with stim-Tg compared to a combination with DxWBS was calculated. We considered non-inferior when the percentage difference is below five. Of the 126 patients with intermediate-risk DTC, persistent diseases were detected in 85 patients and identified by DxWBS, neck ultrasound, and stim-Tg in 24, 14, and 77 patients, respectively. Combined neck ultrasound and stim-Tg could detect persistent disease in 78 patients. Although using only neck ultrasound and stim-Tg could detect 8.2% (95%CI: 1.2 to 15.3) of patients with persistent disease less than that compared with using combined all three modalities, all patients with only positive DxWBS showed thyroid remnants, not the true persistent disease. These findings indicated that DxWBS may not be necessary for initial follow-up in patients with intermediate-risk DTC.

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Introduction

Patients with differentiated thyroid cancer (DTC) generally exhibit a favorable prognosis. While incidence rates of DTC are rising, survival rates have remained stable. These raise concerns about more tailored management[1]. Total thyroidectomy followed by ^{131}I treatment and life-long hormonal treatment were considered standard treatment of almost all these patients. Subsequently, response to therapy was evaluated by combination of diagnostic whole body scan (DxWBS), neck ultrasound (neck US), and serum stimulated thyroglobulin (stim-Tg) level at the initial follow-up (6-12 months after the first ^{131}I treatment). According to the latest American Thyroid Associated (ATA) guidelines, the 2015 ATA initial risk stratification system predicts risk of disease recurrence and guides follow-up management decisions. High-risk patients are recommended to get higher levels of thyrotropin (TSH) suppression and need more frequent follow-up visits than those who have lower risk of recurrence. While, subsequent DxWBS is not recommended for initial follow-up in patients with low risk who are clinically free of residual disease due to its low sensitivity in these patients, it is still recommended in patients with high-risk and intermediate-risk DTC[2].

Conversely, several previous studies demonstrated low value of DxWBS for detection of persistent disease in patients with intermediate-risk DTC[3-8]. However, there are no clear studies that demonstrate additional value of DxWBS in this patient group. In addition, some studies show that DTC patients with high initial stim-Tg, high stim-Tg, T3 or T4 stage, or a large tumor size are associated with a treatment failure founded by DxWBS[9-11] but there is no evidence that demonstrates the factors associated with the positive DxWBS results in patients with intermediate-risk DTC. These factors may be valuable for selection of patients who may benefit from DxWBS. Thus, this study primarily aimed to determine the necessity of using DxWBS for initial follow-up of patients with intermediate-risk DTC and secondarily aimed to determine the factors associated with the positive lesion from DxWBS in these patients.

Materials and methods

Study design

This retrospective cohort study collected record data from patients with DTC who previously received the first ^{131}I treatment at our tertiary care hospital between January 2015 and August 2017. After surgery, patients were evaluated for pathology results. The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging, and 2015 ATA risk of recurrence system were used for patient's risk assessment. The patients were assigned to withdrawal thyroid hormone for four weeks and take a low iodine diet for two weeks. Serum TSH, free triiodothyronine (FT3), thyroglobulin (Tg), and anti-thyroglobulin antibody (TgAb) levels were measured within two days before the first ^{131}I oral administration. The DxWBS, neck US, and serum stim-Tg were generally evaluated at 6-12 months after initial treatment for detection of persistent disease.

^{131}I whole body scintigraphy and biochemical markers measurement

The post-therapy whole body scan (RxWBS) was performed at 5-7 days after oral administration of 1,110-5,550 MBq of ^{131}I. The DxWBS was performed 2-3 days after oral administration of 37-185 MBq of ^{131}I. All ^{131}I whole body scan (WBS) was performed by Discovery NM/CT 670 SPECT/CT system (General Electric, NY, USA) with a high-energy general purpose (HEGP) collimator. A measurement of serum Tg level was used THYROGLOBULINE IRMA, Cisbio Bioassays, France. Serum levels of thyroglobulin antibody (TgAb) and thyrotropin (TSH) were assayed using TGAB ONE STEP kits manufactured by Cisbio Bioassays in France, and RIA-gnost® hTSH kits manufactured by the same company, respectively.

