

# <sup>99m</sup>Tc-pertechnetate-avid metastases from differentiated thyroid cancer are prone to benefit from <sup>131</sup>I therapy

## A prospective observational study

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### Abstract

The aim of this study is to determine the contribution of neck and chest <sup>99m</sup>Tc-pertechnetate scan to the management of postoperative patients with suspicious metastatic differentiated thyroid cancer (DTC), particularly to the prediction of response to radioiodine (<sup>131</sup>I) therapy. Just before <sup>131</sup>I administration, a total of 184 postoperative DTC patients with stimulated serum thyroglobulin (ssTg) > 10 ng/mL were enrolled to undergo neck and chest <sup>99m</sup>Tc-pertechnetate scan, which were directly compared with post-therapeutic <sup>131</sup>I scan to determine the concordance of site and number of metastatic lesions. The percentage changes in ssTg between <sup>99m</sup>Tc-pertechnetate-avid group and <sup>99m</sup>Tc-pertechnetate-nonavid group were compared, and the response to <sup>131</sup>I in both groups was analyzed according to the nature of <sup>99m</sup>Tc-pertechnetate avidity as well. The percentages of concordance between <sup>99m</sup>Tc-pertechnetate and <sup>131</sup>I scan in detecting metastases were 65.7% and 26.0% in per-patient and per-site analyses with low unweighted kappa, respectively. <sup>99m</sup>Tc-pertechnetate scan led to a change in therapeutic decision making in 19/184 (10.3%) patients. In 72 patients with <sup>131</sup>I-avid metastases, the ssTg in <sup>99m</sup>Tc-pertechnetate-avid group (n = 13) decreased significantly compared with that in <sup>99m</sup>Tc-pertechnetate-nonavid group (n = 59) (median: -81.56% vs -48.14%; Z = -4.276, P = .000). The difference of therapeutic response between <sup>99m</sup>Tc-pertechnetate-avid group and <sup>99m</sup>Tc-pertechnetate-nonavid group was statistically significant ( $\chi^2 = 8.4$ ; P = .03). Although the consistency between <sup>99m</sup>Tc-pertechnetate scan before <sup>131</sup>I administration and post-therapy <sup>131</sup>I scan in detecting metastases is low, identifying metastases in postoperative DTC patients with elevated ssTg via <sup>99m</sup>Tc-pertechnetate scan prior to <sup>131</sup>I therapy provides incremental value for therapeutic decision making. Notably, patients with <sup>99m</sup>Tc-pertechnetate-avid metastases may be more prone to benefit from <sup>131</sup>I therapy than those with <sup>99m</sup>Tc-pertechnetate-nonavid metastases.

**Abbreviations:** <sup>131</sup>I = radioiodine, BIR = biochemical incomplete response, DTC = differentiated thyroid cancer, Dx-WBS = diagnostic radioiodine whole body scan, ER = excellent response, IDR = indeterminate response, LN = lymph node, MRI = magnetic resonance imaging, PET/CT = positron emission tomography/computed tomography, Rx-WBS = post-therapeutic radioiodine whole body scan, SIR = structural incomplete response, SPECT/CT = single photon emission computed tomography/computed tomography, ssTg = stimulated serum thyroglobulin, TSH = thyroid-stimulating hormone.

**Keywords:** <sup>99m</sup>Tc-pertechnetate, differentiated thyroid cancer, radioiodine, SPECT/CT, thyroglobulin

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## 1. Introduction

Differentiated thyroid cancers (DTCs) are typically iodine-avid and can be effectively treated with radioiodine (<sup>131</sup>I) when persistent/recurrent or metastatic disease are not amenable to surgery.<sup>[1–4]</sup> In this context, a diagnostic <sup>131</sup>I whole body scan (Dx-WBS) may be useful to detect iodine-avid metastases before <sup>131</sup>I therapy, allowing a more precise selection of therapeutic candidate and appropriate activity of <sup>131</sup>I. If metastases are detected in Dx-WBS, then the prescribed <sup>131</sup>I activity can be increased to maximize therapeutic success at first <sup>131</sup>I treatment.<sup>[5–7]</sup>

However, specialists who favor post-therapeutic <sup>131</sup>I whole body scan (Rx-WBS) argue that scans performed after therapeutic activity of <sup>131</sup>I administration are more sensitive for disease detection and avoid possible stunning of thyroid remnants and distant metastases from thyroid cancer.<sup>[8–12]</sup> Until now the real mechanism of stunning effect has not been known. Some researchers also found molecular-level evidence that the stunning effect exists even at a low activity of <sup>131</sup>I, which further hampered the use of Dx-WBS before <sup>131</sup>I therapy.<sup>[13]</sup> Rx-WBS possibly neglect sufficient radiation activity to metastatic lesions during

the first course of  $^{131}\text{I}$  therapy since disease was not determined timely.<sup>[14]</sup>

