Dosimetric approach to ^{131}I ablation therapy for the differentiated thyroid cancer

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Abstract

Objective: The aim of this study is to compare the activity amounts used in the standard activity approach with the activity amounts calculated with the dosimetric method for the ablation of post-operative differentiated thyroid cancer residual tissue. **Subjects and Methods:** Seventeen patients (mean age=47.5±8.4 years) were included in the study. Time-activity curves were created by measuring iodine-131 (^{131}I) uptake values of residual tissue at 4th, 24th, 48th and 96th hours following oral administration of ^{131}I. In adosimetric approach, activity amounts exposing 300Gy to residual tissue were calculated using medical internal radiation dose (MIRD) formulation. **Results:** Dosimetric calculation could not be made in 3 patients because there was not enough radioactive iodine uptake (RAIU) at the neck to calculate the radioactive iodine treatment (RAIT) dose. The lowest and highest activity amounts determined by dosimetric calculations were 259MBq and 10860MBq, respectively. Dose amounts for the proposed treatment were decreased in 8 and increased in 6 patients compared to the standard activity approach. Cumulative activity (CA) and total cumulative activity (TCA) levels were found to be high in 1 patient who could not achieve adequate ablation. **Conclusion:** We recommend the dosimetric approach for ablation of residual postoperative thyroid tissue to find patients with high levels of CA and TCA levels to consider higher activity doses compared to risk stratification assessment.

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Introduction

Thyroid cancer is the most common type of cancer among endocrine cancers, and its incidence has been increasing in recent years [1]. Histopathologically, there are well-differentiated and poorly differentiated subtypes. Well-differentiated subtypes with papillary and follicular cytology are more common, and prognosis is better than poorly differentiated subtypes [2]. It is crucial to determine low, medium and high-risk patient groups based on histopathological data after total thyroidectomy to make an appropriate treatment plan in accordance with these risk levels [3]. While routine radioactive iodine-131 (^{131}I) treatment is not recommended following surgical treatment in patients who are determined as low risk according to risk classification, radioactive iodine treatment (RAIT) for ablation is considered in selected patients in order to make serum thyroglobulin (Tg) levels more valuable in clinical follow-up [4, 5]. There is no consensus regarding the amount of RAIT activity used for ablation purposes. For low risk patients, studies comparing ablation success of 1110MBq and 3700MBq activity amounts have shown that there is no difference in treatment success between them [6, 7] (for low-risk patients, especially for reference 6). The amount of activity varies considerably according to the routine practice of each nuclear medicine department administering the treatment.

Although the standard activity approach determined according to the histopathological characteristics of the patient is more preferred by nuclear medicine physicians in terms of providing ease of use, the concern of insufficient ablation or unnecessary high radiation exposure makes the use of dosimetric methods more important to provide patient-specific activity determination. The first of the dosimetric methods was defined by Benua et al. in 1962, and it is based on the principle of giving the patient the maximum safe dose in a way that the bone marrow is accepted as the critical organ and the dose to be taken by the bone marrow does not exceed the limit determined as 2Gy [8]. The second method, the lesion-based dosimetric method, was first described in 1983 by Maxon et al. In studies investigating the relationship between the radiation dose given to the target tissue and the clinical response in 76 patients whoreceived RAIT for post-ope-

rative thyroid cancer, it was reported that clinically successful results were obtained if 300Gy was given to the residual tissue and 80Gy to the metastatic focus [9].

In this study, activity amounts were calculated to provide 300Gy dose exposure required for ablation of the remaining thyroid tissue, which is the target organ, on a patient basis and compared with the activity amounts used in standard activity approach.

Subjects and Methods

Patient population

This prospective study was approved by the multi-disciplinary ethics committee of our hospital (E1-20-372- Date: 02 April-2020). A total of 17 patients (3M, 14F) who underwent bilateral total thyroidectomy with the diagnosis of well-differentiated (papillary or follicular subtype) thyroid cancer were enrolled in the study. They were all determined to be in a low-risk group according to American Thyroid Association (ATA) criteria in the postoperative risk classification [3]. Radioactive iodine treatment was planned to make Tg measurements reliable. The mean age was 47.5±8.4 years. Thyroid hormone replacement therapy was discontinued for 3 weeks in all patients and an iodine-poor diet was applied within this period.

