Int J Clin Exp Med 2013;6(5):320-333
www.ijcem.com /ISSN:1940-5901/IJCEM1301011

Original Article

Clinical significance of discordant findings between pre-therapy ^{123}I and post-therapy ^{131}I whole body scan in patients with thyroid cancer

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Received January 17, 2013; Accepted February 1, 2013; Epub May 22, 2013; Published June 1, 2013

Abstract: Radioactive therapy with ^{131}I (RAI) is commonly used during the management of patients with differentiated thyroid cancer (DTC). The aim of this study was to determine the clinical significance of discordant findings between pre-RAI whole body scan (WBS) with ^{123}I and post-RAI WBS in the management of DTC. We retrospectively evaluated 342 individuals between 2002 and 2008 who had a diagnosis of DTC and underwent RAI. All had WBS one day before RAI and WBS one week after RAI. Patients were divided into 3 groups: 1) RAI-naive subjects without known distant metastatic disease (M1); 2) patients with history of prior RAI and persistent disease (except M1); and 3) patients with known M1. In Group 1 (n=311), 7% of patients (n=22) had discordant scans, but in only 4 of these cases did this represent true disease (3 unsuspected lung and 1 mediastinal node metastasis). In the remaining 18 patients, discordant findings corresponded to physiologic or other benign causes. In group 2 (n=23), 7 subjects (30%) had discordant findings and all of the discrepant sites consisted of loco-regional nodal disease in the neck/upper mediastinum (n=6) and M1 in lung (n=1). In group 3 (n=8), 5 patients (62%) showed discordant uptake in lung and bone which corresponded to the locations of known M1. A total of 12 patients with iodine-avid M1 were identified on post-RAI WBS (3.5% of entire cohort). Pre-RAI WBS was only concordant in 3 of these cases (25%). In conclusion, the significance of pre and post-RAI WBS is highly influenced by the clinical setting. Unsuspected distant metastatic disease is infrequent in RAI-naive patients without known M1, where most discordant findings are usually due to benign explanations, and represent false positive findings in this group. In contrast, in patients with history of previous RAI or known M1, discordant results likely correspond to true disease. In our study, pre-RAI scans showed a low yield to detect iodine-avid distant metastatic disease when compared to post-RAI scans.

Keywords: Pre-therapy ^{123}I scan, post-therapy ^{131}I scan, discordance, thyroid cancer

Introduction

Thyroid cancer is the most common malignancy of the endocrine glands. Differentiated thyroid cancers (DTC), the most frequent histological types, generally are associated with a good prognosis [1]. The treatment of DTC consists of total or partial thyroidectomy and in many cases, radioactive therapy with ^{131}I (RAI) following surgery [2]. In many centers, pre- and post-RAI whole body scans (WBS) are performed routinely on patients undergoing RAI for DTC. After surgery and prior to RAI delivery a pre-RAI WBS is performed with either ^{123}I or ^{131}I to identify remnant thyroid tissue and residual local or distant metastatic thyroid cancer. Post-RAI WBS is primarily done to identify metastatic disease not seen by the pre-RAI scan.

A previous study using ^{131}I for pre-planning purposes found that post-RAI scans can detect additional metastatic thyroid disease in 10% of patients compared to pre-RAI with ^{131}I scans. This newly discovered disease affected clinical management in up to 15% of patients receiving RAI [3].

Use of ^{123}I has several advantages over ^{131}I, including a shorter half-life (13.3 hours vs. 8 days), lack of beta emission, and better image

quality. However, ^{123}I is more expensive and not widely available [4-7]. Studies comparing pre-RAI with ^{123}I and post-RAI scans have reported diagnostic concordances ranging from 72% to 94% [8-10]. Nevertheless, previous studies have provided limited information about the clinical implications of these discordant scans [8, 11].

The aim of the present study was to determine the clinical significance of discordant findings between pre-RAI WBS with ^{123}I and post-RAI ^{131}I WBS in patients with DTC.

Materials and methods

Study population

We retrospectively reviewed our database searching for patients of all ages (including 12 patients under 21 years) who received RAI at our institution using the following inclusion criteria: Individuals who underwent near-total or total thyroidectomy and received RAI for the management of DTC, and who underwent both a pre-RAI ^{123}I and post-RAI ^{131}I WBS performed at the Johns Hopkins Hospital between 2002 and 2008 (follow-up data was reviewed up to March of 2012). Patients who had surgery at outside institutions were considered as long as the tumor pathology was submitted for review at our institution. Only patients with complete images, laboratory data and pathology were included. Patients with prior RAI were also included.

The following patients were excluded from the study: Patients with thyroid lymphoma, poorly differentiated and/or medullary thyroid cancer. Individuals not treated at our institution, or those who underwent dosimetry studies or pre-RAI scans using ^{131}I prior to RAI delivery were also excluded. Within the group with discordant scans patients with no follow-up data available were also excluded.

Patients who met our inclusion/exclusion criteria were subsequently divided into 3 main groups: 1) Patients without history of prior RAI (naive) therapy or known distant metastatic disease; 2) Patients with history of prior-RAI and evidence of persistence disease (except distant metastatic disease); and 3) patients who received RAI for treatment of known distant metastatic disease.

Pathology

Differentiated thyroid tumors were divided into 4 categories: 1) Papillary thyroid cancer (PTC) and its follicular variant, 2) Follicular thyroid cancer (FTC), 3) Hurthle cell carcinoma (HCC) and 4) Aggressive variants of PTC including tall cell, columnar cell, and diffuse sclerosing histologies.

Staging

Patients were classified into 5 groups (I, II, III, IVa and IVc) according to the staging system of the American Joint Committee on Cancer [12]. Patients with distant metastatic disease were classified as M1 instead of IVc in order to include them in the same group as the patients under the age of 45 with distant metastatic disease, who would otherwise be classified as stage II. For this study, final staging was made following the pre-RAI WBS and before delivery of RAI.