$^{99\text{m}}\text{Tc}$ -pertechnetate has been widely applied to evaluate thyroid diseases because of its ideal imaging characteristics and favorable price and dosimetry. Pertechnetate-avid metastatic lesions from DTC have been described by several case reports.<sup>[15–18]</sup> However, only 3 comparative studies with  $^{131}\text{I}$  can be retrieved, mainly focusing on the diagnostic efficiency of  $^{99\text{m}}\text{Tc}$ -pertechnetate scan for thyroid remnant.<sup>[19–21]</sup> To date, the value of  $^{99\text{m}}\text{Tc}$ -pertechnetate scan (planar scan combined with SPECT/CT [single photon emission computed tomography/computed tomography]) in the management of DTC patients has not been adequately assessed. The relationship between the therapeutic response to  $^{131}\text{I}$  and the avidity of metastatic lesions for  $^{99\text{m}}\text{Tc}$ -pertechnetate is still unknown. Here, we therefore, designed a dedicated study to determine the contribution of neck and chest  $^{99\text{m}}\text{Tc}$ -pertechnetate scan to the management of postoperative DTC patients with suspicious metastatic lesions.

## 2. Subjects and methods

### 2.1. Study design and population

This study was approved by the ethics board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital before its initiation (No. 2014–0013). All participants were informed of details of the study with the information sheet and had signed the consent form prior to their inclusion in the study.

We prospectively evaluated 184 consecutive patients with DTC who were considered to have suspicious metastatic disease after total or nearly total thyroidectomy ( $\geq 4$  weeks) based on elevated stimulated serum thyroglobulin (ssTg) levels  $>10\text{ ng/mL}$ , with thyroid-stimulating hormone (TSH) level  $>30\text{ mIU/mL}$ . All patients were confirmed with lymph node (LN) metastasis by the pathology of thyroidectomy. Patients with a history of malignant tumor other than DTC were excluded from the study. Thyroxine withdrawal and low-iodine diet for at least 4 week were required before blood samples were drawn and  $^{131}\text{I}$  administered. Serum TSH, Tg, and Tg-antibody levels were measured using a chemiluminescent immunoassay system (Immulite, Diagnostic Products Corp., Los Angeles, CA). Empirically fixed dose of  $^{131}\text{I}$  was given at 5.5 GBq for patients with local or suspected disease and 7.4 GBq for patients with distant metastases. All patients underwent neck and chest  $^{99\text{m}}\text{Tc}$ -pertechnetate planar scan with SPECT/CT just before  $^{131}\text{I}$  administration or switch to reoperation.

### 2.2. Imaging protocol and image analyses

$^{99\text{m}}\text{Tc}$ -pertechnetate planar scan in neck and chest was performed 15 min after intravenous injection of  $^{99\text{m}}\text{Tc}$ -pertechnetate (370 MBq). The neck and chest SPECT/CT images were obtained using a hybrid SPECT/CT imaging system (Millennium VG and Hawkeye, GE Healthcare). The Rx-WBS and SPECT/CT were carried out 5 days after administration of  $^{131}\text{I}$  with the same technique equipped with a high-energy collimator. The detailed parameters have been described previously by our team.<sup>[22]</sup>

Two experienced nuclear medicine physicians, who were aware of the results of all relevant examinations, laboratory investigations, and imaging studies, evaluated the  $^{99\text{m}}\text{Tc}$ -pertechnetate scans and came to an agreement by consensus. The Rx-WBS with SPECT/CT was reviewed by other 2 nuclear medicine physicians who did not know the previous pretreatment pertechnetate scans. Foci of radioactivity identified on planar

imaging were further evaluated on SPECT/CT and classified according to their location and nature as positive scan, which was defined as anatomical finding from CT with increased radiotracer uptake higher than surrounding background excluding thyroid remnant or physiological distribution; equivocal scan, which included the following situations: abnormal anatomical localization from CT without unnatural increased radiotracer uptake or increased radiotracer uptake without corresponded anatomical finding from CT excluding thyroid remnant; and neither increased radiotracer uptake nor unnatural anatomical foci from CT excluding thyroid remnant were considered as negative scan.

Concordant rate of per-patient and per-lesion basis was analyzed and the strength of agreement was obtained using unweighted kappa statistical analysis.

### 2.3. Assessment during follow-up

Nearly 6 months after initial  $^{131}\text{I}$  therapy, patients who had  $^{131}\text{I}$ -avid foci in the post-therapeutic  $^{131}\text{I}$  scan received the second course of  $^{131}\text{I}$  treatment, and ssTg levels were also obtained. The ssTg before the first and second course of  $^{131}\text{I}$  treatment was marked as ssTg1 and ssTg2, respectively. The range of interval between ssTg1 and ssTg2 was 171 to 207 days (median: 187 days). The percentage changes in ssTg were calculated as  $(\text{ssTg2} - \text{ssTg1})/\text{ssTg1}$ . Patients experienced reassessment of therapeutic response to  $^{131}\text{I}$  with TSH suppressive therapy 6 to 12 months after the second course of  $^{131}\text{I}$  therapy. CT or F-18-fluorodeoxyglucose positron emission tomography/computed tomography ( $^{18}\text{F}$ -FDG PET/CT) was conducted if persistent or newly identified evidence was suspected.

