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Unexpected radioactive iodine accumulation on whole-body scan after I-131 ablation therapy for differentiated thyroid cancer

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ABSTRACT

We retrospectively evaluated the frequency of unexpected accumulation of radioactive iodine on the post-therapy whole-body scan (Rx-WBS) after radioactive iodine (RAI) ablation therapy in patients with differentiated thyroid cancer (DTC). We searched our institutional database for Rx-WBSs of DTC patients who underwent RAI ablation or adjuvant therapy between 2012 and 2019. Patients with distant metastasis diagnosed by CT or PET/CT before therapy, and those had previously received RAI therapy were excluded. In total, 293 patients (201 female and 92 male, median age 54 years) were selected. Two nuclear medicine physicians interpreted the Rx-WBS images by determining the visual intensity of radioiodine uptake by the thyroid bed, cervical and mediastinal lymph nodes, lungs, and bone. Clinical features of the patients with and without the metastatic accumulation were compared by chi-square test and median test. Logistic regression analyses were performed to compare the association between the presence of metastatic accumulation and these clinical factors. Eighty-four of 293 patients (28.7%) showed metastatic accumulation. Patients with metastatic RAI accumulation showed a significantly higher frequency of pathological N1 (pN1) and serum thyroglobulin (Tg) > 1.5 ng/ml under TSH stimulation ($p = 0.035$ and $p = 0.031$, respectively). Logistic regression analysis indicated that a serum Tg > 1.5 ng/ml was significantly correlated with the presence of metastatic accumulation (odds ratio = 1.985; $p = 0.033$). In conclusion, Patients with Tg > 1.5 ng/ml were more likely to show metastatic accumulation. In addition, the presence of lymph node metastasis at the initial thyroid surgery was also associated with this unexpected metastatic accumulation.

Keywords: ablation, differentiated thyroid cancer, lymph node metastasis, radioactive iodine, SPECT/CT

Abbreviations:
DTC: Differentiated thyroid carcinoma
RAI: Radioactive iodine
Rx-WBS: Post-therapy whole-body scintigraphy
rhTSH: Recombinant human thyroid stimulating hormone
SPECT/CT: Single photon emission CT and CT
Tg: Thyroglobulin
Tg-Ab: Anti-thyroglobulin antibody
TSH: Thyroid stimulating hormone

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INTRODUCTION

In Japan, the prevalence rate of differentiated thyroid cancer (DTC) has gradually increased with the development of diagnostic imaging modalities such as ultrasound.[1,2] Not only for high-risk and intermediate-risk patients, but also for low-risk patients, total thyroidectomy along with radioactive iodine (RAI) ablation therapy is recommended.[3-11] In Japan, outpatient RAI ablation using a low radiation dose of 1,110 MBq has been approved since November 2010, while hospitalization is required for high-dose adjuvant RAI treatment.[12] One of the characteristics of RAI ablation is that it is theranostic, which means that it is a combination of specific targeted therapy and specific targeted diagnostic tests.[13] After ablation therapy, post-therapy whole-body scintigraphy (Rx-WBS) is usually performed to confirm the site of RAI accumulation. Moreover, single-photon emission computed tomography and computed tomography (SPECT/CT) can more accurately identify the RAI localization than can a conventional planar scan.[14-18]

On the Rx-WBSs, after ablation, unexpected RAI accumulation, including physiologic and pathologic accumulation, are occasionally observed at sites other than the thyroid bed. The pathologic accumulation mainly indicates cervical and mediastinal lymph node metastases, as well as distant metastases.[18] Essentially, for patients with such metastases, adjuvant treatment with high-dose RAI may be recommended. However, there have been limited reports about this unexpected pathological RAI accumulation on Rx-WBSs after ablation therapy in Japan.

In the present study, therefore, we retrospectively evaluated the frequency of unexpected RAI accumulation on Rx-WBSs after ablation and adjuvant therapy performed at our institution. In addition, we investigated whether clinical findings and postoperative pathological invasiveness could predict the presence or absence of abnormal RAI accumulation in order to ascertain which patients may benefit from high-dose RAI.