Imaging procedure

Seven days after RAIT, posttreatment whole body gamma camera scans were obtained in all 17 patients. Eight months after RAIT, diagnostic scans were acquired in 11 patients.

Activity calculation for residual tissue ablation

Medical internal radiation dosimetry (MIRD) formulation (1) was used to determine the activity required to ablate the target tissue, the residual thyroid tissue [10]. According to this:

$$D_{target \leftarrow source} = \frac{k\tilde{A}_{source} \sum_i n_i E_i \phi_i}{m_{target}} \qquad (1)$$

Symbols in the formula are:

$D_{target \leftarrow source}$:Radiation dose absorbed in the target organ (Gy)
A_{source} Cumulative activity in a source organ (MBq.h)
n: The rate of radiation released at energy E per nuclear decay
E: Energy per radiation (MeV)
φ: Absorption rate of the radiation energy released from the source at the target
m_{target}: Mass of target organ (kg)
k: Rate constant (Gy.kg/MBq.h.MeV)

"S" tables developed by Stabin et al. were used in these operations in internal radiation calculations [11]. In these tables, the effect of the source organ on the target organ is indicated with the coefficients and equation (2) becomes:

$$D_{target \leftarrow source} = A_{source} \times S_{target \leftarrow source} \qquad (2)$$

Radioactive iodine uptake (RAIU) measurements of the residual tissue were performed at 4th, 24th, 48th and 96th hours following oral administration of an average of 7.09±2.14 MBq of activity to determine the amount of residual thyroid tissue. Radioactive iodine uptake measurements were made from neck, background and thigh region counts (Captus 3000 thyroid uptake system, Capintec). Radioactive iodine uptake values of the residual tissue were obtained by placing the counts taken in the RAIU formula (3). Then time-activity curves were created by plotting the uptake values corresponding to 4th, 24th, 48th and 96th hours. Radioactivity values on remnant tissue after 96th hours declined significantly, justifying stopping measurements at this time point.

$$uptake(\%) = \frac{Neckcounts\left(\frac{counts}{min}\right) - Thighcounts\left(\frac{counts}{min}\right)}{GlassCounts\left(\frac{counts}{min}\right) - RoomBackgroundCounts\left(\frac{counts}{min}\right)} \times 100 \qquad (3)$$

Planar acquisitions in 128x128 matrix with 600 seconds duration using high-energy general-purpose collimator were taken to image residual tissue volume in the anterior and lateral projections with double-headed gamma camera (General Electric-Discovery NM630 model) at the 24th hours of oral activity administration, because absorption was maximum at this time point. Since it is known that scatter correction is essential for quantitative imaging, a cylindrical source, whose volume and amount of activity are known was placed in the image area at the same distance as the remaining thyroid tissue from the collimator. It was used as a reference image to make a scatter correction.Full width at half maximum height (FWHM) values was determined from the cylindrical reference source and residual tissue images for the three dimensions as width, height and depth values.

Since the residual tissue is smaller than the normal thyroid tissue in the MIRD phantom, residual tissue volumes were obtained using the unit density sphere model formula (4) [11].

$$V = \frac{4}{3}\pi \frac{(w \times h \times d)}{8} \qquad (4)$$

π: pi number, *w*: width, *h*: height, *d*: depth

By applying the obtained values to the MIRD formula, the amount of activity required to expose 300Gy to residual tissue for each patient was calculated.

As a standard activity amount, 1850MBq was determined for all of the patients, although 2 patients received 1100MBq of activity.

Statistical analysis

The difference between values obtained as a result of calculations and standard activity amounts planned to be given to the patients was calculated as a percentage (%).

Percentage difference values were stated as positive when the calculated activities were higher than standard activities and as negative when they were lower.

Results

Patient population

While the histopathological subtype in 16 of 17 patients was papillary carcinoma, papillary and minimally invasive follicular carcinoma histopathology were found together in one patient. Demographic characteristics, histopathological information and laboratory values of the patients are given in Table 1.