According to the therapeutic response assessment system proposed by 2015 American Thyroid Association guidelines, we analyzed the clinical data obtained during follow-up and divided all patients who experienced at least 2 dose of  $^{131}\text{I}$  therapy into 4 categories: excellent response (ER), indeterminate response (IDR), biochemical incomplete response (BIR), and structural incomplete response (SIR) during follow-up.<sup>[2]</sup>

### 2.4. Statistical analyses

All statistical analyses were performed using a statistical software program (SPSS, version 16.0; SPSS, Inc Chicago, IL). The parameters such as age at diagnosis, sex, subtype of DTC,  $^{131}\text{I}$  activity, ssTg level, and the percentage change in ssTg were analyzed by univariate analysis and confirmed by the  $\chi^2$  test or Wilcoxon rank sum tests or Student *t* test. The correlation of the percentage changes in ssTg between pertechnetate-avid group and pertechnetate-nonavid group were evaluated using the Spearman rank correlation. Fisher exact test was used to test the statistical significance of categorical data. All *P* values reported were 2-sided, and a *P* value of less than .05 was considered significant.

## 3. Results

### 3.1. Patient demographic and baseline characteristics

Patient demographic and baseline characteristics are summarized in Table 1. Seventy-four (33.2%) of 184 patients experienced  $^{131}\text{I}$  therapy 2 times or more. The duration of follow-up was a minimum of 18.7 months, and a maximum of 35.8 months after the first  $^{131}\text{I}$  therapy. Tg levels are between 10.1 and 8089.0 ng/mL (median 28.9 ng/mL).

**Table 1****Patient demographic and baseline characteristics.**

Characteristics	N = 184
Age, y	
Range	11–71
Median	42.9
Sex	
Female	118 (63.0%)
Male	66 (37.0%)
Thyroid cancer subtype	
Papillary	174 (94.6%)
Follicular	10 (5.4%)
Surgical option	
Total thyroidectomy	122 (66.3%)
Nearly total thyroidectomy	62 (33.7%)
AJCC TNM stage	
I	125 (67.9%)
II	9 (4.9%)
III	41 (22.3%)
IV	9 (4.9%)
TSH, mIU/L	
>30	184 (100%)
ssTg, ng/mL	
Median	28.9
Range	10.1–8089.0
10–100	153 (83.2%)
100–1000	25 (13.6%)
>1000	6 (3.2%)
Anti-thyroglobulin antibodies	
Positive	2 (1.1%)
<sup>131</sup> I activity, GBq	
Median	5.5
Range	3.7–7.6
Follow-up time (months)	
Range	18.7–35.8
Median	23.4

Data are expressed as n (%) unless otherwise stated.

ssTg = stimulated serum thyroglobulin, TNM = tumor, node, metastasis, TSH = thyroid-stimulating hormone.

### 3.2. Findings in <sup>99m</sup>Tc-pertechnetate planar scans combined with SPECT/CT

In the 184 patients, 236 foci avid for <sup>99m</sup>Tc-pertechnetate were observed on planar scans. <sup>99m</sup>Tc-pertechnetate SPECT/CT led to a revision of the original diagnosis based on planar imaging in 44 of 236 foci (18.6%) (Table 2). In particular, 12 of 23 lesions considered to be LN and 22 of 24 lesions considered to be

indeterminate were clearly reclassified as benign. Three lesions classified as thyroid remnant and 2 equivocal lesions by planar scan had been reclassified as LNs. Furthermore, <sup>99m</sup>Tc-pertechnetate SPECT/CT allowed the identification of 5 mediastinal LNs misinterpreted as metastatic lung nodes.

Besides, there were 151 equivocal foci of 68 patients on <sup>99m</sup>Tc-pertechnetate SPECT/CT distributed to 90 foci in LN, 56 foci in lung nodules, and 5 foci in bone lesions.

### 3.3. Comparison of <sup>99m</sup>Tc-pertechnetate and <sup>131</sup>I scan

Final diagnostic criteria for metastases from DTC were based on pathological findings, serum Tg levels, and other imaging modalities, such as <sup>131</sup>I scan, high-resolution ultrasonography, CT and MRI, and by correlation with clinical follow-up. Seventy-four patients (74/184, 33.2%) showed <sup>131</sup>I-avid metastases in <sup>131</sup>I scans, including 55 patients with only LN metastases, 5 patients with only lung metastases, and 9 patients with LN and lung metastases concurrently. Besides, 6 patients were confirmed with cervical nodal metastases by surgical pathology. There were a total of 7 patients (4 with LN metastases and 3 lung metastases) with negative metastatic foci in <sup>131</sup>I scan diagnosed by serum Tg levels, high-resolution ultrasonography, CT, and clinical follow-up.