Participants

We enrolled patients who fulfilled all of the following criteria; (1) pathological confirmed DTC, (2) underwent total or near-total thyroidectomy with or without lymph node dissection, (3) received the first ^{131}I treatment with performed RxWBS, (4) and underwent neck US, DxWBS, and stim-Tg at about 6-12 months after ^{131}I treatment. Furthermore, patients were excluded, if they had one or more of the following conditions; (1) second primary cancer detected before or during treatment, (2) previously received other treatment modality (eg., radiation therapy), (3) have a gross residual tumor, (4) have pathological high-risk feature(s); follicular thyroid carcinoma (FTC) with extensive vascular invasion (> 4 foci of vascular invasion), pathological N1 with any metastatic lymph node ≥ 3 cm in largest dimension, or macroscopic invasion of tumor into perithyroidal soft tissue, (5) distant metastasis detected before or after ^{131}I treatment, (6) being categorized as a low-risk DTC patient after being evaluated by pathological report and RxWBS, (7) serum TSH level during DxWBS study below 30 IU/mL. The remaining patients would be classified as intermediate risk of recurrence by ATA except some patients with pathological N1 micrometastases that were also included in the final analyses. One hundred and twenty six patients were needed according to the calculation from sample size needed to compare paired proportions: McNemar's Z-test, 1-sided[12] for testing a significant difference proportion that was set as five percent. This study was conducted following the Declaration of Helsinki and approved by the Khon Kaen University Ethics Committee (Reference number: HE621405). Informed consent was waived.

Data collection and interpretation

Data from a total of 126 patients (type of operation, surgical history, dose of ^{131}I administration, pathological and cytological results, level of serum TSH, Tg, TgAb, and neck ultrasound results) were collected. All patients' pathological reports were re-evaluated and re-classified using the eight edition AJCC/ TNM staging, and 2015 ATA risk of recurrence system. Interpretation of DxWBS, neck US and serum tumor marker was evaluated and defined as the following;

DxWBS: Both DxWBS planar image and single-photon emission computed tomography/computed tomography (SPECT/CT) images (if any) were independently reviewed by two nuclear medicine physicians who were blinded to clinical information, pathological results, treatment history, and other imaging studies via Xeleris 3.0 software or PACS. In case of disagreement, images were re-evaluated by both nuclear medicine physicians to make a conclusion. A negative DxWBS was made when there was; (1) no abnormal radioiodine uptake at the thyroid bed or outside thyroid bed region on planar image, or (2) suspicious of radioiodine uptake outside thyroid bed on planar images with proved negative lesion on SPECT/CT images. A positive DxWBS was made when there was; (1) abnormal radioiodine uptake outside thyroid bed from planar image, (2) abnormal radioiodine uptake at thyroid bed (thyroid remnant only), (3) suspicious of radioiodine uptake outside thyroid bed on planar image with proved positive lesion on SPECT/CT images, or (4) lesion from SPECT/CT-images represented metastasis (eg., enlarged mediastinal or cervical lymph node, multiple sharply marginated pulmonary nodules distributed randomly throughout the lung, smooth thickening of interlobular septa, peribronchovascular interstitial surrounding vessels and bronchus, or abnormal osteolytic/blastic bone lesion) without abnormal radioiodine uptake outside the thyroid bed on planar and SPECT images. An equivocal DxWBS was made when there were un-interpreted results from suspicious radioiodine uptake outside thyroid bed on planar images with/without SPECT/CT images.

Neck US: The neck US results and further cytological/pathological report was evaluated and interpreted as negative neck US when there was; (1) no abnormal findings on the neck US

results, (2) abnormal findings on the neck US results without subsequent pathological/ cytological investigation, or (3) abnormal findings on the neck US results with further pathological/ cytological investigation showing negative for thyroid carcinoma. A positive neck US was made only when there was abnormal finding on the neck US results with subsequent pathological/ cytological investigation proving positive for thyroid carcinoma.

