ORIGINAL ARTICLE

Radioiodine Scan Index: A Simplified, Quantitative Treatment Response Parameter for Metastatic Thyroid Carcinoma

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Abstract

Purpose We aimed to develop and validate a simplified, novel quantification method for radioiodine whole-body scans (WBSs) as a predictor for the treatment response in differentiated thyroid carcinoma (DTC) patients with distant metastasis.

Methods We retrospectively reviewed serial WBSs after radioiodine treatment from 2008 to 2011 in patients with metastatic DTC. For standardization of TSH simulation, only a subset of patients whose TSH level was fully enhanced (TSH>80 mU/l) was enrolled. The radioiodine scan index (RSI) was calculated by the ratio of tumor-to-brain uptake. We compared correlations between the RSI and TSH-stimulated serum thyroglobulin (TSH_s_Tg) level and between the RSI and Tg reduction rate of consecutive radioiodine treatments.

Results A total of 30 rounds of radioiodine treatment for 15 patients were eligible. Tumor histology was 11 papillary and 4 follicular subtypes. The TSH_s_Tg level was mean 980 ng/ml (range, 0.5–11,244). The Tg reduction rate after treatment was a mean of −7 % (range, −90 %–210 %). Mean RSI was 3.02 (range, 0.40–10.97). RSI was positively correlated with the TSH_s_Tg level (R^2=0.3084, p=0.001) and negatively correlated with the Tg reduction rate (R^2=0.2993, p=0.037). The regression equation to predict treatment response was as follows: Tg reduction rate=−14.581×RSI+51.183.

Conclusions Use of the radioiodine scan index derived from conventional WBS is feasible to reflect the serum Tg level in patients with metastatic DTC, and it may be useful for predicting the biologic treatment response after radioiodine treatment.

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Introduction

The incidence of thyroid cancer has increased for several decades in many countries [1–3]. Although the overall recurrence and mortality rates are lower than those of most other malignancies, distant metastasis often leads to an unfavorable prognosis with increased morbidity and mortality [4–6]. The two most frequent sites of distant metastases are the lungs and bones [4]. Radioiodine treatment has been successfully used for such metastatic DTCs for 70 years [7, 8]. The outcome of radioiodine treatment in metastatic DTC is related to the radiation dose delivered to the tumor tissue and to its sensitivity to radiation [9]. Thus, evaluation of the delivered dose to tumor tissue is essential to predict the treatment response and plan consecutive management in patients with metastatic DTC.

The radioiodine activity delivered to tumor tissue can be estimated by radioiodine dosimetry, which allows calculation of the absorbed dose to iodine-avid metastatic tissue and determination of the maximized individual dose that is safe from toxicity or serious side effects of radioiodine treatment [10]. However, the methodology, a number of imagings and samplings before or during radioiodine treatment, is cumbersome in routine clinical practice. Instead of dosimetric evaluation, there is currently no simplified, quantitative parameter derived from post-treatment whole-body scans (WBSs) to predict the treatment response in patients with metastatic thyroid carcinoma. Therefore, we aimed to develop a novel and simple quantification method for tumor radioiodine uptake on post-treatment WBS and validate its use as a predictor for the treatment response in patients with metastatic DTC.

Materials and methods

Patients

Serial WBSs after radioiodine treatment from 2008 to 2011 in patients with metastatic DTC were retrospectively reviewed. For standardization of TSH stimulation, only a subset of patients whose TSH level was fully enhanced (TSH>80 mU/l) was enrolled. The patients who underwent other treatments such as an operation, external radiotherapy, or chemotherapy for metastatic lesions were excluded. Radioiodine treatment was performed after at least 4-week withdrawal from levothyroxine and a 2-week low-iodine diet. All patients were admitted for 3–4 days and underwent assays for TSH, TSH-stimulated serum thyroglobulin (TSH_s_Tg), and antithyroglobulin antibodies (ATA) on the day of radioiodine treatment. Repetitive treatment was performed within 6 to 12 months after initial treatment. If the patients underwent F-18 FDG PET/CT (Discovery ST System, GE Healthcare, Milwaukee, WI, USA) scans, the results were also recorded as positive or negative according to the presence of FDG uptake exceeding background activity. The local ethics committees approved the study, and all enrolled patients gave written informed consent.