Time-activity curves derived from RAIU values of residual thyroid tissue after oral administration of radioactivity were generated using measurements at 4th, 24th, 48th and 96th hours (shown in Figure 1 for patient #2). Cumulative activity (CA) of the remaining thyroid tissue by calculating the area under the curve until the last measurement and after the last measurement time, the "total cumulative activity" (TCA) values were determined, assuming that the decrease was only physical decay (Table 2).

Table 1. *Demographic characteristics, histopathological information and laboratory values of the patients.*

Patient No	Sex	Subtype	Age	TSH (mU/L)	Tg (µg/L)
1	E	P	63	59,5	1
2	F	P	47	38,5	33,4
3	F	P	46	125,9	0,4
4	F	P	50	64,8	19,9
5	F	P	55	56,4	<0,2
6	F	P	43	30,2	1,5
7	F	P	42	20,7	11,7
8	E	P	43	29,8	1,5
9	F	P+F	40	34,6	3,6
10	F	P	51	53,8	0,4
11	F	P	47	33	7,5
12	E	P	53	44,7	5,1
13	F	P	45	137	<0,2
14	F	P	52	>150	8,6
15	F	P	34	77,3	14,2
16	F	P	33	144,6	<0,2
17	F	P	65	105,5	<0,2

P: Papillary, F: Follicular

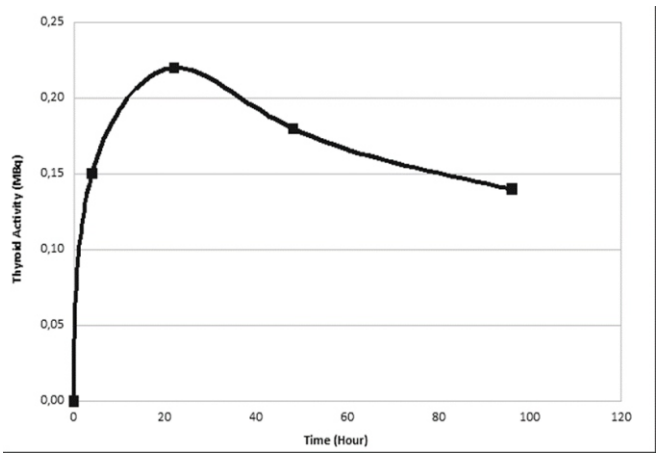

Figure 1. Time-activity curve of patient number 2.

Table 2. *The amount of activity used in the RAIU assay of the patients, the RAIU values at the 24th hour, the CA, total cumulative activity (TCA) amounts of the remaining thyroid tissue and residual thyroid tissue volumes (RTTV) calculated with the aid of gamma camera images.*

Patient #	Uptake activity (MBq)	Uptake at 24 hrs (%)	CA (MBq.hr)	TCA (Mbq.hr)	Calculated RTTV (cm^3)
1	5,6	4	16,8	43,8	3,7
2	5,7	13,4	68,1	189,7	3,3
3	5,5	2,6	14,3	41,3	5,6
4	5,6	20,9	82,9	214,1	10,2
5	5,6	5,5	24,4	67	2,8
6	11,1	7,3	71,8	160,1	3,3
7	9,2	14,2	113,3	259,8	8,1
8	9,3	2,3	19,4	41,2	19,6
9	9,6	3,3	27,1	55,1	4,4
10	5,5	4,6	23,1	77,1	5,1
11	5,5	11	61,3	194,3	13,6
12	11,1	10,3	99,5	198,1	3,5
13	9,2	1,1	8,3	14,6	2,1
14	5,5	3,8	19,4	58,8	11,2
15	5,6	0,6	-	-	-
16	5,6	0,5	-	-	-
17	5,5	1	-	-	-
Mean	7,1	6,3	46,4	115,1	6,9
S.D.	2,1	5,4	34	79,1	4,7

Volume calculation could not be made in 3 of the 17 patients as the residual tissue was not visualized in the gamma camera image (patient 15, 16 and 17). Radioactive iodine uptake at the 24th hour was 1%, 0.6%, and 0.5%, respectively, in accordance with the very small residual tissue in these patients. The profile curves drawn from the areas of the residual tissue and reference source in planar images were fitted to the Gaussian curves and FWHM values of the residual tissue and reference source were determined (Figure 2). Residual tissue sizes and volumes were obtained based on a reference source whose actual size and amount of activity were known. The mean of residual tissue volumes of 14 patients was calculated as 6.9±4.9 cm^3 (Table 2).