Biological marker: Serum Tg and TgAb levels were recorded and interpreted as negative biochemical markers when serum stim-Tg level less than 1 ng/mL and negative for serum TgAb. A positive for biochemical markers was made when there was; (1) serum stim-Tg level 1 ng/mL or more, or (2) positive for serum TgAb.

Statistical analysis

The percentage of persistent-disease detection were compared between three (DxWBS, biochemical markers, and neck US) and two (biochemical markers and neck US) modalities methods by using McNemar's test. A two-sided *p*-value of less than 0.05 and five percentage difference was considered significant. The factors that predict positive DxWBS results (T-stage, extrathyroidal extension, cell type, cervical lymph node metastasis, stim-Tg, and initial stim-Tg) were identified by using bivariate logistic regression analysis. Factors were included in the multiple logistic regression analysis if their bivariate logistic regression *p*-value was < 0.25 or previously known strongly predictive factor from the previous studies such as an initial stim-Tg level more than 10 ng/mL[9,10]. Cohen's Kappa was used for evaluation of inter-observer reliability comparing the DxWBS (planar image or SPECT/CT images) interpretative results from two independent nuclear medicine physicians[13]. The categorical data were reported as number and percentage. The continuous data were reported as mean ± standard deviation (SD) or median and interquartile range. All statistical analyses were performed using STATA 10.1 (StataCorp LP, College Station, TX, USA).

Results

Of the total 328 intermediate-risk DTC patients first treated with ^{131}I were initially recruited in this study. Two hundred seventy-nine of these patients met all inclusion criteria. One hundred fifty-three patients were excluded due to; (1) second primary cancer, (2) having a pathological high-risk feature, (3) distant metastasis detected before or after ^{131}I treatment, (4) categorized as low-risk DTC, or (5) serum TSH level during DxWBS study below 30 IU/mL and 126 were finally evaluated in this study. The patients' characteristics are shown in table 1. The median age at diagnosis was 46 years (range: 14–74 years). Most of the patients were females (n = 104, 82.5%). The most common histological subtype was papillary carcinoma (n = 122, 96.8%) followed by follicular carcinoma (n = 4, 3.2%). Most of the patient's intermediate-risk feature was cervical lymph node metastasis (n = 92, 73%) followed by papillary thyroid carcinoma with vascular invasion (n = 53, 42.1%).

Table 1 Patient characteristics (n=126)

Characteristics	Sample	%
Median age at diagnosis, (IQR) [min-max], (year)	46 (30 - 57) [14 - 74]	
Age group, year		
< 55 years	89	70.6
≥ 55 years	37	29.4
Gender		
Female	104	82.5
Male	22	17.5
Type of operation		
Total thyroidectomy	125	99.2
Near-total thyroidectomy	1	0.8
Cell type		
Papillary thyroid carcinoma	122	
Classical variant	97	77.0
Tall cell variant	2	1.6
Diffuse sclerosing variant	1	0.8
Follicular variant	16	12.7
Oncocytic variant	2	1.6
Solid/trabecular variant	3	2.4
Micropapillary variant	12	9.5
Macropapillary variant	8	6.4
Mixed follicular and papillary variant	1	0.8
Follicular thyroid carcinoma	4	
Classical variant	3	2.4
Hurthle cell variant	1	0.8
Intermediate-risk characteristics		
Minimal ETE	39	31.0
Aggressive histological variant	4	3.2
PTC with vascular invasion	53	42.1
Cervical lymph node metastasis	92	73.0
Pathological diagnosis	70	55.6
RAI avid foci at neck from RxWBS	39	31.0

Table 1 Patient characteristics (n=126) (Cont.)