Radioiodine whole-body scans

A single post-treatment WBS was performed 4–6 days after radioiodine administration. Images were acquired in the anterior and posterior projections using two variable-angle dual-head gamma cameras (Infinia, GE Healthcare, Milwaukee, WI, USA). The instrument has parallel-hole high-energy

collimators, with a matrix size of 256×1024 and a 364-keV photopeak with 10 % windows. The table speed for whole-body imaging was 12 cm/min.

Radioiodine scan index

Radioiodine uptake in each region of interest (ROI) was initially estimated by the arithmetic mean of the anterior and posterior images of post-treatment WBSs (Fig. 1).

Mean counts

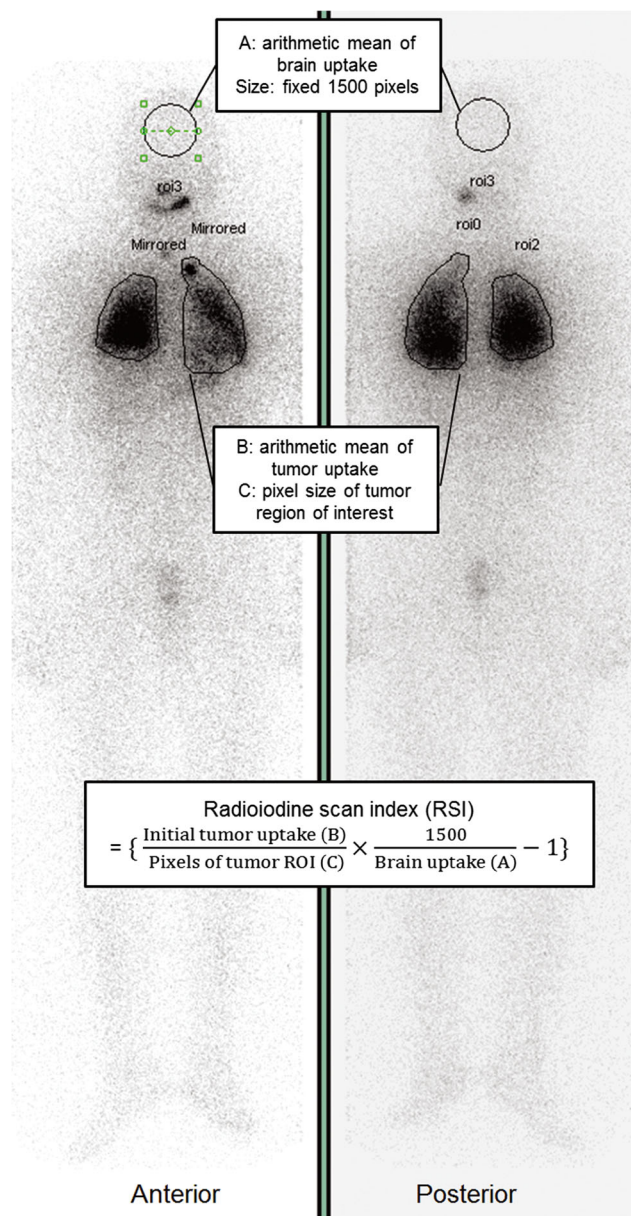$$= \frac{\text{Counts in anterior image} + \text{Counts in posterior image}}{2}$$

Fig. 1 Calculation of the radioiodine scan index

The tumor ROI, which is the fully encasing abnormal radioiodine uptake suggesting metastasis, was drawn manually, and the initial tumor uptake was obtained. A circular ROI with 1500 pixel size was drawn in the middle of the brain for background activity. None of the patients showed abnormally increased radioiodine uptake in the brain or clinical symptoms suggesting brain metastasis. Area-corrected brain uptake was calculated by the following formula:

$$\text{Area-corrected brain uptake} = \frac{\text{Brain uptake}}{1,500}$$
$$\times \text{Pixel size of tumor ROI}$$

Corrected tumor uptake was estimated by subtraction of the area-corrected brain uptake from the initial tumor uptake.