MATERIALS AND METHODS

This retrospective study was approved by our institutional review board, and the need to obtain written informed patient consent was waived (approval no. 2018-0443).

Patient selection

Using the retrieval function of a picture archiving and communication system, we searched our institutional database for Rx-WBSs of DTC patients performed RAI ablation therapy between May 2012 and March 2019. All patients had undergone total thyroidectomy. Patients with distant metastasis diagnosed by CT or positron-emission tomography (PET)/CT before therapy were not included. During this period, a total of 351 ablation therapies were performed in our institution. Because 58 patients had previously received RAI therapy were excluded, 293 treatments of 293 patients (201 females and 92 males, median age 54 years, age range 19–79 years) were finally selected. The pathological T stage and N stage based on TNM staging according to the 7th version of the Union for International Cancer Control are shown in Table 1 and the other clinical information are shown in Table 2.

RAI ablation therapy

Before treatment, patients selected either administration of recombinant human thyroid stimu-

Table 1 T stage and N stage at the initial thyroid surgery based on TNM staging according to the 7th version of the Union for International Cancer Control

		N stage					
		0	1a	1a or 1b	1b	unknown	Total
T stage	1	4	6	1	24	1	36
	2	1	7	2	10	1	21
	3	11	37	5	127	3	183
	4	0	10	3	25	0	38
	unknown	0	0	1	0	14	15
	Total	16	60	12	186	19	293

Table 2 Patient and tumor characteristics

	Number	Median	Range
Age, ≤ 45 years / > 45 years	92 / 201		
Male / Female	94 / 199		
Histopathology **Papillary / Follicular variant / Diffuse sclerosing variant / Follicular / Poorly differentiated**	262 / 11 / 2 / 3 / 15		
Administration dose of RAI **1,110 MBq / 1,850 MBq / 3,700 MBq**	249 / 20 / 24		
Period from total thyroidectomy to ablation **≤ 180 days / > 180 days**	171 / 122		
Withdrawal of thyroid hormone / rhTSH	46 / 247		
TSH (μU/ml)		127.6	8.1–626.3
TSH, ≤ 30 μU/ml / > 30 μU/ml	5 / 288		
Tg (ng/ml)		5.4	< 0.1–21529
Tg, ≤ 1.5 ng/ml / > 1.5 ng/ml	78 / 215		
Tg-Ab (IU/mL)		13.25	< 10–1796
Tg-Ab, ≤ 100 IU/mL / > 100 IU/mL / unknown	266 / 26 / 1		

RAI: Radioactive iodine, rhTSH: Recombinant human thyroid stimulating hormone, Tg: Thyroglobulin, Tg-Ab: Anti-thyroglobulin antibody, TSH: Thyroid stimulating hormone.

lating hormone (rhTSH) or 4-week stepwise withdrawal of thyroid hormone to stimulate TSH production.[19] Consequently, 88 treatments were performed under withdrawal of thyroid hormone and 205 treatments were performed using rhTSH (Table 2). To increase accumulation of I-131 in the thyroid remnant, patients were placed on a low-iodine diet for 2 weeks. On the day of RAI therapy, serum TSH, free-T3, free-T4, thyroglobulin (Tg), and anti-thyroglobulin antibody (Tg-Ab) were measured.[20]

Doses of 1,110, 1,850, and 3,700 MBq RAI were orally administrated to patients. The dose

was decided according to the outpatient or inpatient treatment, and the views of the thyroid surgeon. In outpatient treatment, all patients received a fixed dose of 1,110 MBq and the scintigraphy was performed 4 days after RAI administration. In inpatient treatment, patients were administered doses of 1,850 MBq or 3,700 MBq, and scintigraphy was performed 4 days and/or 7 days after RAI administration.