### 3.4. Per-patient analysis

For the per-patient analysis, data on the relationship between <sup>99m</sup>Tc-pertechnetate and <sup>131</sup>I scan were compared. After exclusion of 6 patients with operable lesions identified by <sup>99m</sup>Tc-pertechnetate scan from the 184 patients in total, 13/178 (7.3%) patients showed tracer-avid metastases in both <sup>99m</sup>Tc-pertechnetate and <sup>131</sup>I scans, 104/178 (58.4%) showed negative metastases in both imaging, and 61/178 (34.3%) showed metastases with <sup>131</sup>I uptake but without pertechnetate uptake. The overall percentage of concordance was 65.7% (117/178). The unweighted kappa was 0.309. A total of 176 patients had identified thyroid remnants by both <sup>99m</sup>Tc-pertechnetate and <sup>131</sup>I scan, and the remaining 2 patients who underwent total thyroidectomy did not show residual thyroid in both imaging.

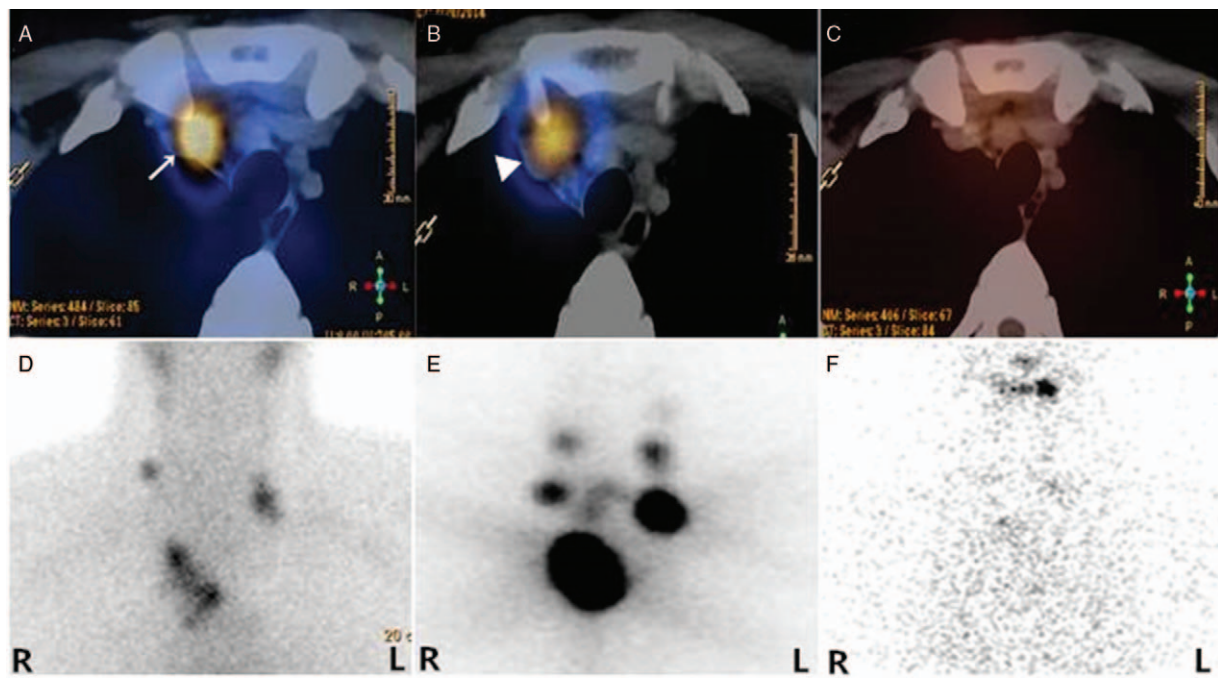
In cervical LN, positive, equivocal, and negative findings by both <sup>99m</sup>Tc-pertechnetate and <sup>131</sup>I scans were found in 11, 8, and 106 patients, respectively. Negative pertechnetate but positive or

**Table 2****Additional value of neck and chest <sup>99m</sup>Tc-pertechnetate SPECT/CT in precise diagnosis.**

Region of body	Planar findings	SPECT/CT characterization	No. of lesions
Neck	Thyroid bed	Thyroid remnant	172
		LN involvement	3*
	LN involvement	Thyroid remnant	12*
		LN involvement	11
	Equivocal	Thyroid remnant	13*
		LN involvement	2*
		Physiological activity	2*
Chest	Lung metastases	Contamination	3*
		Mediastinal LN involvement	5*
		Lung metastases	9
		Physiological breast uptake	4*
Total	Equivocal		236

\* Incremental diagnostic value in 44 lesions.

LN = lymph node, SPECT/CT = single photon emission computed tomography/computed tomography.