The activity amounts required for the residual tissue to be exposed to 300Gy radiation dose were calculated by substituting the residual tissue volumes and the cumulative activity amounts of the tissue in the MIRD formulation. As a result of the calculations, the lowest amount of activity required for ablation was 259MBq in patient 2; the highest amount of activity was 10859,5MBq in patient 8. In a total of 4 patients, the residual tissue volumes were calculated to be greater than 10cm^3, and the patients were evaluated for re-operation, but the RAIT plan was re-established as the second operation was not deemed appropriate. The standard activity amounts planned for the patients based on risk assessment strategy and the activities obtained as a result of dosimetric calculations are given in Table 3. In 8 out of 14 patients whose residual tissue could be calculated, the treatment doses decreased in 8 and increased in 6 patients (Figure 3).

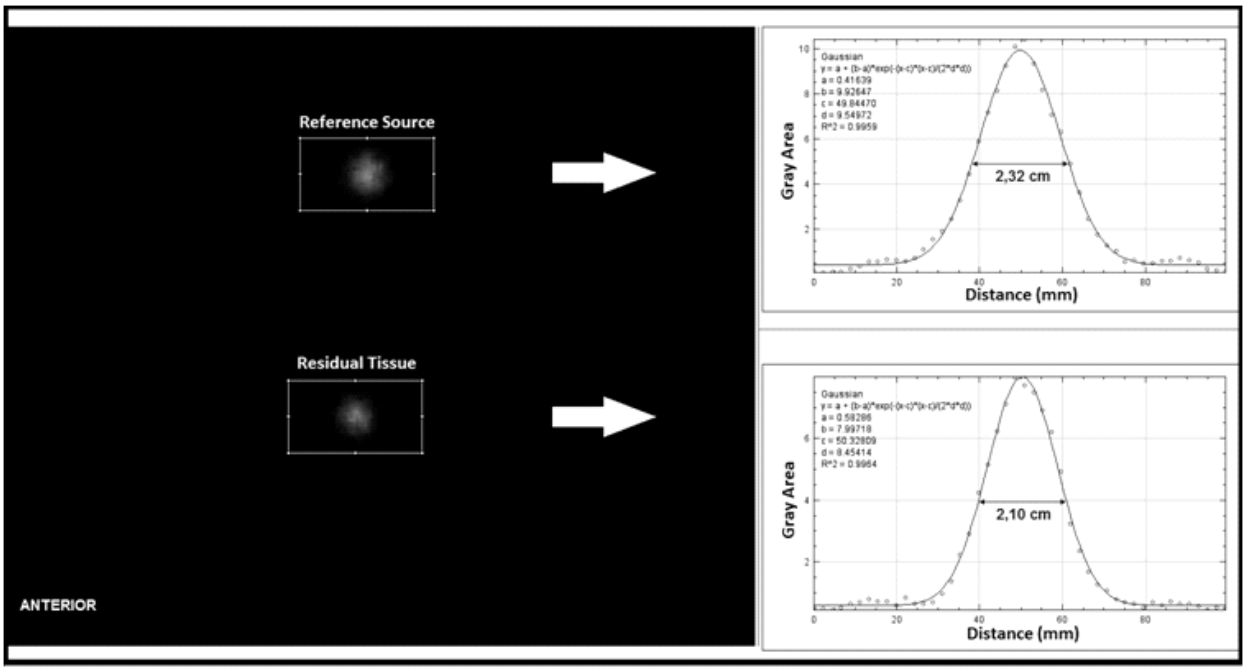

Figure 2. 24th hour planar gamma camera image of patient 2 and FWHM values of reference source and residual tissue.