Corrected tumor uptake
$$= \text{Initial tumor uptake} - \text{Area-corrected brain uptake}$$

The radioiodine scan index (RSI) was calculated by the ratio of the corrected tumor uptake to the area-corrected brain uptake.

Radioiodine scain index(RSI)
$$= \frac{\text{Corrected tumor uptake}}{\text{Area-corrected brain uptake}}$$

The summarized formula for RSI using initial parameter is as follows:

Radioiodine scan index(RSI)
$$= \left(\frac{\text{Initial tumor uptake}}{\text{Pixels of tumor ROI}} \times \frac{1,500}{\text{Brain uptake}} \right) - 1$$

Analysis

The Tg reduction rate was calculated by the ratio of the TSH_s_Tg level between two sequential treatment rounds.

Tg reduction rate(%)
$$= \frac{\text{Latter TSH\_s\_Tg level} - \text{Former TSH\_s\_Tg level}}{\text{Former TSH\_s\_Tg level}}$$
$$\times 100$$

Data analysis using the ATA-corrected serum Tg level was also performed. The ATA-corrected serum Tg level was calculated by the following formula according to a previous report that provided a mathematical equation for estimation of

the true Tg concentration under various concentrations of ATA using data from experiments using patients' serum [11]:

ATA_corrected Tg level(ng/ml)
$$= 1.677 + 0.634 \times \text{measured Tg level (ng/ml)} + 0.313$$
$$\times \text{measured Tg level (ng/ml)} \times \text{logATA (IU/ml)}$$

Comparisons of the TSH_s_Tg level and RSI according to FDG avidity were performed using the Mann-Whitney U test. The Pearson correlation coefficient was used for assessment of correlations between the RSI and TSH_s_Tg level as well as the RSI and Tg reduction rate. The regression equation between the RSI and Tg reduction rate to predict treatment response was also derived. Medcalc software (version 11.4; MedCalc, Mariakerke, Belgium) was used for all statistical calculations, and $p < 0.05$ was considered statistically significant.

Results

Patients

A total of 30 rounds of radioiodine treatment in 15 patients were eligible (Table 1). Tumor histology was 11 papillary and 4 follicular subtypes. Initial T staging was 3 in 10 patients and 4 in 5 patients, and initial N staging was 0 in 3 patients, 1a in 2 patients, and 1b in 10 patients. Treatment dose of I-131 was 5.6 GBq (150 mCi) in 2, 6.7 GBq (180 mCi) in 3, and 7.4 GBq (200 mCi) in 25 rounds of treatment (Table 2). Post-treatment

Table 1 Patient demographics

Patient demographics	Number (%)
Age	50±19 years
F:M	12:3
Tumor histology	
Papillary carcinoma	11 (73 %)
Follicular carcinoma	4 (27 %)
Initial T staging	
3	10 (67 %)
4	5 (33 %)
Initial N staging	
0	3 (20 %)
1a	2 (13 %)
1b	10 (67 %)
Sites of metastasis	
Lung metastasis	15 (100 %)
Bone metastasis	1 (7 %)
Avidity of FDG on lung metastasis	
+	5 (33 %)
-	7 (47 %)
Not assessed	3 (20 %)

Table 2 Treatment demographics

Treatment demographics	Number (%)
Treatment dose	
5.6 GBq	2 (7 %)
6.7 GBq	3 (10 %)
7.4 GBq	25 (83 %)
Scanning time, days after administration of radioiodine	
4	4 (13 %)
5	23 (87 %)
6	3 (10 %)
TSH (mU/l)	
>80	30 (100 %)
Tg (ng/ml)	
Mean±SD	980±2259
Range	0.5–11,244
Anti-Tg antibody (IU/ml)	
Mean±SD	147±121
Range	12–508
Radioiodine scan index	
Mean±SD	3.02±2.76
Range	0.40– 10.97