**Figure 1.**  $^{131}\text{I}$ -avid PTC metastatic LNs accumulating  $^{99\text{m}}\text{Tc}$ -pertechnetate. A 30-year-old male with PTC presented with suspicious metastatic disease 2 months after total thyroidectomy with elevated ssTg of 349 ng/mL and TSH of 107.83 mU/L. Transaxial image of  $^{99\text{m}}\text{Tc}$ -pertechnetate SPECT/CT (A; arrow) and planar image (D) before the initial administration of 5.55 MBq (150 mCi)  $^{131}\text{I}$  followed by  $^{131}\text{I}$  SPECT/CT (B; arrowhead) and planar imaging (E) showed radiotracer-avid LNs in the neck and superior mediastinum. ssTg decreased to 4.48 ng/mL with TSH of 54.0 mU/L just before the third course of  $^{131}\text{I}$  therapy. Decreased uptake of  $^{131}\text{I}$  in LNs in the neck and superior mediastinum was revealed by the SPECT/CT (C) and planar image (F). LN = lymph nodes, PTC = papillary thyroid carcinoma, ssTg = stimulated serum thyroglobulin, TSH = thyroid-stimulating hormone.

equivocal  $^{131}\text{I}$  findings were revealed in 27 and 26 patients, respectively. Thus, the percentage of concordance was 70.2% (125/178) with the unweighted kappa of 0.257. In lung, positive, equivocal, and negative findings by both  $^{99\text{m}}\text{Tc}$ -pertechnetate and  $^{131}\text{I}$  scans were found in 2, 4, and 160 patients. There were 12 patients who showed negative ( $n=8$ )/equivocal ( $n=4$ )  $^{99\text{m}}\text{Tc}$ -pertechnetate but positive  $^{131}\text{I}$  scan. So, the percentage of concordance was 93.2% (166/178) with the unweighted kappa of 0.518. In bone, there were only 5 patients who were defined as positive on  $^{131}\text{I}$  scan but equivocal on  $^{99\text{m}}\text{Tc}$ -pertechnetate scan, yielding a percentage of concordance of 0% with the unweighted kappa of 0.

### 3.5. Per-site analysis

There were a total of 30 positive metastatic foci on  $^{99\text{m}}\text{Tc}$ -pertechnetate scan. Of these, 21 foci were located in LNs (Fig. 1), 9 foci in lung nodules (Fig. 2). Altogether, there were 151 equivocal foci on  $^{99\text{m}}\text{Tc}$ -pertechnetate scan clarified as 90 foci in LN, 56 foci in lung, and 5 foci in bone.

There were 164  $^{131}\text{I}$ -avid metastatic lesions revealed by  $^{131}\text{I}$  scan, including all the aforementioned 30 lesions with  $^{99\text{m}}\text{Tc}$ -pertechnetate uptake. Positive  $^{131}\text{I}$  scan but equivocal  $^{99\text{m}}\text{Tc}$ -pertechnetate scan were found in 134/164 (81.1%) lesions, with 79/134 (59.0%) foci located in LN, 50/134 (37.3%) foci located in lung, and 5/134 (3.7%) located in bone. The remaining 17 (10.7%) foci showed equivocal findings in  $^{131}\text{I}$  scan, including 11 foci located in LN and 6 foci located in lung.

With regard to per-site analysis, the overall percentage of concordance between  $^{99\text{m}}\text{Tc}$ -pertechnetate and  $^{131}\text{I}$  scan was 26.0% (47/181) with the unweighted kappa of 0.027. The