Characteristics	Sample	%
TNM stage (AJCC/TNM 8thed.)		
T1N0	10	7.9
T1N1	41	32.5
T2N0	12	9.5
T2N1	34	27.0
T3N0	11	8.7
T3N1	18	14.3
Stage group		
I	99	78.6
II	27	21.4
T stage		
1a	21	16.7
1b	30	23.8
2	46	36.5
3a	29	23.0
N stage		
0	34	27.0
1	43	34.1
1a	24	19.1
1b	25	19.8
Median tumor size (IQR) [min-max], (cm)	2.65 (1.5 - 4) [0.1 - 8]	
Dose of ^{131}I treatment (mCi)		
30	11	8.7
100	4	3.2
150	111	88.1

Note: The TNM stage, which is based on the examination of the surgical specimen, provides information on the primary tumor (T) and lymph node (N) metastasis. A tumor measuring up to 1 cm confined to the thyroid is classified as stage T1a, while a tumor measuring more than 1 cm but up to 2 cm confined to the thyroid is classified as stage T1b. For tumors measuring more than 2 cm but up to 4 cm confined to the thyroid, they are classified as stage T2, and for tumors larger than 4 cm confined to the thyroid, they are classified as stage T3a. In terms of lymph node involvement, a stage N0 indicates no evidence of regional lymph node metastasis, while N1a indicates metastasis to cervical lymph nodes level VI or VII. Metastasis to cervical lymph nodes level I, II, III, IV, or V is classified as N1b.

Abbreviations: IQR, interquartile range; ETE, extrathyroidal extension; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; RxWBS, post treatment whole body scan; TNM, tumor-node-metastasis; AJCC, the American Joint Committee on Cancer.

Detection of persistent disease

Of the total 126 intermediate-risk DTC patients, persistent disease was found in 14 patients by neck US, 77 patients by biochemical markers, and 24 patients by DxWBS. Among 24 patients with positive DxWBS results, one patient had cervical lymph node metastasis, two had cervical lymph node metastasis with bone metastasis, one had cervical lymph node metastasis with thyroid remnant, and 20 with thyroid remnant only. Furthermore, four patients had equivocal DxWBS results, including one with suspicion of mediastinal lymph node metastasis, two with suspicion of cervical lymph node metastasis, and one with suspicion of pulmonary metastasis. Two of these patients also had serum stim-Tg levels more than 1 ng/mL but the rest showed only equivocal DxWBS results as shown in table 2. Therefore, the overall number of patients with persistent disease detected by neck US, biochemical markers, or DxWBS was 85.

Table 2 Overall persistent disease detection (n=87)

Test	Total	
	Number of patients (%)	95 % CI
Biochemical markers	77 (88.5)	79.88; 94.35
Positive for serum Tg only	57 (65.5)	54.56; 75.39
Positive for serum TgAb only	14 (16.1)	9.09; 25.52
Positive for serum Tg and TgAb	6 (6.9)	2.57; 14.41
Neck ultrasound	14 (16.1)	9.09; 25.52
Diagnostic whole body scan (DxWBS)	24 (27.6)	18.54; 38.21
Positive sites:		
Functioning cervical lymph node metastasis	4 (4.6)	1.27; 11.36
Cervical lymph node metastasis only	1 (1.2)	0.03; 6.24
Cervical lymph node metastasis with bone metastasis (SPECT/CT)	1 (1.2)	0.03; 6.24
Cervical lymph node metastasis with functioning bone metastasis	1 (1.2)	0.03; 6.24
Cervical lymph node metastasis with thyroid remnant	1 (1.2)	0.03; 6.24
Thyroid remnant	20 (23.0)	14.64; 33.25
Equivocal	4 (4.6)	1.27; 11.36
Suspicious for lymph node metastasis	3 (3.5)	0.72; 9.75
Suspicious for mediastinal lymph node metastasis	1 (1.2)	0.03; 6.24
Suspicious for cervical lymph node metastasis	2 (2.3)	0.28; 8.06
Suspicious for pulmonary metastasis	1 (1.2)	0.03; 6.24

Note: The total number of 87 patients is derived from 85 patients who had persistent disease detected by neck ultrasound, biochemical markers, or DxWBS, with an additional two patients with equivocal DxWBS only.