I-131 scintigraphy

I-131 scintigraphy was performed using a gamma camera (Symbia-T6, Siemens Healthcare, Erlangen, Germany) equipped with a high-energy collimator, a symmetrical 15% window set at 364 keV, 10 cm/min scan speed, and a 256 × 1024 matrix. Rx-WBS and SPECT/CT images from neck to chest level were obtained routinely.

Two nuclear medicine physicians, who had both specialized in RAI therapy for more than 10 years, interpreted the Rx-WBS images by determining the visual intensity of radioiodine uptake by the thyroid bed, cervical and mediastinal lymph nodes, lungs, bone, and other organs. For all accumulations detected on Rx-WBS, the sites were accurately confirmed on the SPECT/CT images and the final decision was made by the two physicians in consensus. Additionally, uptakes of the lungs and bone were assigned to metastatic or inflammatory accumulation based on CT images by these physicians. Patients with metastatic lymph node, lung, and bone accumulation were regarded as positive and patients without such metastatic accumulation were regarded as negative.

Statistical analysis

First, the characteristics of the positive and negative patients were compared by chi-square test and median test. Next, univariate logistic regression analyses were performed to compare the association between the presence of metastatic accumulation and clinical factors. Factors yielding a p value < 0.1 by univariate analysis were entered into multivariate logistic regression analyses. Analyses were performed in SPSS (version 23; IBM, Armonk, NY), Microsoft Excel 2013 (Redmond, WA), with add-in statistical software (BellCurve, version 3.20; Social Survey Research Information, Tokyo, Japan). A P value < 0.05 was considered to indicate statistical significance.

RESULTS

Physiological RAI accumulation to the remnant thyroid tissue in the thyroid bed was observed in 282 of 293 patients (96.2%, Fig. 1). Cervical lymph node RAI accumulation was recognized in 61 patients, superior mediastinal lymph node RAI accumulation was recognized in 4 patients, both cervical and superior mediastinal lymph node accumulation was recognized in 17 patients, and, in 82 patients (28.0%), pathological RAI accumulation was recognized in lymph nodes (Fig. 2). In three of nine patients with lung RAI accumulation, lung accumulation was regarded to reflect inflammatory accumulation, and the remaining six patients (2.0%) had metastatic lung accumulation. Four of these six patients also had metastatic lymph node accumulation (Fig. 3). One patient (0.3%) with metastatic lung accumulation also had metastatic rib accumulation. In total, 84 of 293 patients (28.7%) showed metastatic accumulation.

Patients with metastatic RAI accumulation showed a significantly higher frequency of pathological N1 (pN1) and serum Tg > 1.5 ng/ml under TSH stimulation ($p = 0.035$ and $p = 0.031$, respectively; Table 3). Fifteen of 78 patients (19%) with Tg ≤ 1.5 ng/ml had metastatic accumulation, while 69 of 215 patients (32%) with Tg > 1.5 ng/ml had metastatic accumulation.