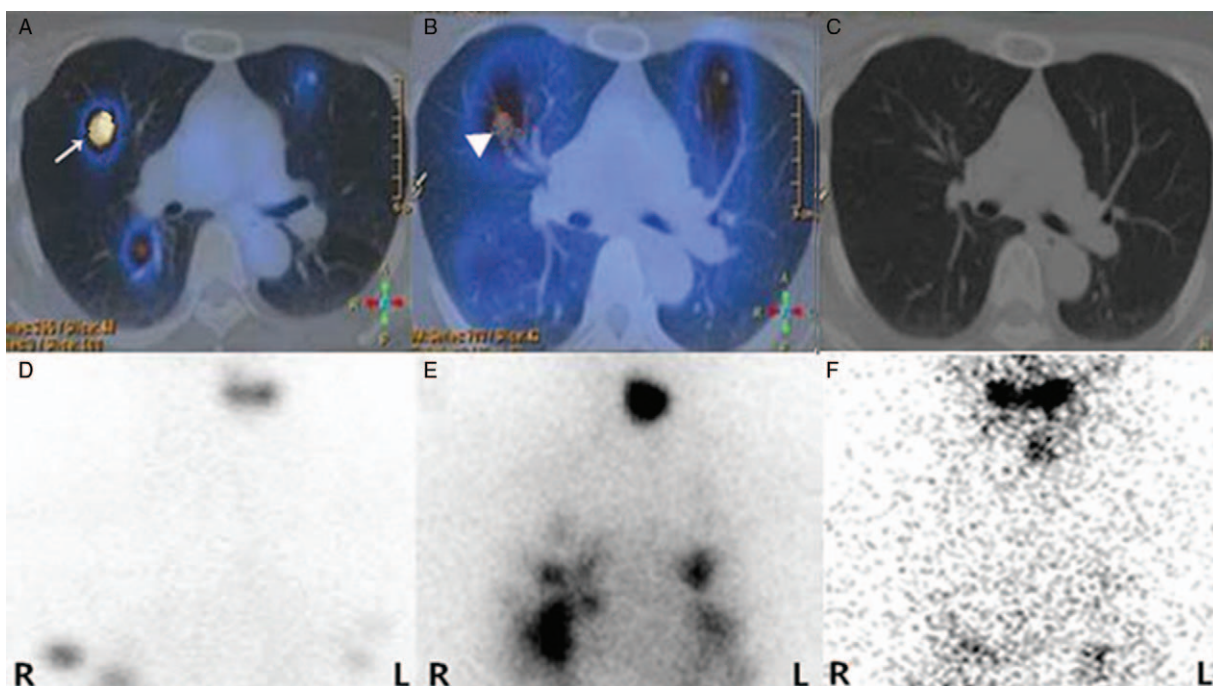
percentages of concordance in LN, lung, and bone subgroups were 28.8%, 23.1%, and 0%, respectively. The unweighted kappas in LN, lung, and bone subgroups were 0.072, 0.032, and 0, respectively.

### 3.6. Impact of $^{99\text{m}}\text{Tc}$ -pertechnetate scan on management

The information obtained at the time of  $^{99\text{m}}\text{Tc}$ -pertechnetate scan led to a change in management decision in 19/184 (10.3%) patients. In 6/184 (3.3%) patients,  $^{99\text{m}}\text{Tc}$ -pertechnetate SPECT/CT showed bulky and/or multiple residual cervical nodal metastases nonavid for  $^{99\text{m}}\text{Tc}$ -pertechnetate with surgical indication, and they were then referred back to surgery for reoperative neck dissection prior to  $^{131}\text{I}$  therapy. Besides,  $^{99\text{m}}\text{Tc}$ -pertechnetate SPECT/CT detected pertechnetate-nonavid regional lung and bone metastases in 4 and 5 patients, respectively, who were then given 7.4 GBq of  $^{131}\text{I}$  in consideration with their high Tg levels (range: 182.0–8089.0 ng/mL).  $^{99\text{m}}\text{Tc}$ -pertechnetate scan detected pertechnetate-avid regional lung metastases in 4/184 (2.2%) patients. Accordingly, the identification of distant metastases by  $^{99\text{m}}\text{Tc}$ -pertechnetate scan resulted in an increase of prescribed  $^{131}\text{I}$  activity to 7.4 GBq in the 4 patients previously recommended for 5.5 GBq.

### 3.7. Association between the avidity of $^{99\text{m}}\text{Tc}$ -pertechnetate and the therapeutic response

Following the exclusion of 2 anti-Tg antibody positive patients from the 74 patients who experienced  $^{131}\text{I}$  therapy 2 or more times, the parameters such as age at diagnosis, sex, subtype of DTC,  $^{131}\text{I}$  activity, ssTg level between pertechnetate-avid group



**Figure 2.**  $^{131}\text{I}$ -avid PTC metastatic pulmonary lesions accumulating  $^{99\text{m}}\text{Tc}$ -pertechnetate. A 50-year-old female patient with PTC presented with suspected metastatic disease in the lungs 1 month after total thyroidectomy with ssTg of 500.0 ng/mL and TSH of 77.45 mU/L.  $^{99\text{m}}\text{Tc}$ -pertechnetate SPECT/CT (A; arrow) and planar image (D) before  $^{131}\text{I}$  therapy showed pulmonary nodules with obviously increased  $^{99\text{m}}\text{Tc}$ -pertechnetate uptake.  $^{131}\text{I}$  SPECT/CT (B; arrowhead) and planar image (E) 5 days after the initial administration of 7.4 MBq (200 mCi)  $^{131}\text{I}$  correspondingly showed the pulmonary nodules with increased  $^{131}\text{I}$  accumulation. Six months later, ssTg decreased to 13.78 ng/mL with TSH of 37 mU/L just before the second course of  $^{131}\text{I}$  administration (7.4 MBq, 200 mCi), and the pulmonary nodules were not found on  $^{131}\text{I}$  SPECT/CT (C) and planar image (F). PTC = papillary thyroid carcinoma.