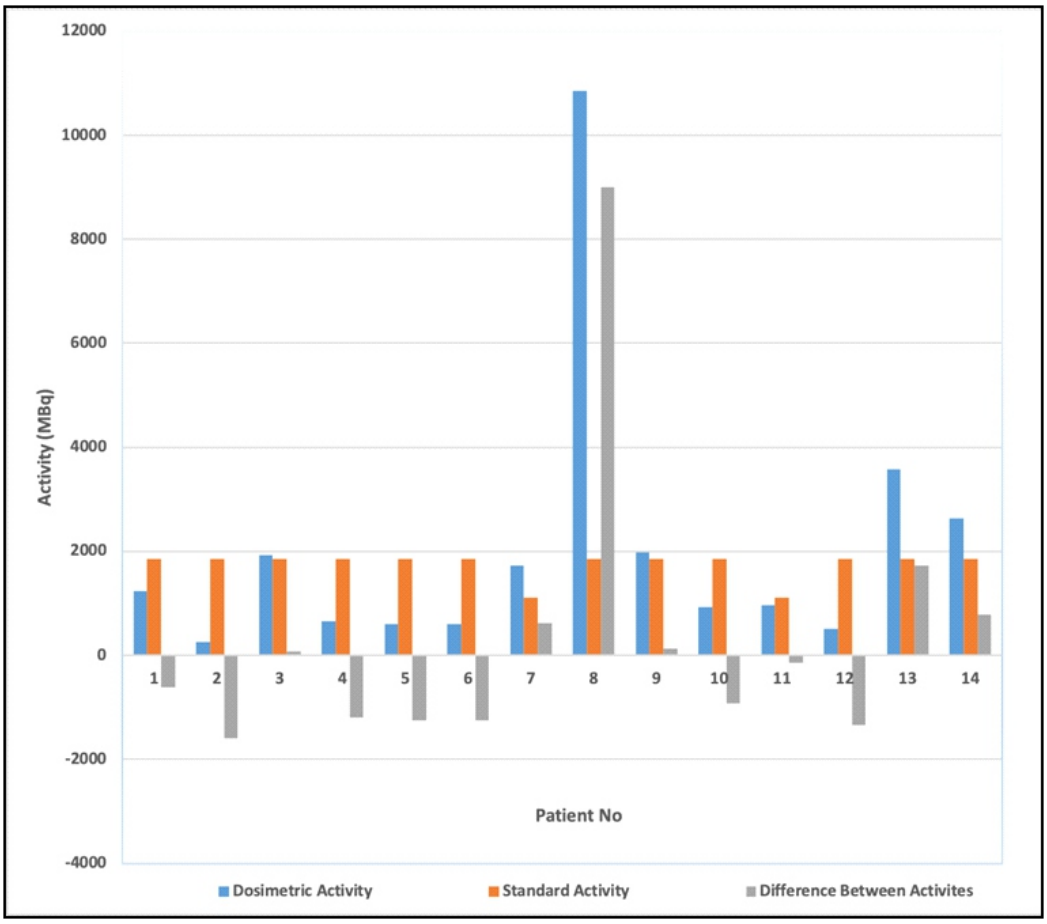

Figure 3. The dosimetric calculated activity amounts of the patients, the planned standard activity amounts and the difference between the activities. In the difference between activities, positive values represent an increase and negative values represent a decrease.

Eleven out of 17 patients have their 8th months ^{123}I scan to determine the result of ablation and remaining 4 patients have their TSH, Tg, anti-Tg results to confirm ablation status. Post-treatment 7th day images (A) along with 8 months images for 11 patients and post-treatment only scans for 6 patients is shown in Figure 4. Ablation could not be achieved in one patient (pt#7) that was demonstrated on the 8th month scan while serum Tg and anti-TG levels were within normal levels while on non-stimulated TSH. This patient had higher CA and TCA levels compared to other patients. Although 1110 MBq of RAIT was given to this patient according to risk stratification assessment in standard approach, dosimetric method suggested to use 1725MBq of activity in this patient to predict ablation.