Abbreviations: Tg, thyroglobulin; TgAb, anti-thyroglobulin antibodies; SPECT/CT, single photon emission computed tomography/computed tomography.

The percentage difference for detection of persistent disease

Patients with equivocal DxWBS results may or may not actually have the persistent disease. Therefore, we decided to analyze the results in both ways, treating equivocal DxWBS results as positive and as negative.

When patients with equivocal DxWBS were grouped as positive DxWBS

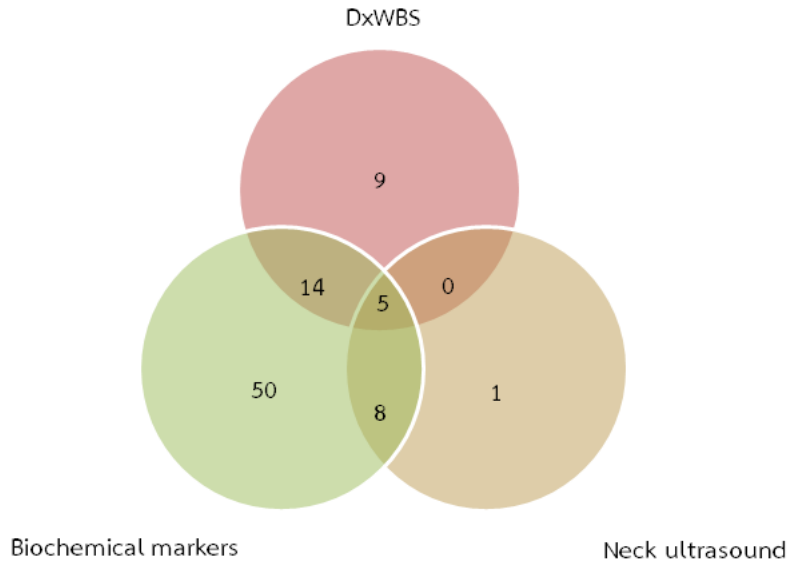
Persistent disease was found as follows; only from biochemical markers in 50 patients, neck US in one patient, or DxWBS in nine patients (seven patients with thyroid remnant and two patients with equivocal DxWBS); both neck US and biochemical markers in eight patients; both biochemical markers and DxWBS (one patient with cervical lymph node metastasis, one patient with cervical lymph node and bone metastasis, one patient with cervical lymph node metastasis and thyroid remnant, eight patients with thyroid remnant only, two patients with equivocal DxWBS, and one patient with thyroid remnant and equivocal DxWBS) in 14 patients; combined neck US, biochemical markers, and DxWBS (four patients with thyroid remnant, one patient with cervical lymph node and bone metastasis) in five patients as shown in table 3 and figure 1 (A). Therefore, a total number of patients with persistent disease detected from neck US, biochemical markers, or DxWBS were 87. Persistent disease identified by both biochemical markers and neck US in 78 patients. The percentage difference for detection of persistent disease when using only in the neck US with biochemical markers compared to combination with DxWBS was 10.3% (95% CI 2.8-17.7, *p*-value = 0.004) as shown in table 4.

Table 3 Persistent disease detection (utilizing dual analysis: initially classifying equivocal DxWBS findings as positive and subsequently as negative)

	Positive-DxWBS group (n = 87)		**Negative-DxWBS group (n = 85)**	
	Number of patients (%)	**95%CI**	**Number of patients (%)**	**95%CI**
Biochemical markers only	50 (57.5)	46.41; 68.01	52 (61.2)	49.99; 71.56
Neck ultrasound only	1 (1.2)	0.03; 6.24	1 (1.2)	0.03; 6.38
Diagnostic whole body scan only	9 (10.3)	4.84; 18.73	7 (8.2)	3.38; 16.23
Biochemical markers or neck ultrasound	78 (89.7)	81.27; 95.16	78 (91.8)	83.77; 96.62
Biochemical markers or diagnostic whole body scan	86 (98.9)	93.76; 99.97	84 (98.8)	93.62; 99.97
Neck ultrasound or diagnostic whole body scan	37 (42.5)	31.99; 53.59	33 (38.8)	28.44; 50.01
Biochemical marker or diagnostic whole body scan or neck ultrasound	87 (100.0)	95.85; 100	85 (100.0)	95.75; 100

Abbreviations: DxWBS, diagnostic whole body scan.