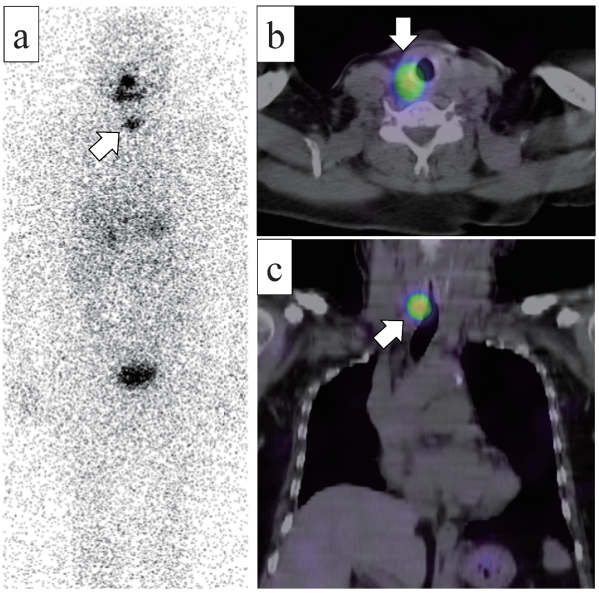

Fig. 1 Whole body scan (WBS) and SPECT/CT after ablation therapy
A 69-year-old female with papillary carcinoma (pT3N0). WBS after ablation therapy using 1,110 MBq radioactive iodine shows a focus only in the thyroid bed (white arrow). Non-specific accumulation were also seen in nasal and oral cavity, stomach, liver and bladder. The serum thyroglobulin value under TSH stimulation was 0.1 ng/ml. (a) WBS (b) axial SPECT/CT image (c) coronal SPECT/CT image.

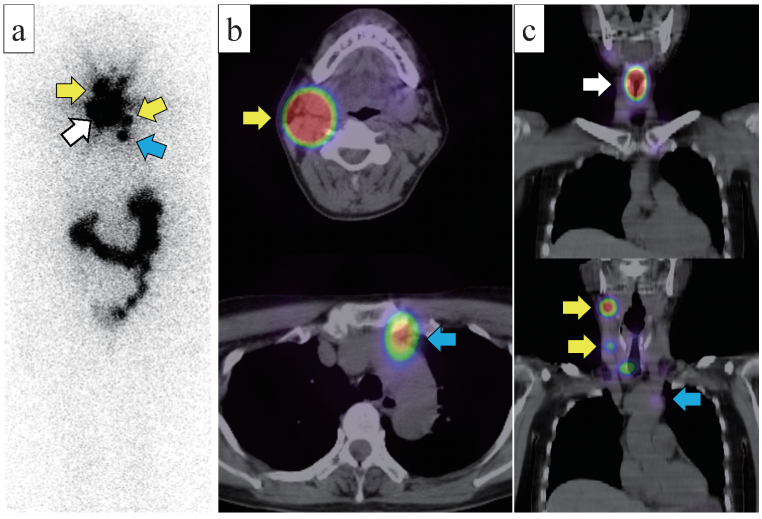

Fig. 2 Whole body scan (WBS) and SPECT/CT after ablation therapy
A 61-year-old female with papillary carcinoma (pT2N1a). WBS after ablation therapy using 1,110 MBq radioactive iodine shows accumulation in the thyroid bed (white arrow), bilateral neck (yellow arrow), and left superior mediastinum (blue arrow). Non-specific accumulation was also seen in colon. Serum thyroglobulin value under TSH stimulation was 3.9 ng/ml.
Fig. 2a: WBS.
Fig. 2b: axial SPECT/CT image.
Fig. 2c: coronal SPECT/CT image.

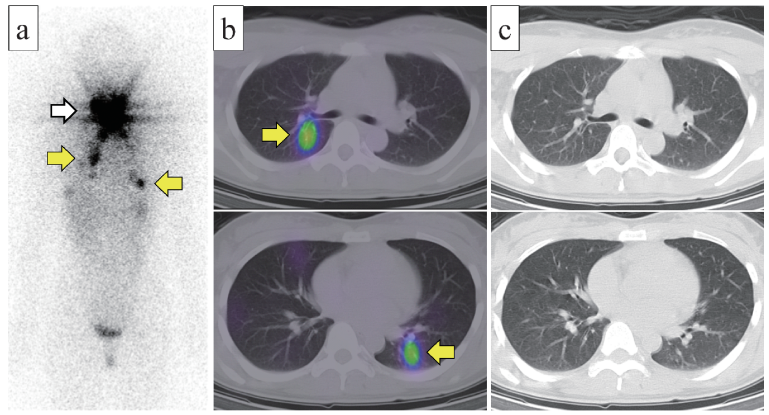

Fig. 3 Whole body scan (WBS) and SPECT/CT after ablation therapy
A 26-year-old female with papillary carcinoma (pT3N1b). WBS after ablation therapy using 1,110 MBq radioactive iodine shows accumulation in the thyroid bed and bilateral neck (white arrow), and bilateral lung (yellow arrow). SPECT/CT also shows bilateral lung accumulation, while no metastatic lesions are seen on the CT image. Non-specific accumulation were also seen in liver, colon and bladder. The serum thyroglobulin value under TSH stimulation was 45.2 ng/ml. (a) WBS (b) axial SPECT/CT image (c) CT image.