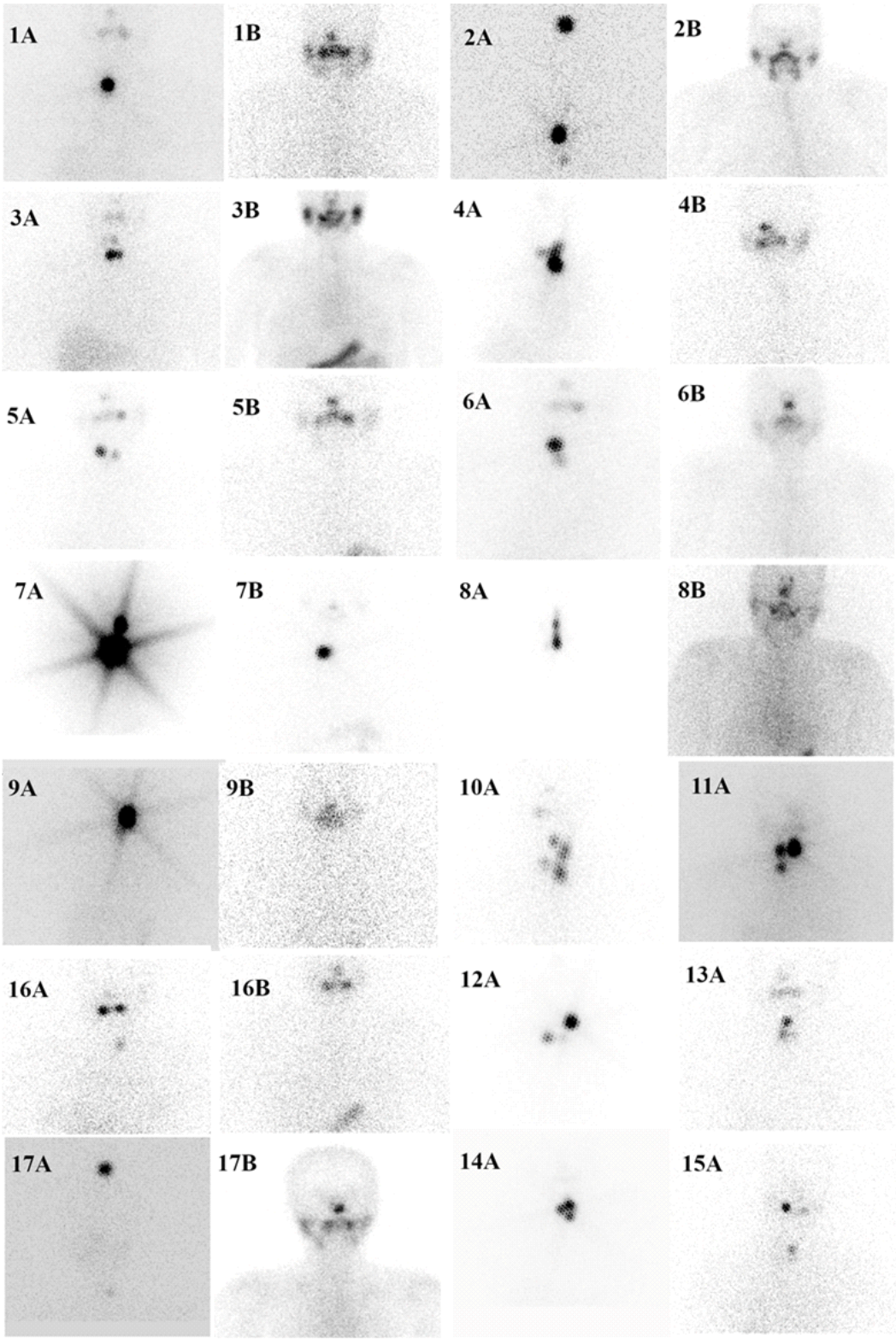

Figure 4. Post-treatment scans at 7th day of RAIT (A) and 8th months scan images (B) for 11 patients and post-treatment scan images for the remaining 6 patients.

Table 3. The relationship between the dosimetric calculated activity amounts of the patients and the standard activity amounts. Positive values represent an increase and negative values represent a decrease.