WBS was performed 5 days after radioiodine administration in a majority of rounds (23/30) and after 4 days in 4 rounds and 6 days in 3 rounds. The TSH_s_Tg level was mean 980 ng/ml (range, 0.5–11,244). Mean Tg reduction rate was −7 % (range, −90 %–210 %). The serum ATA level was mean 147 IU/ml (range, 12–508). The ATA-corrected Tg level was mean 1,336 ng/ml (range, 2–16,143). All patients had lung metastasis, and one patient had an additional pelvic bone metastasis (Table 3). An FDG-avid lesion was detected in five patients, whereas seven had non-FDG-avid metastasis. An F-18 FDG PET/CT scan was not performed in three patients. Mean TSH_s_Tg level and RSI between patients with FDG uptake and without FDG uptake were not statistically different [TSH_s_Tg level: 668±663 ng/ml in FDG-avid patients and 1877±4165 ng/ml in FDG-non-avid patients (p=0.291), RSI: 2.47±2.9 in FDG-avid patients and 0.92±3.24 in FDG-non-avid patients (p=0.213)].

Radioiodine scan index

Mean RSI was 3.02 (range, 0.40–10.97). RSI was positively correlated with the TSH_s_Tg level (R^2=0.3084, p=0.001) and negatively correlated with the Tg reduction rate (R^2= 0.2993, p=0.037) (Fig. 2). In a selected cohort with high TSH_s_Tg levels (Tg>100 ng/ml), the RSI was more strongly correlated with the TSH_s_Tg level (R^2=0.7365, p<0.001, n=15) and showed a weak negative correlation with the Tg reduction rate without statistical significance (R^2=0.1594, p= 0.327, n=8) (Fig. 3). When the TSH_s_Tg level was corrected

by the serum ATA level, the RSI was also positively correlated with the ATA-corrected Tg level (R^2=0.3116, p=0.001). Although it did not reach statistical significance, the RSI was also negatively correlated with the ATA-corrected Tg reduction rate (R^2=0.2386, p=0.065) (Fig. 4). The regression equation to predict treatment response was the following: Tg reduction rate=− 14.581×RSI+51.183. According to the equation, the patients showing 3.5 or more RSI were suggested to have achieved Tg reduction by the radioiodine treatment.

Discussion

The extent of the metastatic tumor burden can be estimated with the serum Tg level and radioiodine WBS. Although Tg synthesis and radioiodine uptake reflect different thyroid tissue functions [12, 13], the radioiodine scan index, the ratio of background-subtracted tumor uptake to background uptake, derived from single post-treatment WBS was feasible as a simplified, quantitative parameter to estimate the metastatic tumor burden. It was well correlated with the TSH_s_Tg level and Tg reduction rate. The avidity of radioiodine is a well-known favorable prognostic factor in patients with DTC [8, 14–16]. The dose of radioiodine delivered to metastatic tissue can be calculated by a dosimetry-based regimen, but the methodology is quiet cumbersome in routine clinical practice [10, 17, 18]. Our results showed a simplified index also predicts the response, the decline of the serum Tg level, to radioiodine treatment during multiple cycles of radioiodine treatment.

Tg, which is produced only by cancerous or noncancerous thyroid follicular cells, is an excellent tumor marker for patients with DTC [19]. The sensitivity of Tg, however, depends on the serum TSH level and is much greater under TSH elevation>30 mU/l (98 %) than under TSH-suppressive thyroid hormone therapy (80 %)[19]. Because the serum Tg level is highly variable according to the serum TSH level, we enrolled only patients with a fully enhanced serum TSH level (>80 mU/l) corresponding to the upper limit of measurement in our institution.