Patient preparation and procedure protocol

Patients' TSH levels were stimulated by one of two methods: 1) thyroid hormone withdrawal, in which thyroxine (T4) was withheld for at least 4 weeks or triiodothyronine (T3) for 10 days before the pre-RAI WBS, or 2) use of recombinant human thyroid-stimulating hormone (rh-TSH, Thyrogen®, Genzyme, Cambridge, MA), 0.9 mg intramuscularly daily for two days. The pre-RAI ^{123}I WBS was acquired one day after the second activity. Radioactive therapy with ^{131}I occurred one day after the ^{123}I WBS. Post-therapy scans were performed one week after RAI for both protocols (**Figure 1**) [13]. The method employed was based on the referring physician and patient's preference choice, except in patients with evidence of metastatic thyroid cancer, in which case thyroid hormone withdrawal was preferred.

Independent of the preparation method used, all patients underwent ^{123}I WBS one day before RAI and ^{131}I WBS one week after RAI as detailed in **Figure 1**. Serum for assays of TSH (usually on or the day before ^{123}I WBS) and thyroglobulin (TG) were obtained during the procedure week. TG was taken together with serum TSH if patient has been withdrawn or 48-72 hrs after second rh-TSH injection. We used 3 different TG antibody assays during the study period, as follow-

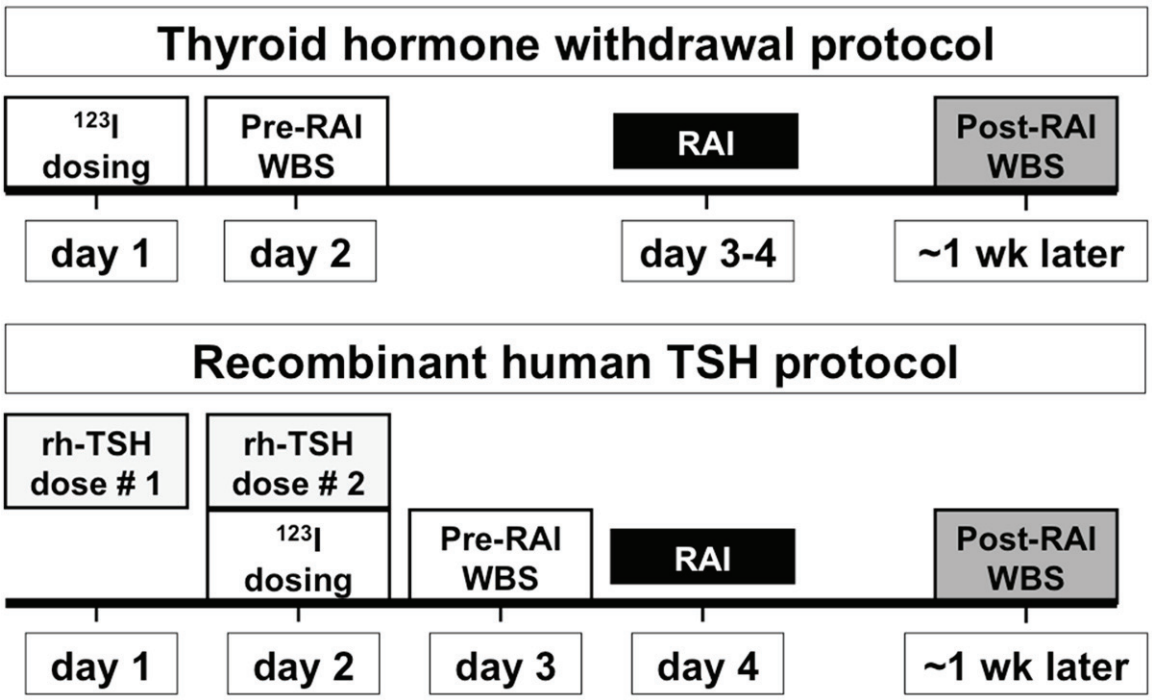

Figure 1. Preparation methods and procedure protocols during therapy week (RAI=radioactive therapy with ^{131}I, WBS=whole body scan).

ing: Nichols Institute Diagnostics Advantage (≤0.3 IU/mL), Siemens Immulite (Quest Diagnostics) (≤20 IU/mL), and Beckman Coulter Access (≤2.2 IU/mL).

Acquisition protocols for pre-therapy ^{123}I whole body scan

Patients received 1.5 mCi of ^{123}I as a sodium iodide capsule orally if withdrawn from thyroid hormone, or 2.0 mCi if stimulated with rh-TSH. Prior to dosing, the capsules were measured using a thyroid phantom at a distance of 6 cm for 1 minute and the counts for each capsule recorded in a spreadsheet to estimate the 24 hour neck uptake. Imaging was performed on a Millennium VG Hawkeye system (GE Healthcare) equipped with SPECT/CT capability using a medium energy, parallel-hole collimator, with a 20% energy window centered at 159 keV.

At approximately 24 hours after ^{123}I intake, an anterior neck image over the thyroid was obtained at 6 cm for 10 minutes before the WBS acquisition. Time and counts were recorded within a region of interest over the thyroid in order to calculate the 24 hour % neck uptake. WBS imaging was performed in the anterior and posterior projections at 5 cm/min.

Radioactive iodine therapy with ^{131}I (RAI)

All patients were treated as outpatients, and the final ^{131}I administered activity was estimated the day before RAI delivery based on staging and the pre-RAI WBS findings including the percentage of ^{123}I uptake in the neck. There is no accepted consensus as to how much ^{131}I activity a patient should receive as part of the management of thyroid cancer, but in general at our institution low-risk patients receive anywhere between 25-75 mCi, those with nodal disease 75-125 mCi, and subjects with history of prior RAI and persistent TG levels as well as those with higher staging usually receive 125 mCi or more.

Acquisition protocols for post-treatment ^{131}I whole body scan

Approximately 7 days after RAI delivery, imaging was performed using the same gamma camera system with a high energy parallel hole collimator and a 20% energy window centered at 364 keV. Anterior and posterior WBS images were obtained at 5 cm/min. An anterior and posterior image of the neck was also obtained for 75K.

Comparison between pre- and post-RAI whole body scan

Both sets of original images were re-uploaded and interactively reviewed on a Xeleris workstation (GE Healthcare-Applications) by a board certified nuclear medicine physician (PB). The scans were considered to be completely discordant if the post-RAI scan demonstrated at least one new area of increased radiotracer activity at sites where no uptake was visualized on the corresponding pre-RAI scan.