(A) Grouped as positive DxWBS



(B) Grouped as negative DxWBS

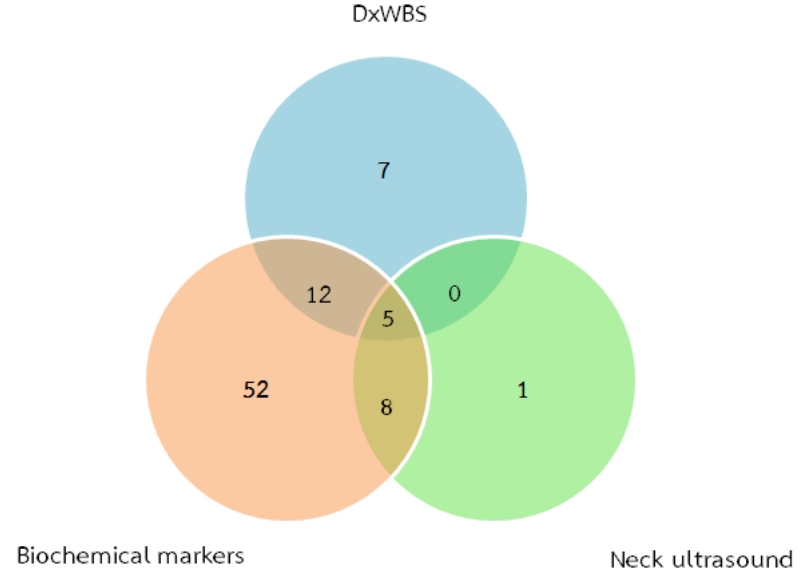


Figure 1 The number of patients with persistent disease detected by DxWBS, neck US, or biochemical markers.

Table 4 Percentage difference for detection of persistent disease when using only in the neck ultrasound with stim-Tg compared to combination with DxWBS in all patients (utilizing dual analysis: initially classifying equivocal DxWBS findings as positive and subsequently as negative)

Biochemical marker and diagnostic whole body scan and neck ultrasound					
		Positive-DxWBS group Number (%)		Negative-DxWBS group Number (%)	
Biochemical markers and neck ultrasound		Positive	Negative	Positive	Negative
	Positive	78 (89.7)	-	78 (91.8)	-
	Negative	9 (10.3)	-	7 (8.2)	-
	p-value	0.004		0.016	
Proportion difference (95%CI)		10.3% (2.8; 17.7)		8.2% (1.2 to 15.3)	

Note: Proportion of detection of persistent disease were compared between three methods (DxWBS, biochemical markers, neck US) and two methods (biochemical markers and neck US) using McNemar's test. Significance was determined by a two-sided *p*-value below 0.05 and a five percentage point difference.
Abbreviations: stim-Tg, serum stimulated thyroglobulin; DxWBS, diagnostic whole body scan.

When patients with equivocal DxWBS were grouped as negative DxWBS

Persistent disease was found as follows; only from biochemical markers in 52 patients, neck US in one patient, or DxWBS in seven patients (thyroid remnant for all); both neck US and biochemical markers in eight patients; both biochemical markers and DxWBS (one patient with cervical lymph node metastasis, one patient with cervical lymph node and bone metastasis, one patient with cervical lymph node metastasis and thyroid remnant, and nine patients with thyroid remnant only) in 12 patients; combined neck US, biochemical markers, and DxWBS (four patients with thyroid remnant, one patient with cervical lymph node and bone metastasis) in five patients as shown in table 3 and figure 1 (B).