Patient #	Treatment Activity Calculated with Dosimetric Approach (MBq)	Scheduled activity with standard approach (MBq)	% Difference between the 2 approaches
1	1232,1	1850	-%33,30
2	259	1850	-%86,10
3	1927,7	1850	%4,30
4	662,3	1850	-%64,30
5	599,4	1850	-%67,60
6	603,1	1850	-%67,40
7	1725,2	1110	%55,40
8	10859,5	1850	%487,00
9	1979,5	1850	%7,00
10	925	1850	-%50,00
11	958,3	1110	-%13,70
12	514,3	1850	-%72,20
13	3581,6	1850	%93,60
14	2638,1	1850	%42,70

Table 4. *8th months control scan, dosimetry and ablation status of the patients. (1=Yes, 0=No)*

Pt#	8th month scan	Dosimetry	Ablation
1	1	1	1
2	1	1	1
3	1	1	1
4	1	1	1
5	1	1	1
6	1	1	1
7	1	1	0
8	1	1	1
9	1	1	1
10	0	1	1
11	0	1	1
12	0	1	1
13	0	1	1
14	0	1	1

Discussion

Although postoperative RAIT application has been used for a long time in the treatment of thyroid cancer, discussions on determining the appropriate amount of activity for the patient remains to continue. There are mainly two procedures to determine the amount of activity in RAIT for remnant ablation of post-operative well-differentiated thyroid cancer. One is the standard activity approach and the other is the dosimetric approach. In the standard activity approach, which is frequently preferred by nuclear medicine physicians due to its ease of use in routine application, the dose amount decided to be given to the well-differentiated and low-risk patients varies in a wide range from 1110MBq to 3700MBq for ablation therapy. In the randomized study of Schlumberger et al. (2012) involving 729 patients with low-risk thyroid cancer, no difference was found in terms of residual tissue ablation success between the patient groups treated with 1110MBq and 3700MBq of activity [6]. In a similar study conducted by Mallicket al. (2012) in which 421 patients were evaluated, no difference was found between 1110 MBq to 3700MBq of activity [7]. In the ATA guideline, 1110 MBq activity is recommended to be preferred over higher doses when RAIT is considered in low-risk differentiated thyroid cancer patients [3].

Currently, dosimetric applications enable the determination of the optimum activity that provides ablation based on the target tissue volume. Thus, not only effective treatment can be obtained but also radiation exposure can be reduced by using generally lower doses of radioactive iodine compared to fix-dose application, and secondary problems that may develop due to higher than necessary dose application can be prevented. Anatomical imaging methods such as ultrasound (US) and computed tomography (CT) can be used for target tissue volume calculation, which forms the basis of dosimetric calculations. However, when it comes to the evaluation of the remaining thyroid tissue, it has been reported that the US and CT findings are not reliable due to changes secondary to the recent operation and the low volume of the target tissue [13, 14]. The evaluation of the tissue that needs to be ablated with anatomical neck imaging is sub-optimal because of the post-operative structural changes. In the study of Selcuk et al. (2018), both US and gamma camera images were used for residual tissue measurement. The measurements made with the US were smaller than the actual residual tissue volume. On the other hand, it was stated that results larger than the real volume were obtained with the gamma camera method [15]. In our study, when gamma camera image is used for volume calculation, scattering correction was made by using the reference source placed in the image area.

In this study, the rate of decrease in activity was determined to be greater than 30% in 8 out of 14 patients whose activity amounts were determined to be lower than the planned standard activity amount as a result of the calculation. In other words, if the activity determined as a result of the dosimetric calculation was given, there was a minimum 30% decrease in the dose exposure of the patients. In addition, we found CA and TCA levels are more determinant to ablation status in the late term. When high CTA and TCA levels are found, standard dose application has the risk of insufficient ablation. In case of low TA and TCA levels, if the dose amounts calculated according to the risk assessment are lower than the amount calculated by the dosimetric approach, we think that there is no need to use high calculated dose amounts, since adequate ablation is provided.

In conclusion, because the dosimetric method is impractical in terms of application and requires repetitive measurements, it usually tends to be preferred in selected patients instead of a part of routine clinical practice. We think that the dosimetric application could be combined with standard activity approach in every patient and obtaining CA and TCA levels in a patient candidate for RAIT, can make suggestion to give higher or lower doses to accomplish successful ablation of the residual tissue. Our study also showed that it is not necessary to exceed higher limit of ablation dose amount in standard approach which is 1850MBq in low-risk patients even if we found much higher levels with the dosimetric method in some patients.

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