Radioiodine Remnant Ablation in Low-Risk Differentiated Thyroid Cancer

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Objective: *Evaluate the success rate of first high dose 100 mCi (3.7 GBq) radioiodine remnant ablation (RRA) in low-risk differentiated thyroid cancer (DTC) patients after surgery and determine factors influencing the success.*
Material and Method: *Between 1994 and 2011, a retrospective analysis was performed of 166 low-risk DTC patients after surgery (age range 18-76 years, mean age 38 years, 147 women and 19 men) with primary tumor >1 cm of diameter, stage 52 pT1pN0, 85 pT2pN0, 12 pT3pN0, and 17 pTxN0 underwent high dose 100 mCi (3.7 GBq) RRA. Successful RRA was defined as visually undetectable thyroid bed activity or elsewhere on the first follow-up whole body scan (WBS) six to 12 months after RRA and the stimulated thyroglobulin (st-Tg) levels <2 ng/mL at the same time of follow-up WBS and without interfering thyroglobulin antibodies (TgAb). Additional I-131 treatment was individualized depending on clinical characteristics with 100 to 150 mCi (3.7-5.5 GBq) I-131 six to 12 months intervals to achieve no thyroid bed uptake.*
Results: *Successful RRA was achieved in 122 of the 166 patients (73.5%). Failure by both criteria was seen in nine patients (5.4%). Of the 44 patients with ablation failure, additional I-131 treatment was individualized in 26 patients (59.1%). St-Tg levels at time of ablation and tumor size had significance influences on the success of RRA. The st-Tg levels at time of ablation were 7.5±11.5 ng/mL (0.1-80.3) in the ablation success group as compared with the ablation failure group of 24.1±24.9 ng/mL (1.3-97), p-value <0.001. Patients with ablation failure group had statistical significance of average tumor size greater than patients with ablation success group (3.2±1.1 and 2.7±1.1 cm), p-value = 0.012.*
Conclusion: *The efficacy of first high dose RRA in low-risk DTC after surgery shows comparable rates with those reported in the literature. The two factors influencing ablation success are st-Tg levels at time of ablation and tumor size.*

Keywords: *Differentiated thyroid carcinoma, Remnant ablation, Thyroglobulin, Radioactive iodine, Whole body scanning*

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Initial treatment of differentiated thyroid carcinoma (DTC) is near-total or total thyroidectomy mostly followed by radioiodine remnant ablation (RRA) and thyroid hormone suppression[1]. The rationales of RRA are to destroy any residual normal thyroid tissue, to destroy occult microscopic carcinoma and to allow a post-ablative follow-up WBS being a sensitive study for detecting metastasis or persistent tumor outside the thyroid bed[2]. It also shows a proper role in ensuring the accuracy of long-term follow-up. Activities between 30 mCi (1.1 GBq) and 100 mCi (3.7 GBq) of I-131 usually result in similar rates of successful RRA[3-5] and recurrent rates[6] but a trend toward higher ablation rates with higher activities was observed[7,8]. The aim of the present study was to determine the success rate of ablation with first high dose 100 mCi (3.7 GBq) RRA in patients with low-risk DTC after surgery. In addition, factors influencing the ablation success were also analyzed.

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Material and Method

One hundred sixty six patients (147 women and 19 men) with low-risk DTC after surgery (no local or distant metastasis, all macroscopic tumor being resected, no tumor invasion of locoregional tissues, no aggressive histology) and primary tumor size >1 cm in diameter treated with first high dose 100 mCi (3.7 GBq) RRA at Rajavithi Hospital between 1994 and 2011 were studied retrospectively. Pre-ablative I-131 diagnostic WBS was performed in all patients four to five weeks after surgery (near-total or total thyroidectomy or complete thyroidectomy). The age, sex, histological type, size of tumor, pre-treatment thyrotropin (TSH), stimulated Tg (st-Tg), and thyroglobulin antibody (TgAb) levels were collected. TNM classification and staging of patients were

evaluated according to the American Joint Committee on Cancer (AJCC) system[9]. The study was approved by the Research Ethics Committee of Rajavithi Hospital.