As grouped patients with equivocal DxWBS within the negative DxWBS group, the total number of patients with persistent disease detected from neck US, biochemical markers, or DxWBS was 85. Persistent disease identified by both biochemical markers and neck US in 78 patients. The percentage difference for detection of persistent disease when using only in the neck US with biochemical markers compared to combination with DxWBS was 8.2% (95% CI 1.2-15.3, *p*-value = 0.016) as shown in table 4.

Factors associating with positive DxWBS

Out of 126 intermediate-risk DTC patients, 28 had abnormal DxWBS results; 24 were positive, and four were equivocal. Bivariate logistic regression analysis found no significant factors associated with positive DxWBS, even when equivocal results were considered positive or negative. Previous strong predictive factors were analyzed using multiple logistic regression, which also showed no significance. However, the initial stim-Tg level more than 10 ng/mL tended to have an association with positive DxWBS in both analyses (*p*-value = 0.062, adjusted OR = 3.77 and *p*-value = 0.087, adjusted OR = 3.30).

Inter-observer reliability

One hundred twenty-eight lesions on planar images of DxWBS were detected from 126 patients by two readers. There were four lesions in two patients that had non-concordant results. The first patient was interpreted to have two lesions by reader A but interpreted to have one lesion by reader B. Conversely, the second patient was interpreted to have two lesions by reader B but interpreted to have one lesion by reader A. Other two lesions in one patient were interpreted concordantly by both readers. Consequently, the compared lesions from the planar images of

DxWBS were 127. A strong overall agreement (114 lesions, 89.76%) was found between two readers, with a Kappa score of 0.75 which was considered substantial[13]. Of the total 29 patients who did the SPECT/CT images, two lesions in one patient were concordantly interpreted by both readers. Thus, overall, 31 lesions from SPECT/CT images were compared. From the SPECT/CT images interpretation, there was also strong agreement (27 lesions, 87.1%) between two readers, with Kappa score of 0.77 which was considered substantial[13].

Discussion

The findings of this retrospective study show that the percentage difference for detection of persistent disease when using only in the neck ultrasound with biochemical markers compared to combination with DxWBS was 10.3% when patients with equivocal DxWBS were grouped as positive DxWBS and was 8.2% when they were grouped as negative DxWBS (Table 4). Even when patients with equivocal-DxWBS grouping as positive DxWBS or negative DxWBS, the percentage difference is more than five percent which is considered significant. However, a follow-up evaluation of equivocal DxWBS patients at the median follow-up time of three years showed no further management needed in all these patients. We thus assumed that the equivocal-DxWBS patients had no true persistent disease and the percentage of difference from this study was only 8.2%.

Previously, there was no published literature studying the percentage difference for detection of persistent disease when using only neck US with biochemical markers compared to combination with DxWBS in patients with intermediate-risk DTC. However, the percentage difference can be calculated from individual data in some previously studied sources [3-5,7]. A percentage difference calculated from a study that determined the necessity of a DxWBS after ^{131}I ablation in intermediate-risk DTC patients by Eon et al[7] was 7.8%. This minimally lower value of a percentage difference compared with our study may occur from that the neck US was not used for evaluation of persistent disease in this study. Moreover, only intermediate-risk-DTC patients who received 1,110 MBq of ^{131}I ablation even when more than half of them were stage III (63.1%) and no patient with metastasis from RxWBS were included in this study. This may represent that they selected only patients with low-risk features. This may be another reason for the lower percentage difference. Similarly to a study by Cailleux et al[3] which calculated the percentage difference as 5.9%. This study assessed whether routine control DxWBS should be routinely performed within 1 year after 3,700 MBq of ^{131}I treatment in low-to-high risk DTC patients. The conclusion that DxWBS only confirmed the completeness of thyroid ablation was made by only thyroid remnants was detected from DxWBS in 20 patients. Even though they included all-risk recurrence patients, there were only patients who had no functioning uptake outside the thyroid bed from RxWBS; this may cause a lower percentage difference.