Cervical uptake reflecting the radioiodine concentration in remnant thyroid tissue is conventionally measured using a gamma probe [20–22]. However, measurement of the whole metastatic tumor burden using a gamma probe is not easy. Instead of this, ROI-based measurement can be applied using a reference region in the brain area [23]. Brain is feasible as a background, because it only has blood pool activity, as sodium iodide cannot pass through the blood-brain barrier [24, 25]. Lim et al. [23] simply used the count ratio between the same-sized rectangular ROIs in the anterior neck and brain as the thyroid-to-background ratio in a single anterior image. We used mean counts of anterior and posterior images because metastatic organs, such as the lung, have more three-dimensional structures than the neck area. Additionally,

Table 3 Summary for patients and treatment cycles

Patient no.	Sex	Age	Histology	Initial stage			Treatment		Site of metastasis	FDG avidity	Interval between RIT and WBS (days)	TSH (mU/l)	ATA (IU/ml)	Tg (ng/ml)	Tg reduction rate (%)	ATA-corrected Tg (ng/ml)	RSI
				T	N	M	Cycle	Dose (GBq)									
1	F	17	Papillary	3	1b	0	1	6.7	Lung	-	5	>80	85	898	11	1112	3.17
							2	7.4	Lung	-	5	>80	173	998	28	1333	5.80
							3	7.4	Lung	-	5	>80	107	1273	19	1616	3.22
							4	7.4	Lung	-	4	>80	107	1515		1925	0.92
2	F	37	Papillary	3	1b	1	1	7.4	Lung	-	6	>80	118	102	-8	132	3.84
							2	7.4	Lung	-	5	>80	68	94	-38	115	3.24
							3	7.4	Lung	-	5	>80	98	58		75	3.26
3	F	74	Follicular	4	1a	1	2	7.4	Lung	+	6	>80	139	1355	33	1770	2.28
							3	7.4	Lung	+	5	>80	278	1796	-14	2514	2.33
							4	7.4	Lung	+	5	>80	133	1547		2011	2.47
4	F	28	Papillary	3	1b	0	1	6.7	Lung	na	5	>80	496	37	210	56	1.91
							2	7.4	Lung	na	5	>80	508	113	-14	170	1.60
							3	7.4	Lung	na	5	>80	284	98		139	0.83
5	M	53	Papillary	4a	1b	0	2	7.4	Lung	-	5	>80	61	67	-57	81	5.69
							3	7.4	Lung	-	5	>80	94	29		38	1.83
6	F	46	Papillary	4	0	0	2	7.4	Lung	na	5	>80	52	17	-5	22	1.34
							3	7.4	Lung	na	4	>80	12	17		18	0.60
7	F	65	Follicular	3	0	0	2	7.4	Lung	+	5	>80	196	5963	-80	8059	6.36
							3	7.4	Lung	+	5	>80	96	1206		1514	2.90
8	M	43	Follicular	4	1b	1	1	7.4	Lung	-	5	>80	100	74	-80	95	6.80
							2	7.4	Lung	-	5	>80	90	15		20	0.66
9	F	41	Papillary	3	1b	1	1	5.6	Lung	+	4	>80	93	91	-22	116	1.44
							2	6.7	Lung	+	5	>80	92	71		90	0.58
10	M	73	Papillary	4	1b	1	1	5.6	Lung	na	5	>80	44	5	-90	8	10.97
							2	7.4	Lung	na	6	>80	126	0.5		2	0.40
11	F	70	Papillary	3	1a	1	1	7.4	Lung	+	4	>80	82	299		370	3.16
12	F	67	Papillary	3	1b	0	2	7.4	Lung, pubic bone	+	5	>80	130	216		281	0.60
13	F	49	Papillary	3	1b	0	1	7.4	Lung	-	5	>80	119	53		70	1.00
14	F	65	Follicular	3	0	1	3	7.4	Lung	-	5	>80	69	153		187	0.98
15	F	23	Papillary	2	1b	1	2	7.4	Lung	-	5	>80	364	11,244		16,144	10.57