Exclusion criteria

Patients were excluded from analysis if the TSH was <30 mIU/L at time of ablation or at time of follow-up WBS, the ablation dose was <100 mCi (<3.7 GBq), the pre-ablative diagnostic WBS did not reveal any uptake at the thyroid bed, patient with TgAb levels was >30 IU/mL, either pre-ablative or 72 hour post-ablative WBS showed extrathyroid bed uptake due to metastasis.

RRA

After surgery for four to five weeks, patients did not receive thyroid hormone therapy. Patients followed a low-iodine diet at least one week before the WBS. Diagnostic WBS was performed with a tracer dose of 1 to 3 mCi (37-111 MBq) I-131 during patients with hypothyroidism and serum TSH >30 mIU/L. The diagnostic WBS was then performed 72 hour after the tracer dose administration. A first high dose 100 mCi (3.7 GBq) RRA was given within one week. Post-ablative WBS was also obtained 72 hour after the ablative dose. Images were acquired using a large field of view gamma camera (Toshiba GCA-901A or GE Millennium) equipped with a high energy parallel-hole collimator. Any discrete uptake in the thyroid bed on either diagnostic or post-ablative WBS was evaluated as a remnant. Patients with abnormal foci of uptake outside the thyroid bed in either diagnostic or post-ablative WBS due to metastasis were excluded from the present study since these patients were not in the low-risk group.

Tg, TgAb, and TSH measurements

Tg was performed using immunoradiometric assay (Cisbio International, France) with a functional sensitivity of 0.7 ng/mL. It has been assessed as being 0.2 ng/mL for detection limit, with the measuring range 0.7 to 500 ng/mL.

TgAb was measured by competitive radio-immunoassay (Cisbio International, France) with an analytical sensitivity of 6 IU/mL and functional sensitivity lower than 15 IU/mL.Samples with TgAb >30 IU/mL were determined interfering levels with Tg measurement.

TSH was determined using immuno-radiometric assay (Cisbio International, France) with 0.03 mIU/L detection level limit with normal thyroid function range 0.25 to 4 mIU/L.

TSH, Tg and TgAb levels were measured at time of ablation and during follow-up studies. Before WBS, patients were hypothyroid with TSH level >30 mIU/L.

St-Tg level was defined as the Tg level during hypothyroidism or thyroid hormone withdrawal and suppressed Tg (sp-Tg) level was defined as the Tg level during patient on L-thyroxine.

Follow-up and assessment of ablation success

The first follow-up WBS was performed six to 12 months after RRA with 3 mCi (111 MBq) I-131. Thyroid hormone withdrawal four to five weeks and low iodine diet were obtained as previously described. Successful RRA was defined as no visible thyroid bed activity or elsewhere on the first follow-up WBS six to 12 months after RRA and the st-Tg levels <2 ng/mL at the same time of follow-up WBS (Fig. 1), without interfering TgAb (TgAb <30 IU/mL). Later, the second follow-up WBS six to 12 months after successful RRA, st-Tg and TgAb levels were also performed for repeated evaluation.

Any focal uptake in the neck in the follow-up WBS was determined to represent ablation failure and additional I-131 treatment with 100 to 150 mCi (3.7-5.5 GBq) was repeated subsequently every six to 12 months depending on patient characteristics until