When the post-RAI scan showed one or more additional areas of increased radiotracer activity at sites that had already demonstrated radiotracer uptake on the corresponding pre-RAI WBS they were considered partially discordant and not included in the discordant group. The additional information obtained from the ones with partial discordance was unlikely to have an impact on clinical staging or patient management since the findings were already available to the clinician from the pre-therapy scan prior to RAI delivery.

Completely discordant findings were analyzed on a site and patient-basis. Any extra uptake seen on the post-RAI WBS within the nasopharynx, salivary glands, gastrointestinal and/or urinary system was considered a result of normal radioiodine metabolism, secretion and/or excretion, and thus not considered discordant.

In patients with evidence of complete discordance between scans, further attempts to assess the significance and/or clinical implication(s) of the discordant findings were made by reviewing and analyzing further information including clinic notes, laboratory, operative and pathology reports, and cross-sectional multimodality images, according to the following criteria:

1) Nodal or metastatic disease was considered likely at the site of complete discordance if there was biopsy-proven disease, and/or ultrasonographic, CT, MRI, SPECT/CT, or PET/CT evidence of disease, and/or abnormal uptake in same location on subsequent post-RAI examinations.

2) Disease was unlikely or negative at the site of discordance if the above-mentioned evaluations were unrevealing and/or stimulated TG levels were below 2 ug/L at least 8 months post-RAI on follow-up [14, 15].

No reverse discordance (findings seen on pre-RAI and missed on post-RAI WBS) was observed in this study.

Statistical analysis

Statistical analyses were performed using SPSS (version 21.0). Continuous variables were presented as mean±SD and median. An independent-measures t-test and Mann-Whitney U test (for non-parametric distributions) were used to assess differences between 2-tail subgroups. Categorical variables were compared between groups using chi-square (x^2) tests and are presented as percentages. A P value <0.05 was considered statistically significant for all calculations.

Results

A total of 342 patients were included in the study. Group 1 (RAI-naive) was made up of 311 patients; group 2 (history of prior RAI) of 23 individuals; and group 3 (known distant metastatic disease) consisted of 8 patients.

Concordance/discordance of scans in RAI-naive patients without known distant metastatic disease prior to RAI delivery (group 1)

Complete discordance was observed in 7% (22/311) of patients within this group. Except for certain racial differences and a higher ^{131}I activity received by patients with discordant scans (85±21 vs. 97±18 mCi, P=0.007), baseline characteristics were similar between individuals with concordant and discordant pre/post WBS in this group (**Tables 1** and **2**).

The discordant sites were in order of frequency in the extra-thyroidal neck (n=9), lungs (n=7), mediastinum (n=4), and abdomen (n=2). Clinical follow-up information was available for all discordant patients with a median follow-up of 2.9 years (**Table 3**). These data demonstrated that in only 4 cases (18% of discordant cases and 1.3% of the total patients in group 1), the activity that localized at the discordant sites corresponded to persistent disease, including 3 patients with unsuspected metastatic lung disease shown on a chest CT and 1

Table 1. Baseline characteristics of patients with differentiated thyroid cancer

Characteristics	No prior RAI or evidence of distant metastatic disease (Group 1)			History of prior RAI and/or known distant metastatic disease (Group 2/Group 3)		
	Concordant scans (n=289)	Discordant scans (n=22)	*P*	Concordant scans (n=19)	Discordant scans (n=12)	*P*
Age (yrs)	47±15	51±17	0.2	44±20	52±14	0.2
Tumor size (cm)	2.1±1.5	2.6±2.7	0.2	3.6±2.3	3.6±1.8	0.9
^{123}I activity (mCi)	1.6±0.2	1.7±0.3	0.3	1.5±0.2	1.6±0.1	0.3
^{123}I neck uptake (%)	1.6±2.8	0.9±0.9	0.2	0.36±0.58	0.26±0.52	0.6
Thyroglobulin (ug/L), median	3.1	2.2	0.4	10	126	0.007
TSH (mIU/L)	103±61	120±69	0.2	110±88	94±48	0.6
RAI activity (mCi)	85±21	97±18	0.007	130±52	197±20	<0.0001

Values are mean±SD unless otherwise indicated. RAI=radioactive therapy with ^{131}I.

Table 2. Baseline characteristics of patients with thyroid cancer (continuation)

Characteristics		No prior RAI or evidence of distant metastatic disease (Group 1)			History of prior RAI and/or known distant metastatic disease (Group 2/Group 3)		
		Concordant scans (n=289)	Discordant scans (n=22)	*P*	Concordant scans (n=19)	Discordant scans (n=12)	*P*
Gender, n (%)	Female	188 (65)	13 (59)	0.6	11 (58)	5 (42)	0.4
Race, n (%)	White	229 (79)	13 (59)	0.04	16 (84)	7 (59)	0.2
	Black	37 (13)	4 (18)		2 (11)	4 (33)	
	Other	23 (8)	5 (23)		1 (5)	1 (8)	
Pathology, n (%)	PTC	241 (83)	19 (86)	0.6	11 (58)	9 (75)	0.4
	FTC	14 (5)	2 (9)		3 (16)	0	
	HCC	15 (5)	0		1 (5)	0	
	Other*	19 (7)	1 (5)		4 (21)	3 (25)	
Staging, n (%)	Stage I	194 (67)	15 (68)	0.7	9 (47)	3 (25)	0.07
	Stage II	25 (9)	1 (5)		0	0	
	Stage III	57 (20)	4 (18)		6 (32)	1 (8)	
	Stage IVa	13 (4)	2 (9)		1 (5)	3 (25)	
	M1	0	0		3 (16)	5 (42)	
Preparation method, n (%)	Hormone withdrawal	187 (65)	11 (50)	0.2	18 (95)	12 (100)	0.4
	rh-TSH	102 (35)	11 (50)		1 (5)	0	

PTC=papillary thyroid cancer, FTC=follicular thyroid cancer, HCC=Hurthle cell carcinoma, Other PTC variants, rh-TSH=recombinant human TSH, RAI=radioactive therapy with ^{131}I.