No. number, RIT radioiodine treatment, WBS whole-body scan, TSH thyroid-stimulating hormone, ATA antithyroglobulin antibody, Tg thyroglobulin, RSI radioiodine scan index, na not assessed

Fig. 2 Relationship between the radioiodine scan index and TSH-stimulated Tg level (**a**) and the radiodiodine scan index and Tg reduction level (**b**) in all cohorts
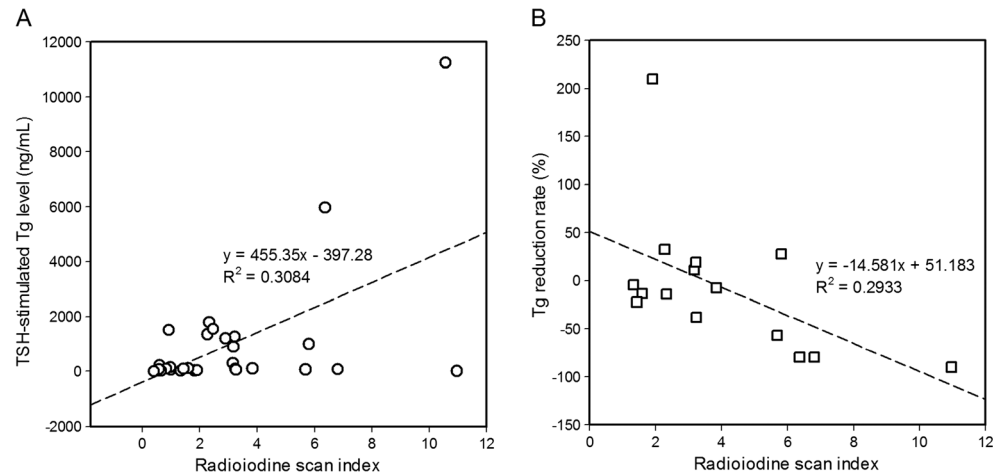
background activity is subtracted from initial tumor activity before calculating the ratio of tumor uptake and background activity, because initial tumor uptake includes background blood pool activity. The radioiodine scan index was calculated as the ratio of 'true' tumor uptake to background uptake. The last step could partly correct the influence of the treatment dose and scanning time.

We acknowledge there are many limitations to this study. First, this is a retrospective analysis with a small sample size; therefore, any conclusions may be limited in their implications. Second, although the serum TSH level was well controlled, variation still remains in the serum Tg level influenced by the TSH level beyond the measurement limit (>80 mU/l). Third, circulating the ATA may cause false-negative or -positive results in the serum Tg level [11, 13, 26]. Although we observed similar results with the ATA-corrected serum Tg level compared to the measured serum Tg level, the mathematical correction cannot replace the true serum Tg level. Fourth, in WBS, the scanning time and treatment dose, which can cause variation in the radioiodine uptake, were not fully

controlled. However, we tried to minimize the variation using background brain activity when determining the RSI, and the change of radioiodine activity in 4–6 days is less remarkable than that in 0–4 days [27, 28]. The last limitation is that neither the serum Tg level nor radioiodine WBS can accurately predict the 'true' metastatic tumor burden. Although the radioiodine WBS is the most specific imaging method to diagnose recurrence or distant metastasis of DTC, less or dedifferentiated thyroid carcinoma may lose the ability to concentrate radioiodine. The serum Tg level also depends on the capacity of the tumor to respond to TSH stimulation and the ability of the tumor to synthesize and release immunologically active Tg [29]. Hook effects arise when an excessive amount of Tg in the specimen overwhelms the antibody test reagent, also causing false-negative Tg results [13]. The dedifferentiated cancer cells that can still concentrate iodine can lose the ability to synthesize or release Tg [13]. This limitation is inherent to most other studies attempting to evaluate the radioiodine uptake and serum Tg level as an indicator reflecting tumor burden in patients with metastatic DTC.