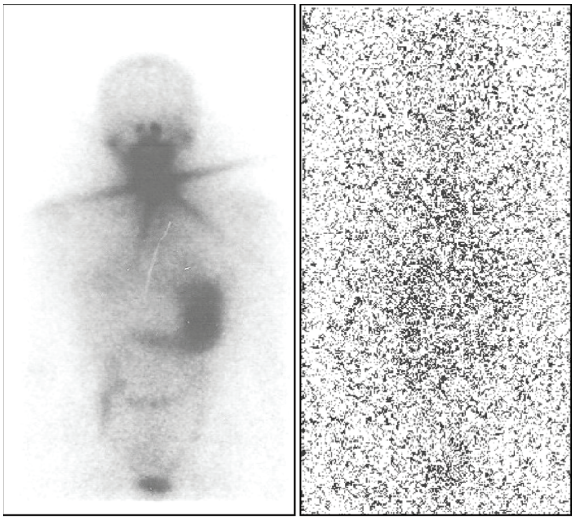

Fig. 1 (a) WBS of a patient 72 hrs after RRA showed residual uptake at the thyroid bed. (b) 9 months later, follow-up WBS revealed no visible activity.

the end point (no thyroid bed uptake) was reached. Once a negative follow-up WBS had been reached, the final follow-up WBS six to 12 months later, st-Tg and TgAb levels were also repeated. Follow-up clinical status, serum TSH, serum thyroxine, sp-Tg and TgAb levels, and other imaging (CXR, US, CT, MRI, PET-CT) were available for evaluation of clinical outcome during median follow-up time of eight years.

Statistical analysis

Quantifiable data were shown as mean ± SD, or median (followed by range). The continuous variables were analyzed to compare between two groups with Student t-test and Mann-Whitney U test. Chi-squared test or Fishers' exact test was used for categorical data analysis. P-values <0.05 were considered significant. SPSS 17.0 for Windows was used for statistical analysis.

Results

Patients and tumor characteristics

The patient and tumor characteristics were reported in the Table 1. The mean age of 166 patients with DTC was 38.08±11.55 years (18-76 years). The female to male ratio was 7.8:1. There were 119 patients (71.7%) with age <45 years and 47 patients (28.3%) with age ≥45 years.

According to the American Joint Committee on Cancer sixth edition (AJCC6), the low-risk patients were classified as 128 stage I (77.6%) of which 119 were aged <45 years 43 pT1, 55 pT2, 5 pT3, 16 pTx, and nine were aged ≥45 years 9 pT1. There were 30 stage II (18.2%) of which were ≥45 years 30 pT2. There were seven stage III (4.2%) of which were ≥45 years 7 pT3, and one unclassifiable stage aged ≥45 years 1 pTx.

The tumor histology was papillary carcinoma in 114 patients (68.7%), follicular carcinoma in 48 patients (28.9%), mixed type in two patients (1.2%), and Hurthle cell in two patients (1.2%). Of these, there were 12 patients (7.2%) with multifocal tumors.

Results of I-131 remnant ablation

Pre-ablative diagnostic WBS showed no uptake outside the thyroid bed. All patients received 100 mCi (3.7 GBq) RRA after pre-ablative diagnostic WBS. On 72 hours post-ablative WBS, all patients showed thyroid bed uptake (100%) and no I-131 uptake outside the thyroid bed. There was no less uptake of the thyroid bed in the 72 hours post-ablative WBS as compared with the pre-ablative WBS. One hundred of 166 patients (60.2%) demonstrated visually moderate amount of thyroid bed uptake and the rest 66/166 patients (39.8%) revealed visually minimal amount (Fig. 2).

One hundred twenty two of 166 patients (73.5%) were successfully ablated after the first dose

Table 1. Pateint and tumor characteristics

Factors	Total (n = 166)	
	Number	Percent
Age		
Mean ± SD (years)	38.08±11.55	
Min-max	18-76	
Gender		
Female	147	88.6
Male	19	11.4
Histological type		
Papillary	114	68.7
Follicular	48	28.9
Mixed	2	1.2
Hurtle	2	1.2
Tumor size		
Tx (unknown)	17	10.2
Tl (2 cm or smaller)	52	31.3
T2 (>2 to 4 cm)	85	51.2
T3 (> 4 cm limited to thyroid)	12	7.2
Stage		
I	128	77.6
II	30	18.2
III	7	4.2
Not classifiable	1	
Multifocal	12	7.2