Table 3. Baseline and follow-up evaluations of patients with completely discordant scans and without a history of prior RAI or known distant metastatic disease at the time of first study (Group 1)

ID	Age (yrs)	Stage	^{131}I (mCi)	Location of discordance	Examination modality for follow-up	Findings	TG* (ug/L)	f/u time (yrs)	Evidence of disease on follow-up
1	39	I	103	Bilateral lung	SPECT/CT, CT	No abnormality	U	2.1	Negative
2	51	I	108	Liver/hepatic flexure	US, CT, SPECT/CT	5 mm liver cyst	U	1.3	Negative
3	34	I	76	Bilateral neck	U/S, CT, FNA	Reactive LN	U	1.2	Negative
4	44	I	101	Left upper neck region	SPECT/CT, U/S	Benign-appearing left submandibular LN	U	6.9	Negative
5	18	I	75	Anterior mediastinum	SPECT/CT	Thymic tissue uptake	U	3.4	Negative
6	61	I	77	Right neck	U/S	Benign-appearing LN	U	7.9	Negative
7	77	I	78	Anterior mediastinum	SPECT/CT	Anterior mediastinal density, likely thymus	U	1.8	Negative
8	46	I	107	Left upper abdomen	Stimulated TG	Felt to be benign	U	4.6	Negative
9	50	I	102	Lower neck	U/S, FNA	Negative, left level IV LN	U	3.8	Negative
10	40	I	128	Right posterior neck	CT, U/S	benign-appearing LN	U	5.9	Negative
11	29	I	103	Anterior mediastinum	Stimulated TG	Felt to be thymus	U	1.7	Negative
12	41	I	100	Anterior mediastinum	Stimulated TG	Felt to be thymus	U	7.2	Negative
13	66	I	103	Lower neck	Stimulated TG		U	2.5	Negative
14	35	I	77	Left lung	SPECT/CT	No abnormality	U	2.1	Negative
15	60	I	100	Right lateral thorax	SPECT/CT	No abnormality	U	4	Negative
16	45	II	74	Right posterior thorax	SPECT/CT, CT	No abnormality	0.4†	4.5	Negative
17	84	III	75	Bilateral lung	CT, SPECT/CT, ^{131}I WBS	Multiple lung nodules bilaterally	187.7	2	Positive
18	71	III	146	Lower neck	CT, U/S, FNA	Metastatic PTC in right level VI LN	1312	0.8	Positive
19	46	III	103	Lower neck	U/S	benign-appearing LN	0.3†	6.8	Negative
20	85	III	102	Lower neck	Stimulated TG		2.5†	1.5	Likely negative
21	53	IVA	103	Bilateral lung	CT	Multiple lung nodules bilaterally	60.9	4.5	Positive
22	54	IVA	101	Right lower lung	CT, excision biopsy	Single lung nodule. Biopsy metastatic PTC	0.4	1.8	Positive

TG*=follow-up stimulated serum thyroglobulin (TG) levels at least 8 months after RAI. †=presence of anti-TG antibodies. U=undetectable stimulated TG levels. U/S=ultrasound. FNA=fine needle aspiration. LN=lymph nodes. ^{131}I WBS=subsequent post-RAI scan. PTC=papillary thyroid cancer. f/u=follow-up.