Table 3 Comparison between characteristics of patients positive and negative for metastatic accumulation on Rx-WBS

	Metastatic Accumulation		
	Positive	**Negative**	*P value*
Number	84	209	
Age, Median (range) [years]	52.5 (19–79)	55 (20–79)	0.147
Age, ≤ 45 years / > 45 years	28 / 56	64 / 145	0.651
Female / Male	52 / 32	147 / 62	0.162
Papillary / Others	76 / 8	186 / 23	0.709
pT1 / pT2 / pT3 / pT4	13 / 6 / 50 / 14	23 / 15 / 133 / 24	0.545
pN0 / pN1	1 / 80	15 / 178	0.035
Administration dose of RAI 1,110 MBq / 1,850 MBq / 3,700 MBq	69 / 8 / 7	180 / 12 / 17	0.504
Period from total thyroidectomy to ablation ≤ 180 days / > 180 days	51 / 33	120 / 89	0.605
Withdrawal thyroid hormone / rhTSH	15 / 69	31 / 178	0.520
TSH (μU/ml), Median (range)	127.5 (21.9–403.4)	128.0 (8.1–626.3)	0.925
TSH, ≤ 30 μU/ml / > 30 μU/ml	2 / 82	3 / 206	0.572
Tg (ng/ml), Median (range)	5.48 (< 0.1–1612)	5.26 (< 0.1–21529)	0.722
Tg, ≤ 1.5 ng/ml / > 1.5 ng/ml	15 / 69	63 / 146	0.031
Tg-Ab (IU/mL), Median (range)	13.7 (< 10–307.1)	13.2 (< 10–1796)	0.561
Tg-Ab ≤ 100 IU/mL / > 100 IU/mL	79 / 5	180 / 21	0.230

RAI = Radioactive iodine, rhTSH = Recombinant human thyroid stimulating hormone, Tg = Thyroglobulin, Tg-Ab = Anti-thyroglobulin antibody, TSH = Thyroid stimulating hormone

The sensitivity and specificity were 0.82 and 0.30, respectively. Similarly, one of 16 patients (6%) without lymph node metastases after thyroid gland surgery had metastatic accumulation, while 80 of 258 patients (31%) with lymph node metastases also had metastatic accumulation. On the other hand, there were no significant differences between accumulation-positive patients and accumulation-negative patients in terms of age, sex, histopathology, pathological T stage, doses of RAI, period from total thyroidectomy to ablation, TSH stimulating method, TSH level, and Tg-Ab.

Univariate logistic regression analysis indicated that serum Tg > 1.5 ng/ml was significantly correlated with the presence of metastatic accumulation (odds ratio [OR] = 1.985; p = 0.033; Table 4) and that pN1 showed a tendency for correlation with metastatic accumulation (OR = 6.742, p = 0.067; Table 4). Multivariate logistic regression analysis using these two factors indicated that only Tg > 1.5 ng/ml was significantly correlated with the presence of metastatic accumulation (OR = 1.929; p = 0.046; Table 4).