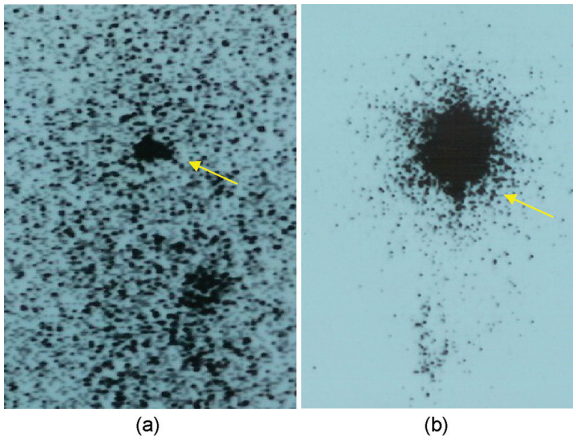

Fig. 2 Different thyroid bed uptake in pre-ablative diagnostic WBS (a) Minimal amount of thyroid bed uptake (arrow). (b) Moderate amount of thyroid bed uptake (arrow).

of I-131 according to both criteria (WBS-ve and st-Tg levels <2 ng/mL, Table 2). Failure by both criteria was seen in nine patients (5.4%). There were 23 patients (13.9%) with WBS-ve and st-Tg levels ≥2 ng/mL and 12 patients (7.2%) with WBS+ve and st-Tg levels <2 ng/mL. The efficacy of RRA in stage I patients was 73.4%, stage II 76.7%, and stage III 57.1% (Fig. 3). Unclassifiable staging was noted in one patient with Tx >45 years.

For evaluation of risk factors associated with unsuccessful ablation, there was no statistically significant difference between the ablation success group and ablation failure group in terms of age, sex, histological type, AJCC stage, TNM classification, multifocal cancer, or surgical completeness (Table 3). The two factors associated with significant differences between the two groups using univariate analysis was st-Tg levels at time of ablation and tumor size. The st-Tg levels at time of ablation were 7.52±11.50 ng/mL (0.1-80.3) in the ablation success group as compared with the ablation failure group 24.05±24.90 ng/mL (1.3-97), p-value <0.001. Patients with ablation failure group had statistical significance of average tumor size greater than patients with ablation success group (3.2±1.1 and 2.7±1.1 cm) p-value = 0.012. With multivariate analysis, the two factors were still significantly different between the two groups, p-value 0.001 for st-Tg levels and p-value 0.031 for tumor size (no data shown).

St-Tg levels at time of ablation (Table 3)

St-Tg levels at time of ablation were missing in five patients with unsuccessful ablation. St-Tg levels of 36/161 patients (22.4%) were <2 ng/mL and 35/36 of these patients (97.2%) revealed successful ablation. 77/161 patients (47.8%) had st-Tg levels 2-10 ng/mL, and 63/77 (81.8%) of these patients had successful ablation. St-Tg levels were >10-20 ng/mL in 22/161 patients (13.7%) and 13/22 patients (59.1%) had successful ablation. 26/161 patients (16.2%) had st-Tg levels >20 ng/mL, and 11/26 patients (42.3%) had successful ablation.

Additional I-131 treatment (Table 4)

In general, additional I-131 treatment 100-150 mCi (3.7-5.5 GBq) was actually indicated in patient with definite thyroid bed uptake (WBS+ve) and the number of doses were acquired until non-visualized thyroid bed uptake. Additional I-131 treatment was also optionally indicated in patients with high st-Tg levels usually >10 ng/mL although WBS-ve since WBS 72 hours after high dose of I-131 would have more affinity to detect residual thyroid bed uptake, residual tumor or silent metastasis. Of the 44 patients with ablation failure after first dose I-131 (RRA), additional I-131 treatment was administered individually as described above criteria with 100-150 mCi (3.7-5.6 GBq) six to 12 months intervals in 26 patients (54.1%) to achieve non-visualized thyroid bed activity. There were 140 patients given only single dose 100 mCi (3.7 GBq) including 122 patients with successful ablation criteria. There were WBS-ve in 139/140 patients and no need for further dose. However no I-131 treatment was added in one patient with WBS+ve st-Tg levels <2 ng/mL since there was faint uptake at thyroid bed and the second WBS at six to 12 months later showed disappearance of thyroid bed uptake. Seventeen of 23 patients in WBS-ve st-Tg levels >2 ng/mL group were given only single dose since all these patients had st-Tg levels <10 ng/mL at the six to 12 or 18 to 24 months later after RRA.