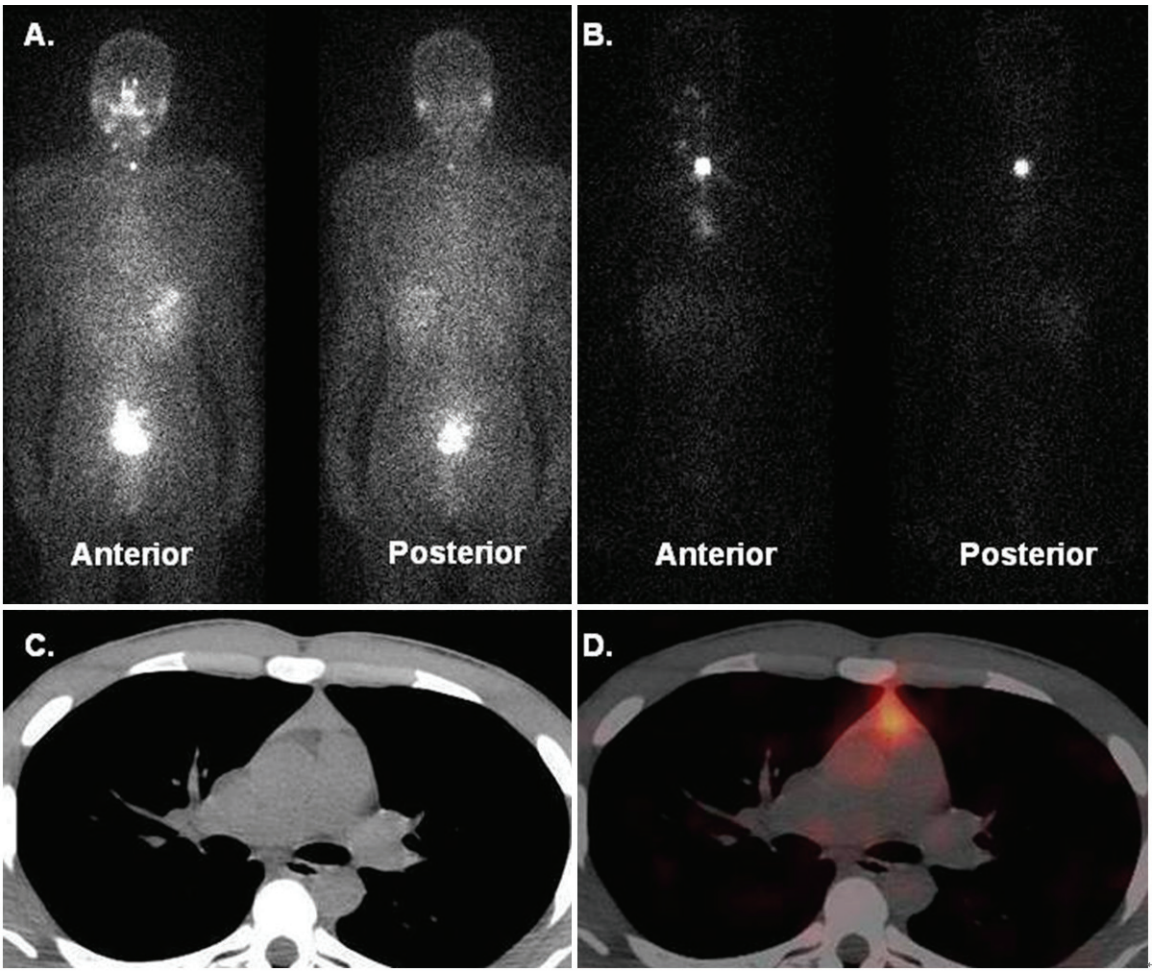

Figure 2. Patient (ID #5) shows a large area of increased radiotracer uptake in the mediastinal region on post-RAI scan (B) not seen on pre-RAI study (A). SPECT/CT (C, D) demonstrates radiotracer activity localizing to the anterior mediastinum, corresponding to thymic tissue on CT. Stimulated Thyroglobulin remained undetectable 3.4 years after initial RAI delivery consistent with physiologic ^{131}I uptake in the thymus.

patient who was diagnosed with metastatic PTC to a right level VI lymph node by fine needle biopsy during follow-up.

No evidence of persistent disease was documented in the remaining 18 cases (82% of discordant scans) on subsequent evaluations (**Table 3**). In these cases the discordant findings were considered to correspond to physiologic uptake (**Figure 2**), benign conditions or spurious findings (**Figure 3**), as following:

Physiologic uptake: thymus (ID #5, 7, 11, 12) and bowel (ID #8). TG levels were undetectable on follow-up.

Benign uptake/conditions: liver cyst (ID #2), reactive lymph nodes on biopsy (ID #3, 9) and benign-appearing lymph node findings on ultrasound or CT (ID #4, 6, 10, 19). TG levels were undetectable on follow-up, except for case #19.

Spurious uptake/findings: bilateral lung (ID #1), left lung (ID #14), right lateral thorax (ID #15), and right posterior thorax (ID #16). No abnormality was detected on SPECT/CT and CT scans. TG levels were undetectable on follow-up, except for case #16.

There were 2 patients with lower neck ^{131}I uptake wherein follow-up TG became undetectable in one case (ID #13) and persisted only mildly detectable on the other one (ID #20), both cases were considered negative for thyroid cancer.

The 4 patients with confirmed disease at the discordant sites had a significantly higher presenting stage of disease (III and IVa vs. I, II, III;

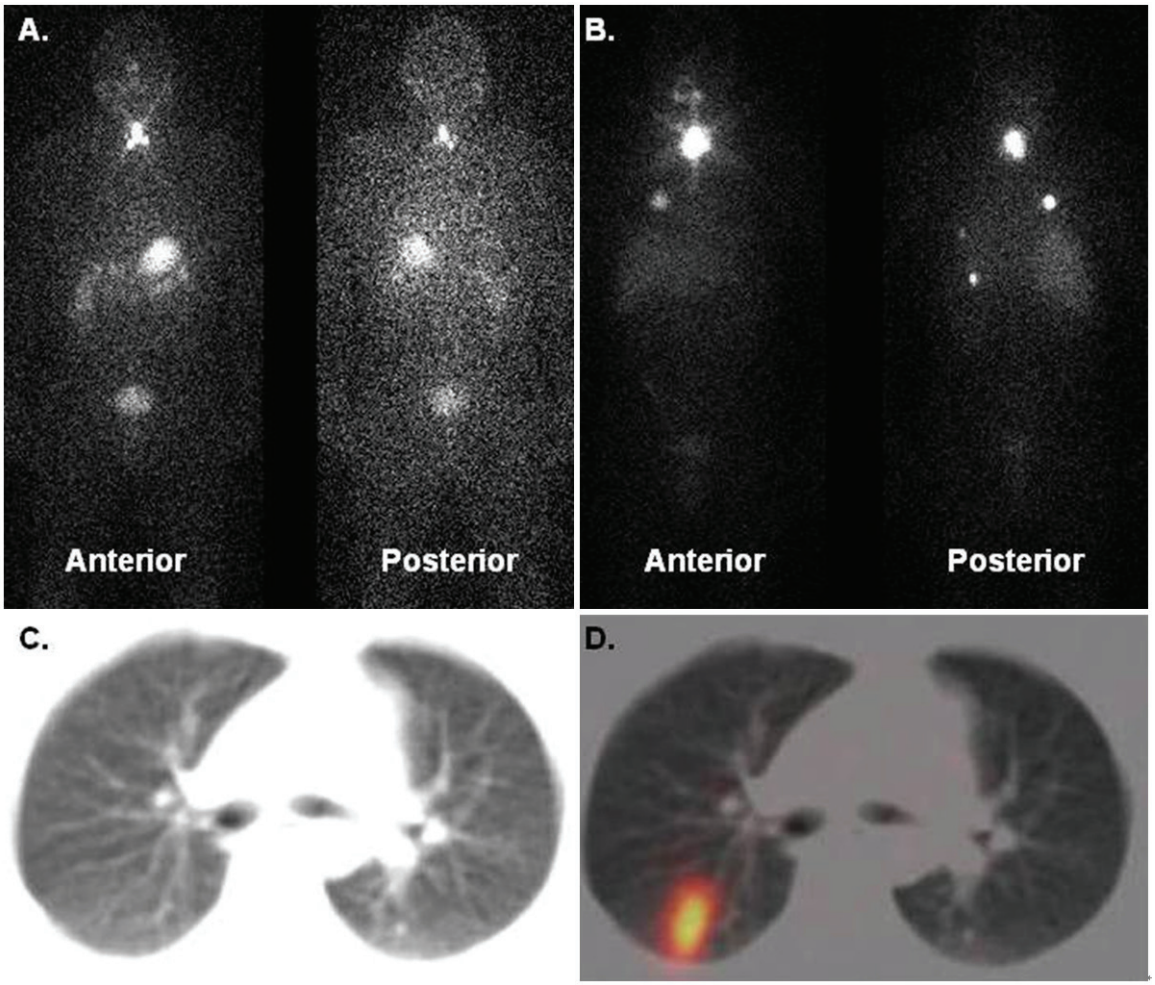

Figure 3. Patient (ID #1) has 3 foci of ^{131}I increased uptake in the right and left lower lungs in the post-RAI scan (B and D) with no ^{123}I uptake on pre-RAI study (A) and no CT abnormality (C). Stimulated Thyroglobulin remained undetectable 2.1 years after initial therapy.