( $n=13$ ), and pertechnetate-nonavid group ( $n=59$ ) were analyzed, and no differences were observed. The percentage changes in ssTg levels between pertechnetate-avid group and pertechnetate-nonavid group were compared (Table 3). As a result, ssTg decreased  $81.56\% \pm 31.22\%$  (median  $\pm$  interquartile range) in pertechnetate-avid group and  $48.14\% \pm 44.70\%$  (median  $\pm$  interquartile range) in pertechnetate-nonavid group with statistical significance ( $Z = -4.276$ ;  $P = .000$ ) and correlation ( $r = 0.506$ ;  $P = .000$ ).

During the follow-up with a median duration of 13.4 months after the first  $^{131}\text{I}$  therapy, the proportion of ER, IDR, BIR, and SIR in  $^{99\text{m}}\text{Tc}$ -pertechnetate-avid group amounted to 61.5% (8/13), 15.4% (2/13), 7.7% (1/13), and 15.4% (2/13), respectively. In  $^{99\text{m}}\text{Tc}$ -pertechnetate-nonavid group, 21.3% (13/61), 29.5% (18/61), 32.8% (20/61), and 24.6% (15/61) of patients were categorized to ER, IDR, BIR, and SIR, respectively. The difference of therapeutic response between  $^{99\text{m}}\text{Tc}$ -pertechnetate-avid group and  $^{99\text{m}}\text{Tc}$ -pertechnetate-nonavid group was statistically significant ( $\chi^2 = 8.4$ ;  $P = .03$ ).

#### 4. Discussion

The assessment of postoperative disease status has vital role in the management of advanced DTC patients.<sup>[2,23]</sup> The likelihood of identifying either loco-regional recurrent/persistent disease or distant metastases on the Rx-WBS increases as either the suppressed or ssTg values rise above 5 to 10 ng/mL.<sup>[24,25]</sup> However, the localization of metastatic DTC lesions commonly falls back on imaging modalities. Although ultrasonography is very sensitive for the identification of cervical nodal compartments metastases, the specificity is low and the prescribed regions

are limited, which impedes its use in the identification of distant metastases.<sup>[26,27]</sup> Meanwhile, controversies on the utility of Dx-WBS in guiding  $^{131}\text{I}$  therapeutic decision making still exist, and predictors on the outcome of  $^{131}\text{I}$  therapy of DTC are unavailable at present.<sup>[2]</sup>

$^{99\text{m}}\text{Tc}$ -pertechnetate is a monovalent anion similar to iodide and can be accumulated by sodium/iodide symporter located in the membrane of thyrocytes. Theoretically, visualization of metastatic deposits on pertechnetate scans can hint at their strong capacity to concentrate  $^{131}\text{I}$  and therefore assure the potential to respond to  $^{131}\text{I}$  therapy.<sup>[17]</sup> However, there is limited literature describing the value of pertechnetate scans in detecting metastatic disease, and its clinical implication has not been fully assessed.<sup>[16-18,20]</sup> Our group demonstrated that the information obtained at the time of  $^{99\text{m}}\text{Tc}$ -pertechnetate scans led to a change in management decision in 19/184 (10.3%) patients, including referral for resection ( $n=6$ ) or alternating the prescribed  $^{131}\text{I}$  dose ( $n=13$ ). More importantly, during analysis of association between avidity of  $^{99\text{m}}\text{Tc}$ -pertechnetate and the response of  $^{131}\text{I}$  therapy in 72 patients who had  $^{131}\text{I}$ -avid foci in the Rx-SPECT/CT, we found that ssTg in pertechnetate-avid group decreased more significantly than in pertechnetate-nonavid group. Furthermore, the difference of therapeutic response between the 2 groups was also statistically significant. It suggests that in patients with  $^{131}\text{I}$ -avid metastases, more favorable therapeutic response to  $^{131}\text{I}$  therapy may be obtained in pertechnetate-avid group compared with pertechnetate-nonavid group. This can be explained by that  $^{99\text{m}}\text{Tc}$ -pertechnetate-avid lesions may concentrate more  $^{131}\text{I}$  than those nonavid for  $^{99\text{m}}\text{Tc}$ -pertechnetate, yielding a higher radiation dose.<sup>[22,28]</sup> Besides, our study also demonstrates that the percentages of concordance

**Table 3****Comparison between  $^{99m}\text{Tc}$ -pertechnetate-avid group and  $^{99m}\text{Tc}$ -pertechnetate-nonavid group.**