Thirteen patients were given two doses of I-131 and 11/13 patients were in WBS+ve group and the other two patients were in WBS-ve, st-Tg levels ≥2 ng/mL showing high st-Tg levels 39.6 and 92.9 ng/mL. Four patients were given three doses of I-131 although their stimulated Tg levels were revealed 1.5, 1.9, 9.2, and 10.1 ng/mL. One patient was given four doses despite minimal remnant and low st-Tg level 1.9 ng/mL. Eight patients were given more than four doses with all of them showed high stimulated Tg level, 4/8 patients from WBS+ve group with st-Tg levels 13.6, 23.5, 42.2, and 440 ng/mL and 4/8 patients from WBS -ve group with st-Tg levels 18.3, 19.6, 91.7 and 151 ng/mL. The mean value of st-Tg levels of these eight patients was 101.26±144.66 ng/mL (13.6-440 ng/mL) and median value of 26 ng/mL.

Diagnostic WBS results and post-ablative st-Tg levels obtained at first follow-up, six to 12 months (Table 5)

St-Tg levels obtained at first follow-up, six to 12 months of 134/166 patients (80.7%) were <2 ng/mL and 122 /134 of these patients (91.0%) revealed negative WBS. Thirteen of 166 patients (7.8%) had st-Tg levels 2 to 10 ng/mL and 12/13 (92.3%) of these patients had WBS-ve. St-Tg levels were >10 to 20 ng/mL in eight of 166 patients (4.8%) and five of eight patients (62.5%) had WBS-ve. Eleven of 166 patients (6.6%) had st-Tg levels >20 ng/mL and six of 11 patients (54.5%) had WBS-ve. In addition, after RRA, there were 145/166 patients (87.3%) with WBS-ve.

Table 2. Comparison of RRA results as defined by WBS and st-Tg levels

WBS	St-Tg levels	
	Positive (≥2 ng/ml)	Negative (<2 ng/ml)
Positive (uptake at thyroid bed)	9	12
Negative (no uptake at thyroid bed)	23	122
Total	32	134

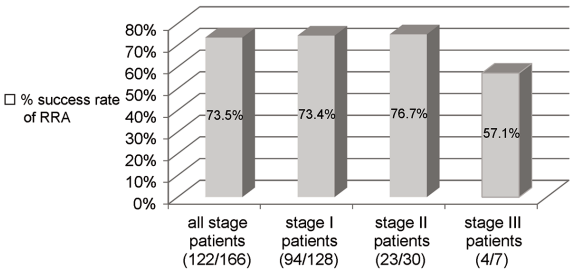

Fig. 3 The success rate of RRA determined by staging.

Table 3. Clinical characteristics of patients with 1st dose RRA between successful and failure groups