P=0.002) and stimulated TG (median 270 vs. 1.3 ug/L; P=0.002) prior to RAI delivery compared to those with no evidence of disease on follow-up evaluations.

Concordance/discordance of scans in patients with history of prior RAI therapy and evidence of persistent disease, except distant metastasis (group 2)

In this group, 23 patients had history of prior RAI therapy and evidence of persistent disease (except M1) by elevated stimulated TG and/or cross-sectional imaging. Discordant findings were seen in 7 (30% of patients with prior RAI) of these patients, and consisted of new uptake in the neck or upper mediastinum that represented loco-regional nodal disease in the neck (n=5) and a left mediastinal paratracheal node (n=1). The last patient (stage IVa) showed discordant uptake in the posterior thorax, and cross-sectional imaging demonstrated unsuspected distant metastasis at the right transverse process of 10th thoracic vertebra (**Table 4**).

Patients with discordant findings (n=7) received a significantly greater ^{131}I activity (205±3 vs. 122±48 mCi; P<0.0001) and had higher stimulated TG levels (median 102 vs. 5.7 ug/L; P=0.003) prior to repeat RAI than individuals without discordance (n=16).

Concordance/discordance of scans in patients with known distant metastatic disease (group 3)

A total of 8 patients had known M1 in the lung (n=4), bone (n=3) and pleura (n=1) prior to RAI, but only 3 of them were identified by the pre-therapy ^{123}I scan (2 lung and 1 bone). The

Table 4. Baseline and follow-up evaluations of patients with completely discordant scans and history of prior RAI (Group 2) or known distant metastatic disease at the time of first study (Group 3)

ID	Age (yrs)	Stage	^{131}I (mCi)	Location of discordance	Examination modality for follow-up	Findings	TG* (ug/L)	f/u time (yrs)	Evidence of disease on follow-up
23	37	I	206	Left neck	U/S	3 suspicious left neck LN	5.8	9.2	Positive
24	43	I	201	Left neck	PET/CT, excision biopsy	Metastatic PTC involving left parapharyngeal LN	45.3	0.9	Positive
25	33	I	203	Left neck	U/S	Suspicious left level IIB LN	44.9	0.8	Positive
26	66	III	209	Right lower neck	SPECT/CT, U/S, CT	Suspicious left level IV LN	1274	3.8	Positive
27	48	IVA	206	Upper mediastinum	SPECT/CT	Left paratracheal LN	12.5	2.9	Positive
28	68	IVA	205	Lower neck/upper mediastinum	U/S, CT	Cluster of 3 suspicious level IV LN	26.3	2.7	Positive
29	59	IVA	206	Posterior thorax	SPECT/CT, CT, PET/CT	Expansile lytic metastasis at right T10 transverse process	305.6	4.2	Positive
30	69	M1	209	Right occipital bone	MRI, PET, ^{131}I WBS, bone scan	Cystic rim enhancing mass in right occipital bone on MRI	1266	4.8	Positive
31	49	M1	205	Left femur	Plain films, PET/CT, excision biopsy	Metastatic PTC to femur	216.2	4.9	Positive
32	68	M1	157	Bilateral lung	SPECT/CT, CT	Bilateral pulmonary nodules	126.5	0.9	Positive
33	40	M1	152	Bilateral lung	CT, ^{131}I WBS	Multiple lung nodules bilaterally	596.1	8	Positive
34	51	M1	203	Posterior chest	CT, PET/CT, biopsy	pleura-based mass in posterior thorax	361.2	3.4	Positive

TG*=follow-up stimulated serum thyroglobulin levels at least 8 months after RAI. †=Individuals without history of prior RAI. M1=Subjects with known distant metastatic disease. U/S=ultrasound. LN=lymph nodes. ^{131}I WBS=subsequent post-RAI scan. PTC=papillary thyroid cancer. T10=thoracic vertebrae 10. f/u=follow-up. Red text indicates a case where M1 was unknown by referring physician.