Fig. 3 Relationship between the radioiodine scan index and TSH-stimulated Tg level (**a**) and the radiodiodine scan index and Tg reduction level (**b**) in a selected cohort with a high TSH-stimulated Tg level (Tg>100 ng/ml)
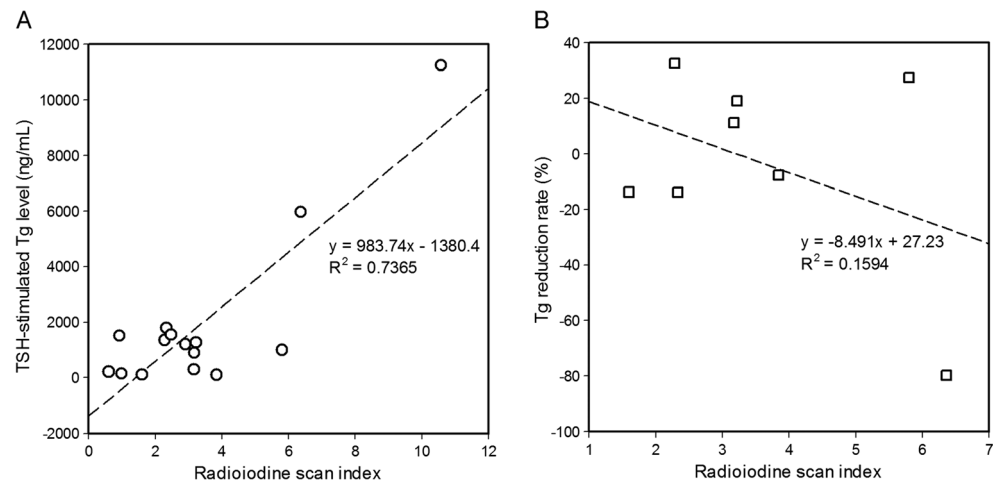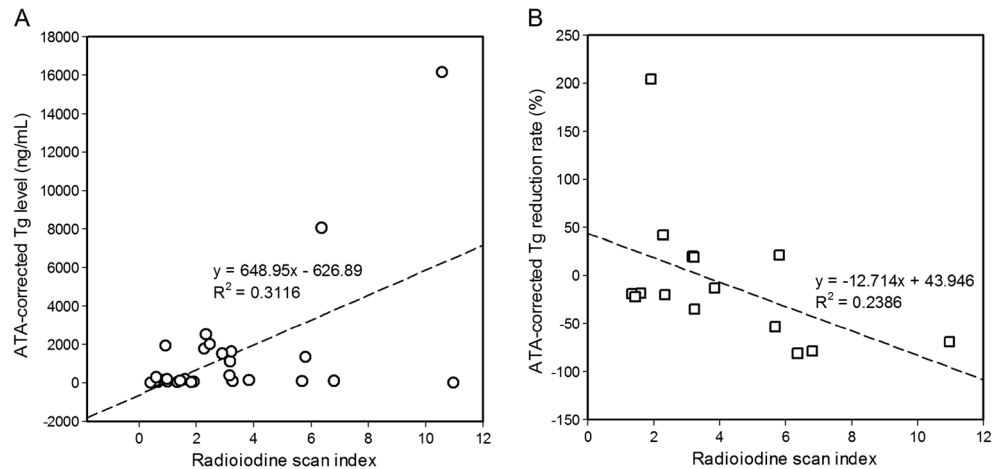
Fig. 4 Relationship between the radioiodine scan index and ATA-corrected TSH-stimulated Tg level (**a**) and the radiodiodine scan index and ATA-corrected Tg reduction level (**b**) in all cohorts

A

y = 648.95x - 626.89
$R^2 = 0.3116$

B

y = -12.714x + 43.946
$R^2 = 0.2386$

Conclusions

Use of the radioiodine scan index derived from conventional WBS is feasible to reflect the serum Tg level in patients with metastatic DTC, and it may be useful to predict the biologic treatment response after radioiodine treatment. More controlled study in a uniform clinical setting, such as a protocol using recombinant human TSH, is needed to validate the usefulness of the simplified quantitative index in radioiodine WBS.

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