	$^{99m}\text{Tc}$ -pertechnetate-avid group	Non- $^{99m}\text{Tc}$ -pertechnetate-avid group	Wilcoxon rank sum tests	
			Z/U/ $\chi^2$	P
Total no. patients	13	59		
Age, y			1.52	.13
Range	30–67	15–69		
Median	54	44		
Sex			−0.136	.892
Female	7	33		
Male	6	26		
Surgical option			0.23	.63
Total thyroidectomy	8	43		
Nearly total thyroidectomy	5	16		
Thyroid cancer subtype			/	.25
Papillary	11	51		
Follicular	2	8		
Metastatic site			0.40	1.0
LN	10	39		
Lung	1	8		
LN and lung	2	12		
Laboratory results				
ssTg before $^{131}\text{I}$ therapy, ng/mL			−0.06	.95
Range	10.1–978.0	11.45–8089		
Median	54.7	55.8		
The percentage changes in ssTg			−4.28	.000
Range	−99.01% to −55.79%	−96.23% to 881.66%		
Median	−81.56%	−48.14%		
$^{131}\text{I}$ activity			3.02	.08
5.55 GBq	9	59		
7.4 GBq	4	0		
Clinical outcome				
ER	8	13	8.5	.03
IDR	2	18		
BIR	1	20		
SIR	2	15		

BIR = biochemical incomplete response, ER = excellent response, IDR = indeterminate response, SIR = structural incomplete response.

between  $^{99m}\text{Tc}$ -pertechnetate and  $^{131}\text{I}$  scan in detecting metastases were as low as 65.7% and 26.0% in per-patient and per-site analysis, respectively, indicating that  $^{99m}\text{Tc}$ -pertechnetate scan cannot be regarded as an attractive alternative for evaluating suspicious metastases in postsurgical DTC patients. Several factors may be involved in the discrepancy between  $^{99m}\text{Tc}$ -pertechnetate and  $^{131}\text{I}$  scan.  $^{99m}\text{Tc}$ -pertechnetate can be concentrated by thyroid follicular cells, but do not undergo the organification process, which might cause insufficient visualization because of lower accumulation and target/background ratio and much shorter deposit time compared with  $^{131}\text{I}$ .<sup>[22,28,29]</sup>

Our findings on the diagnostic value of  $^{99m}\text{Tc}$ -pertechnetate scan are inconsistent with study by Chantadisai et al, which demonstrated that preablative  $^{99m}\text{Tc}$ -pertechnetate planar scan with neck and chest SPECT/CT has good correlation with post-therapeutic  $^{131}\text{I}$  planar scan with SPECT/CT per-patient basis.<sup>[20]</sup> However, our group reports a relatively lower overall patient-based or lesion-based percentage of concordance. The possible explanation is that our study focused mainly on metastatic lesions, but Chantadisai et al cared mainly about thyroid remnant (92.2%). Other studies have also revealed that postoperative  $^{99m}\text{Tc}$ -pertechnetate scan has a high positive predictive value to detect remnant tissue in DTC patients in the literature.<sup>[19,21,29–31]</sup> Their studies were limited to scan of the thyroid bed, so no comments can be made about the value of  $^{99m}\text{Tc}$ -pertechnetate scan in detecting extrathyroidal or metastatic sites. Additionally,

a low sensitivity of  $^{99m}\text{Tc}$ -pertechnetate scan compared with diagnostic  $^{131}\text{I}$  WBS in detecting extrathyroidal and metastatic disease was reported in 1990 with an obvious limitation of very small sample size as 5.<sup>[32]</sup> Different from the previous reports, our study focused on the value of  $^{99m}\text{Tc}$ -pertechnetate neck and chest planar scan combined with SPECT/CT in the management of patients with suspicious metastatic DTCs post-total or near total thyroidectomy in a much larger size of sample.

The pertechnetate avidity of metastatic deposits beyond thyroid bed determined by SPECT can provide features of lesions and has incremental value over planar scan in increasing diagnostic accuracy, reducing pitfalls, and yielding a specific diagnosis. Meanwhile, the CT component of hybrid SPECT/CT can be used to determine the location and size of metastatic lesions without radiotracer uptake.<sup>[22]</sup> Therefore, proceeding with a  $^{99m}\text{Tc}$ -pertechnetate planar scan combined with SPECT/CT may lead to cost savings and streamlined management decisions in patients with suspicious metastases.

Inevitably, there were some limitations in our study. We did not compare  $^{99m}\text{Tc}$ -pertechnetate scan to diagnostic scan using low activity  $^{131}\text{I}$  in this series directly. Besides, the value of  $^{99m}\text{Tc}$ -pertechnetate scan in patients with metastases in other sites beyond neck and chest is still unknown. Finally, we admit that assessing the outcome of therapeutic interventions requires prolonged follow-up in this relatively indolent malignancy, studies with longer follow-ups are still needed.

In conclusion, although the consistency of  $^{99m}\text{Tc}$ -pertechnetate scan before  $^{131}\text{I}$  administration and  $^{131}\text{I}$  scan post- $^{131}\text{I}$  therapy in detecting metastases is low, identifying metastases via  $^{99m}\text{Tc}$ -pertechnetate scan prior to  $^{131}\text{I}$  therapy has incremental value in making therapeutic decision. Notably, patients with  $^{99m}\text{Tc}$ -pertechnetate-avid lesions may be more prone to benefit from  $^{131}\text{I}$  therapy than those with  $^{99m}\text{Tc}$ -pertechnetate-nonavid lesions.

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