Clinical characteristics	Ablation success (n = 122) (%)	Ablation failure (n = 44) (%)	p-value (t-test significant)
Mean age (± SD, years)	38.90±11.15	35.87±12.43	0.133[a]
Gender			0.641[b]
Female	108 (89.3)	39 (86.7)	
Male	13 (10.7)	6 (13.3)	
Histological type			0.784[b]
Papillary	85 (69.7)	29 (65.9)	
Follicular	35 (28.7)	13 (29.5)	
Mixed	1 (0.8)	1 (2.3)	
Hurtle cell	1 (0.8)	1 (2.3)	
Tumor size			0.138[b]
Tx (unknown)	12 (9.8)	5 (11.4)	
T1 (2 cm or smaller)	44 (36.1)	8 (18.2)	
T2 (>2 to 4 cm)	59 (48.4)	26 (59.1)	
T3 (>4 cm limited to thyroid)	7 (5.7)	5 (11.4)	
Multifocal cancer	8 (6.6)	4 (9.1)	0.735[c]
Surgical completeness			0.633[c]
Free margin	119 (98.3)	44 (97.8)	
Not free margin	2 (1.6)	1 (2.2)	
Disease stage (not classifiable 1)			0.612[b]
Stage I	94 (77.7)	34 (77.3)	
Stage I	23 (19.0)	7 (15.9)	
Stage III	4 (3.3)	3 (6.8)	
St-Tg levels (ng/mL) at time of ablation			<0.001*[a]
Mean ± SD	7.50±11.50	24.10±24.90	
<2	35 (28.7)	1 (2.6)	
2-10	63 (51.6)	14 (35.9)	
>10-20	13 (10.7)	9 (23.1)	
>20	11 (9.0)	15 (38.5)	
(data missing in 5 patients of failure group)			
Tumor size (cm)			0.012*[a]
Mean ± SD	2.70±1.10	3.20±1.10	
Median (min-max)	2.5 (1-8)	3 (1.5-7)	

* Significant p-value <0.05

[a] Student t-test

[b] Chi-square test

[c] Fishers' exact test

Table 4. Number of I-131 doses administration in different groups of patients defined by results of WBS and st-Tg levels after RRA

Patient groups after RRA	1 dose	2 doses	3 doses	4 doses	>4 doses
WBS-ve Tg <2	122				
WBS+ve Tg <2	1	8	2	1	0
WBS-ve Tg ≥2	17	2			4
WBS+ve Tg ≥2	0	3	2	0	4
Total patients	140	13	4	1	8

Table 5. Diagnosis WBS results and st-Tg levels obtained at 1st follow-up 6-12 months after RRA

St-Tg (ng/mL)	WBS-ve (%)	WBS+ve (%)	Total
<2	122 (91.0)	12 (9.0)	134
2-10	12 (92.3)	1 (7.6)	13
>10-20	5 (62.5)	3 (37.5)	8
>20	6 (54.5)	5 (45.5)	11
	145	21	166

Discussion

One hundred sixty six patients with low-risk DTC were treated with first high dose 100 mCi (3.7 GBq) RRA after surgery in the presented study. Post-surgical RRA is almost always needed since remnant is commonly detected in diagnostic WBS[11]. In this study, all patients showed positive uptake for thyroid remnant. Generally, in low risk patients, remnants usually represent normal thyroid tissue, which show high capacity of iodine accumulation rather than tumor tissue. Tissue mass is clearly and inversely correlated with the success of ablation[7,12]. Masses weighing >2 g (by ultrasonogram) or cervical uptake >5% on post-ablative scan shows a less chance of successful ablation. Ablation of the small amount of residual thyroid tissue remaining after surgery may facilitate the early detection of recurrence based on serum Tg measurement and/or WBS. However, the effectiveness of RRA in low risk patients with DTC could not be verified and no definite answer, reviewed by Sawka et al[13] in a large meta-analysis. In general, RRA was based on the risk profile of each patient, preference of patient and physician, in order to ensure the accuracy of long-term follow-up[14].