Some studies showed higher percentage differences compared to our study. Pacini et al[4] evaluated the diagnostic accuracy of recombinant human TSH (rhTSH)-stimulated WBS and serum Tg alone or in combination in DTC patients. The percentage difference of this study was calculated as 15.69%. This may be explained by they included some 2015 ATA high-risk DTC patients; however, the characteristic of patients was not sufficiently provided. Rosario et al[5] determined whether DxWBS with stim-Tg was necessary for patients with negative RxWBS, neck US, suppressed thyroglobulin, and TgAb after ablation, who are considered to be at high or intermediate risk for recurrence (only patients with large tumor size or tumor extension beyond thyroid capsule). At the follow-up time of 8-12 months after radioiodine ablation, they found that there was no functioning metastasis from DxWBS in all patients, only thyroid remnant was detected in 46 patients from a total 318 patients. Furthermore, when dividing patients

into two groups by stim-Tg level (below 1 ng/mL or at least 1 ng/mL), thyroid remnant was detected in 33 patients from stim-Tg below 1 ng/ mL group and in 13 patients from stim-Tg at least 1 ng/mL group. At the median follow-up time of 60 months, a recurrent disease occurred in only one patient from stim-Tg below 1 ng/ mL grouped. They concluded that DxWBS can be avoided in patients who have the same included characteristics in their study. The calculated percentage difference from this study was 10.4% which is slightly higher than our study. Therefore, the percentage difference from our study cannot completely be compared to others because of many differences in study setting. These included; (1) each study have different criteria for persistent disease; some studies included only patients with negative neck US results[5]; or some studies did not use neck US results[3,7], (2) some studies included patients with other risks of recurrence[3-5] or included only intermediate-risk DTC patients with low-risk features[7].

Despite having a significant percentage difference, all positive-DxWBS lesions in our study were only thyroid remnants. This is consistent with findings from several previous studies[3,5,7] including study by Kim et al[14] which evaluated the clinical outcomes of DTC patients with thyroid remnants detected by DxWBS after initial therapy. After follow-up DTC patients whose has none of the following; (1) functioning metastasis, (2) serum TgAb more than 100 U/mL, and (3) serum TSH at the time of DxWBS performing lower than 30 IU/mL, recurrent disease occurred in 72 patients dividing into 5 patients (20%) from the remnant-positive group (total 25) and 67 patients (12%) from the remnant-negative group (total 547). There was no significant difference in disease-free survival (DFS) between these two groups at the median follow-up time of 65.7 months. They concluded that DxWBS was not needed in these patients. Interestingly, 12 patients from a total 25 patients in the remnant-positive group had negative for neck US and undetectable stim-Tg which has the same characteristic as patients with positive DxWBS in our study. After the end of study, none of them showed recurrent disease. Assuming from this finding, if we follow-up our patients with positive DxWBS, they may also have no recurrent disease.

Although we found no significant factor associated with positive DxWBS results, initial stim-Tg at least 10 ng/mL tended to have an association with positive DxWBS. This finding is similar to those in the previous studies which found that the initial stim-Tg at least 10 ng/mL had an association with positive DxWBS results or stim-Tg more than 2 ng/mL[9,10]. One of the causes of unidentified significant factor associated with positive DxWBS from our study may be from the low number of positive DxWBS patients in our study. Further prospective studies with a larger number of patients are required to confirm if the initial stim-Tg of at least 10 ng/mL is associated with positive DxWBS results in these patients.

This study has limitations. Uncontrolled data were recorded from a retrospective study. Intermediate-risk DTC patients were not identically defined as ATA 2015 criteria. Patients with one or more cervical lymph node metastases smaller than 3 cm were included. The follow-up time of this study was only three years, which may not be sufficient to detect recurrence[15]. Further study should employ a prospective design, with stringent criteria for patient selection, and extended period of follow-up.

Conclusion

DxWBS add little value for initial follow up in intermediate-risk DTC patients who had done neck US and stim-Tg. This may not be necessary in patients with intermediate-risk DTC.

Take home messages

Combined neck US and stim-Tg might be a sufficient tool for identifying persistent disease during the initial post-treatment monitoring of patients with intermediate-risk DTC.

Conflicts of interest

The authors declare no conflict of interest.

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