Table 4 Results of univariate and multivariate logistic regression analysis to compare the association between the presence of metastatic accumulation and clinical factors

	Univariate analysis		**Multivariate analysis**	
Factors	OR 95% CI	*P value*	OR 95% CI	*P value*
Age > 45 years **(vs. ≤ 45 years)**	0.883 0.514–1.516	0.651		
Male **(vs. Female)**	1.459 0.858–2.481	0.163		
rhTSH **(vs. Withdrawal of thyroid hormone)**	0.801 0.407–1.575	0.520		
Dose of RAI > 1,110 MBq **(vs. 1,110 MBq)**	1.349 0.682–2.670	0.390		
Period from total thyroidectomy to ablation > 180 days **(vs. ≤ 180 days)**	0.872 0.520–1.463	0.605		
pT3-4 **(vs. pT1-2)**	0.815 0.437–1.520	0.520		
pN1 **(vs. N0)**	6.742 0.875–51.917	0.067	6.264 0.808–48.564	0.079
TSH > 30 μU/mL **(vs. ≤ 30 μU/mL)**	0.597 0.098–3.639	0.576		
Tg > 1.5 ng/ml **(vs. ≤ 1.5 ng/ml)**	1.985 1.055–3.733	0.033	1.929 1.013–3.672	0.046
Tg-Ab > 100 IU/mL **(vs. ≤ 100 IU/ml)**	0.564 0.205–1.548	0.266		

OR: odds ratio, 95%CI: 95% confidence interval, RAI: Radioactive iodine, rhTSH: Recombinant human thyroid stimulating hormone, Tg: Thyroglobulin, Tg-Ab: Anti-thyroglobulin antibody, TSH: Thyroid stimulating hormone.

DISCUSSION

Rx-WBS is routinely used to confirm the accumulation site after RAI therapy. Additional SPECT/CT can identify the exact site of the RAI accumulation, and helps to distinguish physiological accumulation in residual thyroid tissue and pathological accumulation in lymph nodes in the neck and superior mediastinum. We here evaluated the frequency of unexpected RAI accumulation on Rx-WBSs after ablation and adjuvant therapy in patients with DTC and identified characteristics that could predict the presence or absence of abnormal RAI accumulation in these patients.

In the present study, 28.7% of patients who received ablation therapy had pathological accumulation that was regarded as lymph node or distant metastases, but which was invisible on CT or PET/CT. In the report of Robenshtok et al, metastatic lymph nodes were identified on post-therapy SPECT/CT imaging in 16% and pulmonary metastases were identified in 1.4% of intermediate-risk DTC patients.[18] The reason for the higher incidence of metastatic lymph node accumulation in our study than in the study of Robenshtok et al may be that our cohort included more pN1-patients. In Japan, RAI ablation therapy is performed more often in high-risk patients. While low-dose RAI activities can ablate the normal thyroid tissue remnant located in the thyroid bed, effective treatment for regional lymph node metastases and distant metastases has traditionally required a higher dose of RAI[21] Wu et al reported that patients with small metastatic lymph nodes detectable on Rx-WBS at the initial ablation showed a good response to RAI therapy.[22] Therefore, these unexpected micro-metastases may disappear if adjuvant treatment with 3,700 MBq RAI is performed with the initial treatment.

In the RAI therapy for DTC, numerous clinical and pathological factors affect the degree of accumulation to the metastatic lesion. However, in this retrospective study, most factors were not associated with the unexpected RAI accumulation after ablation. Only serum Tg levels under TSH stimulation were significantly correlated with the metastatic accumulation: patients with Tg > 1.5 ng/ml had about twice the risk of metastatic lesions after total thyroidectomy as compared to patients with Tg ≤ 1.5 ng/ml. Tg is produced by thyroid follicular cells.[23] After total thyroidectomy, serum levels of Tg decrease usually. However, since papillary and follicular cancer derived from follicular cells also produce Tg, serum Tg level remains high if their metastases remain in the body. The Tg level under TSH stimulation is known to be a predictive indicator for prognosis in DTC. Brassard et al reported that a cutoff level of Tg = 1.4 ng/ml under TSH stimulation is considered to be the optimal threshold for predicting long-term recurrence.[24] Shangguan et al reported that the Tg under TSH stimulation was a significant factor affecting the outcome of RAI therapy and that a suitable cutoff value of Tg was 2.69 ng/ml.[25] Considering these previous studies and our own result, high-dose RAI therapy may be recommended for patients with serum Tg > 1.5 ng/ml under TSH stimulation. The TSH level after thyroidectomy are often normal or suppressed. Without TSH simulation, the Tg level has a lower value. However, patients with Tg > 1.5 ng/ml even under normal or suppressed TSH situation are more likely to show metastatic accumulation, because they would have even higher Tg level under TSH stimulation. Therefore, adjuvant therapy using 3,700 MBq RAI may be recommended for Tg > 1.5 ng/ml.