Successful ablation was appropriately defined as no visible uptake at the thyroid bed on a subsequent diagnostic WBS or an undetectable st-serum Tg[11]. Nevertheless, the presented study defines for use of both criteria in order to assure complete ablation without silently microscopic disease in these low- risk patients according to Vianello F et al[10]. In previous published studies, the ablation successful rates were variable mostly from different activities of I-131 administered. Activities between 30 mCi (1.2 GBq) and 100 mCi (3.7 GBq) I-131 obtained similar rates of successful ablation[3-5] Some data suggests that these will be true only in patients with small remnants, so they recommended measurement of cervical uptake before ablative dose[15,16]. A systemic review by Hackshaw A et al[8] showed that the pool overall successful rate from 22 studies associated with using 100 mCi (3.7 GBq) was 79%, greater than the estimating of 51% using 30 mCi (1.2 GBq) in nine studies. Consequently, a trend toward higher ablation rates with high activities was revealed[17] but doses higher than 100 mCi (3.7 GBq) were not necessary for RRA only[4] since a plateau of efficacy demonstrated at 50 mCi (1.85 GBq). However, post-operative cervical uptake was not performed in this study. So, high dose 100 mCi (3.7 GBq) I-131 was used for ablation since high dose I-131 would be effective in either small or large remnants[18]. It was associated with a high rate of successful ablation[5].

In the past, the published studies revealed that 100 mCi (3.7 GBq) I-131 was associated with a high rate of successful ablation about 80 to 90% with majority using single criterion of negative neck uptake of diagnostic WBS approximately six to 12 months follow-up[8,19,20]. Hackshaw et al[8] revealed 80% successful rate with 100 mCi (3.7 GBq) I-131. Rosario PW et al[3] reported successful ablation with 100 mCi (3.7 GBq) I-131 in stage I DTC 78.7% according to negative WBS criterion. Ablation failure seemed to be related to the size of thyroid remnants and the presence of metastasis. Rosario PW et al[21] also reported successful ablation with 100 mCi (3.7 GBq) I-131 in 155/186 (83%) patients with DTC and without metastasis. Pre-ablative cervical uptake values <2% were associated with a higher ablation efficacy 94%, 2 to 5% showed 80% success and values >5% revealed 60% success. Arslan N et al[22] reported 74.3% successful ablation in 162/218 patients with DTC after a single dose I-131 treatment ranged from 50 mCi (1.85 GBq) to 200 mCi (7.4 GBq). For the present study, the ablation success rate will rise from 73.5% (122/166 patients) to 87.3% (145/166 patients) if only single criteria of negative neck uptake is applied (Table 2) as in some published series.

For up to date, the majorities of published studies using two criteria for successful ablation, negative WBS and undetectable Tg or st-Tg levels <2 ng/mL, the successful rates were 60 to 90%[8,18]. In the presented study, the successful rate was 73.5% (122/166 patients) which was comparable with the other reports. However, for Tg criterion for evaluation of successful ablation, there is still no definite agreement for the cut-off values for sp-Tg and st-Tg levels as a gold standard for complete remission or no evidence of disease. Some authors used higher cut-off st-Tg levels mostly <10 ng/mL that could result in additional I-131 treatment[23]. Lower cut-off sp-Tg levels <1 ng/mL and st-Tg levels <2 ng/mL were considered to differentiate residual normal thyroid tissue from low-level persistent thyroid cancer[11]. If two criteria of negative WBS and higher cut-off st-Tg levels <10 ng/mL are applied, the success rate in this study will be greater from 73.5% to 80.7% (134/166 patients Table 5), which is in accordant with the previous report by Sirisalipoch et al[24] who obtained successful rate 65% and 87% with 50 mCi (1.8 GBq) and 100 mCi (3.7 GBq) I-131 respectively using higher cut-off st-Tg levels <10 ng/mL.

Evaluation of ablation success was usually performed six to 12 months in nearly all published series but extend the time for first follow-up WBS 18 to 21 months after ablation can be accepted in the lower risk patients with DTC. Kusacic KS et al[25] proposed that the successful rate was significantly higher at the second than at the first follow-up WBS performed between six and nine and 18 to 21 months after RRA since a complete destruction of thyroid cancer cells in vivo and under thyroid hormone suppression therapy could take much longer time than the generally presumed time interval of three to 12 months. In the present study, the successful rate would be increased from 73.5% (122/166 patients) to 77.1% (128/166 patients) in terms of both negative WBS and st-Tg levels criteria evaluated at second follow-up WBS (12-24 months) without additional I-131 treatment.