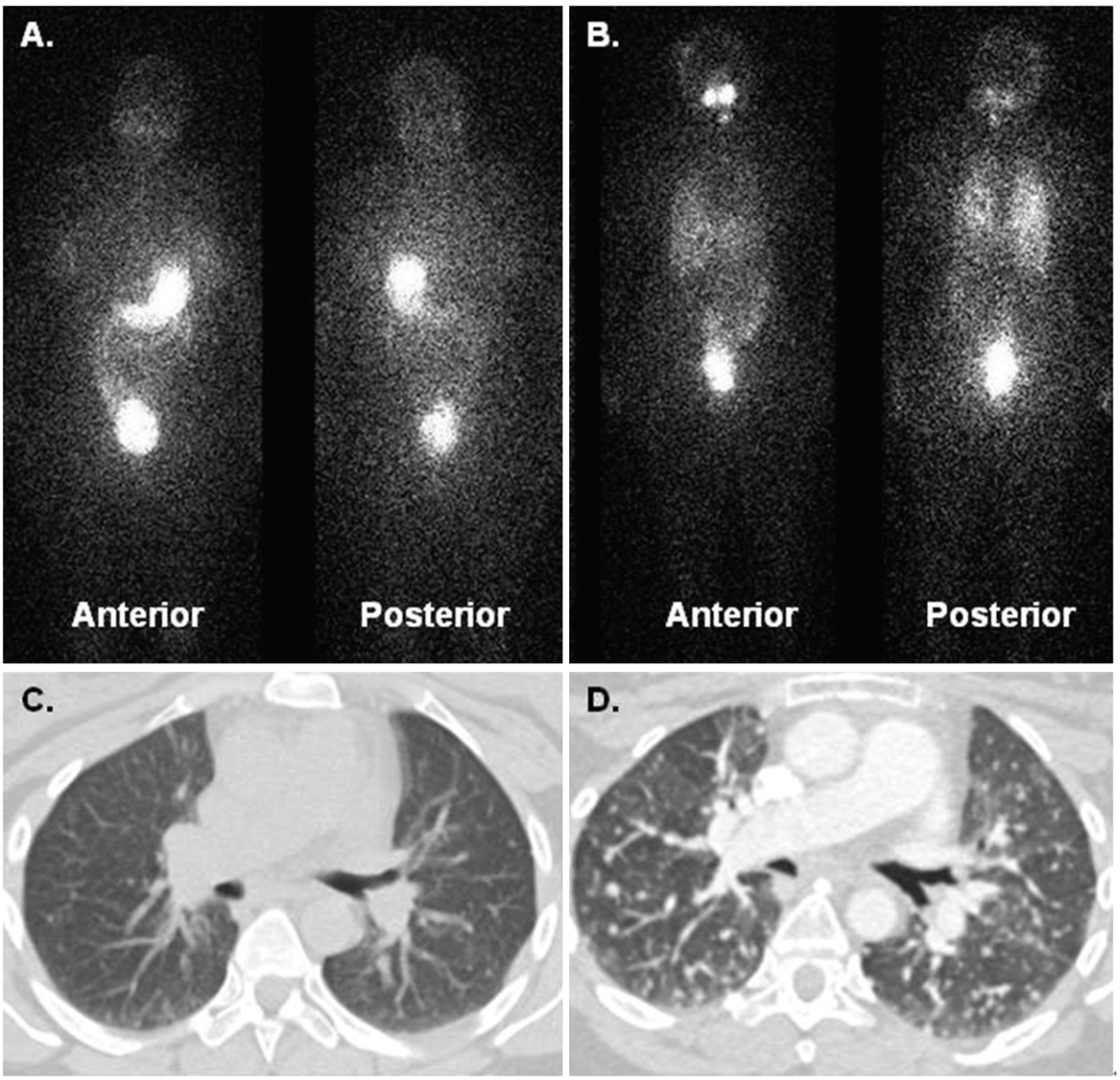

Figure 4. Patient (ID #33) has evidence of diffuse lung uptake on post-RAI scan (B) not seen on pre-RAI study (A). Chest CT one month prior to RAI delivery showed scatter lung nodules suspicious for metastasis (C). Chest CT seven years following therapy revealed innumerable pulmonary nodules consistent with widespread metastatic lung disease (D).

remaining 5 patients (62.5% of known M1) showed discordant uptake in the bilateral lung (n=2) (**Figure 4**), occipital bone, left femur and posterior thorax (pleura-based mass), which corresponded to the locations of known M1 (**Table 4**). There was no significant difference in the ^{131}I administered activity to M1 patients with and without discordant scans (172±59 vs. 185±28 mCi, P=0.7).

Detection of Iodine-avid distant metastatic disease by pre and post-RAI scans

A total of 12 patients with M1 were identified by post-RAI scan in this cohort (3.5%). This includes 8 patients of group 3 who were known M1 prior to RAI delivery, 3 new patients discovered during group 1 evaluations, and one additional patient unrevealed by post-therapy scan of group 2. Pre-RAI WBS only detected 3 (25%) of these M1 findings.

Discussion

The main findings of this study are the following: 1) the detection likelihood of loco-regional or distant metastatic disease by a post-RAI scan not visualized by a pre-RAI study is greatly influenced by the presenting stage of disease. It can be as low as 1.3% in RAI-naive patients

without known M1 on presentation, 30% in patients with history of prior RAI delivery and evidence of persistent disease (except M1), and as high as 63% in patients with known M1; 2) the majority (82%) of the additional findings observed on post-RAI WBS performed with higher activities in RAI-naive patients without known M1 were physiologic or otherwise spurious findings; and 3) pre-RAI WBS only detected 25% of all iodine-avid M1 lesions subsequently identified on post-RAI scans.

The frequency and clinical significance of discordant scans is to a great extent affected by the clinical scenario. In RAI-naive patients without clinical evidence of M1 (91% of studied patients) the pre- and post-RAI WBS discordance was 7%. However, only 18% of these discordant cases (1.3% of total studied patients within this population) resulted in loco-regional (n=1) or distant metastatic disease (n=3). The disease in these four patients had not been suspected by the referring physician, but was confirmed by following examinations. As expected, those patients with confirmed disease on follow-up had a significantly higher presenting disease stage and stimulated TG prior to RAI delivery compared to those with no evidence of disease on subsequent evaluations.

In contrast, 82% of discordant scans within this group were considered negative for disease after further evaluation with different cross-sectional imaging modalities, stimulated TG, and/or tissue biopsy, which revealed no pathologic abnormalities. In this regard, there are well known physiologic as well as pathologic states associated with radioiodine uptake not necessarily related to DTC. Inflammatory lung tissue and bronchiectasis can take up radioiodine, which leads to false positive findings on post-RAI WBS [16-18]. The thymus is also known for concentrating iodide, similar to the salivary glands, stomach, kidneys, breasts, sweat glands, choroid plexus and hair follicles, which may be falsely interpreted as nodal disease in the mediastinum on planar images [16, 17, 19-21]. Likewise, uptake in the esophageal region due to swallowed saliva and/or anatomical abnormalities (strictures, scarring or hiatal hernias) can be confused with disease [17, 22]. This demonstrates that most often completely discordant findings are due to physiologic or other benign causes in RAI-naive patients without known M1.

Discordance increased to 30% in patients with a history of previous RAI and evidence of persistent disease found by different tests (except M1) before RAI delivery. In our series, all discordant findings represented loco-regional disease in the neck and upper mediastinum, and M1 in one case (T10 transverse process), indicating an absence of false positive findings within this higher risk group.