The presence of lymph node metastasis at the initial thyroid surgery also showed a trend for association with the unexpected metastatic accumulation after ablation therapy. Patient with lymph node metastasis at surgery have about six times the risk of metastatic lesions after total thyroidectomy as compared to patients without such lymph node metastasis. pN0-patients showed significantly lower rates of metastatic accumulation than did pN1-patients. Although the results of logistic regression analysis were not statistically significant, this may be because only 16 pN0-patients were included in our cohort. Shangguan et al reported that metastases affecting

only few lymph nodes is more likely to be cured by RAI ablation.[25] Therefore, RAI ablation therapy using a dose of 1,110 MBq may be sufficient for pN0-patients.

On the other hand, the pathological T stage was not significantly correlated with the unexpected metastatic accumulation. From these results, even for pT1- or pT2-patients, pN1-patients may benefit from high-dose adjuvant therapy after total thyroidectomy.

The age of DTC patients was correlated with not only prognosis but also with RAI accumulation. Nakanishi et al indicated that the prevalence of RAI uptake for the metastatic site was 41.5% for patients < 55 years, but this decreased significantly to 8.1% for those ≥ 55 years.[26] On the other hand, our results indicated that the prevalence of RAI uptake at metastatic sites was 32.6% in patients ≤ 45 years and 28.9% in patients > 45 years, without statistical significance. This discrepancy between studies in terms of age may be due to the difference in the RAI doses administered and the cohorts: 37–185 MBq of RAI were administered for the diagnostic scan of recurrent DTC in the study of Nakanishi et al, while 1,110–3,700 MBq were administered for the initial ablation in the present study.

The duration of the period from total thyroidectomy to RAI therapy is a known significant prognostic factor in patients with metastatic DTC lesions. Higashi et al reported that delaying initial RAI therapy until more than 180 days after total thyroidectomy may result in poor survival.[27] However, in our study, patients with distant metastases diagnosed by CT or PET/CT before therapy were excluded, and this period was not significantly correlated with metastatic accumulation.

In Japan, RAI therapy with a dose exceeding 1,110 MBq requires radioisotope hospitalization facilities, although the number of hospitalized beds is limited.[12] Much of the impatient therapy is therefore occupied by patients with obvious recurrence and metastasis. Therefore, it is necessary to select patients requiring RAI therapy as an adjuvant therapy using a dose of 3,700 MBq. From our results, patients with a serum Tg > 1.5 ng/ml or patients with lymph node metastasis at the initial surgery should be treated as inpatients with 3,700 MBq RAI. However, further predictors of unexpected metastatic accumulation should be explored.

This study has two limitations. First, it was a retrospective and a single-center study and the RAI dose was influenced not only by the physician's point of view, but also by whether the patient received outpatient or inpatient treatment. Second, recurrence and survival after ablation was not investigated. Long-term follow-up is necessary to determine the effect of the ablation therapy.

In conclusion, in this study, 28.7% of patients who received ablation therapy had unexpected accumulation on Rx-WBS, which was regarded as lymph node or distant metastases and which was invisible on CT or PET/CT. Although it was difficult to predict the unexpected metastatic accumulation precisely, patients with Tg > 1.5 ng/ml under TSH stimulation were more likely to show metastatic accumulation. In addition, the presence of lymph node metastasis at the initial thyroid surgery was also associated with this unexpected metastatic accumulation.

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