Discordance between pre- and post-RAI WBS peaked to 63% in patients with known M1. In this subgroup, discordant sites on post-RAI scans corresponded to the locations of known M1 missed by pre-RAI WBS. Moreover, pre-RAI WBS only detected 25% of all M1 patients identified by post-RAI scans in all studied patients. These findings point out to a significant limitation of this pre-RAI scan for detection of iodine-avid M1.

Potential reasons for this discrepancy between pre- and post-RAI scans for disease detection include differences in imaging time. The pre-RAI scan was acquired 24 hrs after ^{123}I dosing in contrast to the one-week delay in the acquisition following ^{131}I therapy. A longer delay increases the target-to-background ratio and may improve lesion identification. Previous work has shown a higher detection of iodine-avid lung or bone metastasis on post-therapy scans at 7 vs. 3 days [23]. Gerard et al evaluated the diagnostic accuracy of pre-RAI scans at 4, 24 and 48 hrs after ^{123}I dosing and observed that 48-hr imaging is feasible and may improve detection of weakly avid tumor seen only on post-RAI scans [5].

We found that patients with discordant findings received significantly higher ^{131}I activity in groups 1 and 2 (but not in 3), suggesting that higher activities of ^{131}I may be required for identification of loco-regional and distant metastatic disease. In this respect, expression of the human sodium iodide symporter (hNIS) system is considered a required step for radioiodine uptake in normal and malignant thyroid cells [24]. Studies have documented that lymph node and distant metastatic tissue exhibit significantly lower or absence of expression of hNIS than the primary thyroid tumor, suggesting a mechanistic explanation for the lack of iodine-avidity of some thyroid cancer [25, 26]. It is conceivable that the reduced hNIS expression of some tumor cells may limit their visual-

ization when using the low radioiodine activities in pre-RAI scans.

Using varying definitions of pre- and post-RAI scan discordance, a number of studies have previously attempted to evaluate its frequency and clinical significance in the management of DTC. The results of these studies vary widely [8-10]. Alzahrani et al, reported higher discordance rates in patients undergoing a second cycle of RAI (18%) than in those receiving their first RAI (6%) [10]. Urhan et al, compared patients with either a positive or negative pre-RAI ^{123}I vs. post-RAI scans and found higher discordance in the latter group of patients (13 vs. 28%) [9]. They also reported that 21 of 292 patients with thyroid cancer (7% of study population) exhibited completely discordant findings in the lungs, bone, mediastinum, thyroid bed and neck comparing pre- and post-RAI scans [9], although the authors did not establish how many of them were due to thyroid cancer. Donahue et al observed that 19 of 108 RAI-naive patients with thyroid cancer had totally discordant scans, with 11 (10% of total group) showing clinical upstaging and 6 patients (5.5% of the total study group) showing scintigraphic patterns suggestive of distant metastatic disease [8].

Similar to previous studies, the authors did not confirm the veracity of the discordant findings with additional diagnostic modalities. It is worth-mentioning again that we did not consider the findings discordant where the post-RAI scan showed one or more additional areas of increased radiotracer activity at sites already demonstrating radiotracer uptake on the corresponding pre-RAI WBS. These findings were already available to the clinician prior to RAI, and the clinical information obtained from this group was unlikely to have any impact on clinical staging or patient management.

Another important observation is the fact that discordance rates between pre- and post-RAI scans in group 2 (30%) and group 3 (63%) were quite high in our study when compared to previous studies (6~28%). This difference is likely due to selection bias, and dilutional effect, such as when occurs by including patients with low- and high-risk characteristics in the same group. For instance, the overall discordance rate when combining groups 1-3 was only 10% (34/342) in our study, which falls well within the reported range in the literature.

We used SPECT/CT in 38% of the discordant cases (13/34). This technique played an important role for the detection of metastases not seen on planar WBS (nodal, lung, pleural, mediastinal, and bone metastases), and for precise localization of physiologic (thymus), benign (lymph nodes, liver cyst) and spurious findings. Previous studies have found SPECT/CT to be a useful tool to characterize atypical or cryptic findings on WBS by differentiating thyroid remnant or cancer from physiologic activity or non-thyroid pathology [16].

There are important clinical considerations derived from our study: 1) our results suggest that post-RAI WBS may not need to be routinely performed in RAI-naive patients without clinical evidence of M1 as the likelihood of unmasking metastatic disease by the post-RAI scan is approximately 1 in 100 according to our results, and discordant findings are more likely to represent false positive findings. Instead, they should be obtained on a case-by-case basis, based on the clinical suspicion for occult M1; 2) our study also indicates that in patients with clinical evidence of persistent disease after RAI and/or M1status, the post-RAI scan appears to yield greater iodine-avid disease detection than the pre-RAI study. This raises the question of the role of these pre-RAI-planning scans in this clinical scenario. This is especially relevant in patients with suspected or known M1 for whom pre-RAI scans are often used in the decision-making for delivery of higher RAI doses; 3) Additional research is required to assess the use of a higher ^{123}I activity (5.0 vs. 2.0 mCi) and image acquisition delay to 48 hrs (instead of 24 hr) with pre-RAI WBS in higher-risk DTC patients, which may result in higher target to background ratios and enhanced disease detection, and 4) SPECT/CT should be considered in discordant cases to exclude metastatic DTC, especially in higher risk patients such as those with history of previous RAI.

Finally, it is worth mentioning potential limitations of this work, including its retrospective design, as well as the fact that our findings are limited to a single tertiary referring institution and may not be applicable to other centers. Another limitation is the heterogeneity of the 3 groups with a limited number of DTC patients in

group 2 (n=23) and group 3 (n=8) compared to group 1 (n=311).

In summary, the significance of pre- and post-therapy scans during the management of patients with thyroid cancer is highly influenced by the clinical setting. Unsuspected distant metastatic disease is infrequent in RAI-naive patients and most discordant findings are usually due to physiologic or other benign conditions, and represent false positive findings. In contrast, in higher risk-patients, including those with previous RAI and/or known distant metastatic disease, discordant results likely correspond to true disease.

Acknowledgment

We thank Judy Buchanan from the Division of Nuclear Medicine and Lori Sokoll from the Division of Endocrinology and Metabolism at Johns Hopkins for their assistance in the preparation of this manuscript.

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