For determination of significant factors associated with ablation success or failure in the present study, st-Tg levels at time of ablation ($p<0.001$) is one of the two factors associated with significant differences between the two groups using univariate analysis. Lin JD et al[26] reported that patients with ablation failure group had statistical significance of average st-Tg levels at the time of ablation higher than patients with ablation success group (78.1 and 27.3 ng/mL, $p = 0.0034$). Heemstra KA et al[27] revealed that st-Tg levels at the time of ablation were an independent prognostic indicator for disease-free remission (st-Tg cut-off levels 27.5 ng/mL, positive predictive value 98%). The highest diagnostic accuracy of Tg level for tumor presence was found during st-Tg measurements, six months after initial therapy (st-Tg cut-off levels 10 ng/mL; sensitivity 100%, specificity 93%). St-Tg levels before ablation and six months after initial therapy were independent prognostic indicators for deaths. Lin JD et al[28] also showed that st-Tg levels could be used as a prognostic factor in DTC patients. Post-operative high Tg levels implied that residual cancer cells presented in the body, which may not be detected by I-131 WBS or other conventional examination. Ozata et al[29] demonstrated that only 10.5% of patients who underwent successful surgery and RRA had st-Tg levels >10 ng/mL. Verberg FA et al[30] reported that st-Tg levels at time of ablation ($p<0.001$), lymph node metastasis ($p = 0.04$), and distant metastasis ($p<0.001$) had a significant influence on the success of ablation. In the present study, low-risk patients with ablation failure group had statistical significance of average st-Tg level at time of ablation higher than patients with ablation success group (24.1±24.9 and 7.5±11.5 ng/mL, $p<0.001$). High st-Tg levels at time of ablation are associated with ablation failure of statistical significance. This result supported the study by Muratet JP et al[31] who showed that there was a significant relationship between Tg levels and the chance of successful ablation. Since Tg is produced by normal or neoplastic thyroid cell, higher st-Tg levels indicate a larger mass of functioning thyroid cells that determined the chance of successful ablation[30]. Another factor influencing the ablation success in the present report is tumor size. It is generally accepted that tumor size is of prognostic value in DTC patients[32]. Machens et al[33] found increased risk of distant metastasis for primary tumors larger than 2 cm. Bal CS et al[34] reported that patients with small tumor size ≤5 cm with adequate surgery (total/near total thyroidectomy) and radioiodine neck uptake ≤10% had odds ratios of 2.4 [confidence interval (CI), 1.3-3.98] for successful remnant ablation. In the presented study, patients with ablation failure group had statistical significance of average tumor size greater than patients with ablation success group (3.2±1.1 and 2.7±1.1 cm, $p = 0.012$).

All 122 patients with successful ablation (WBS-ve and st-Tg levels <2 ng/mL group) were shown with no clinical evidence of disease during median follow-up of eight years. These verify that

success of ablation is a prognostic factor for disease free interval and survival[30]. In the present study, it is also 100% of patients with stimulated Tg levels <2 ng/mL showing no clinical evidence of disease for the whole follow-up time and no patient has persistent disease or recurrence. It has become clear that st-Tg levels without interfering of TgAb has high negative predictive value for subsequent disease recurrence from a recent consensus report[35] which concluded that cutoff st-Tg <2ng/mL was appropriately sensitive for follow-up and management of low-risk DTC patients. On contrary, WBS-ve was not a good single criterion for successful ablation since 6/145 (4.1%) patients with WBS-ve turned into persistent disease during follow-up particularly in patients with high st-Tg levels >10 ng/mL.

Eleven of 12 (91.7%) patients in WBS+ve and st-Tg levels <2 ng/mL group were added with two to four doses of I-131 treatment after RRA despite st-Tg level <2 ng/mL. All these patients had st-Tg levels range of 0.5 to 1.9 ng/mL. However, many authors suggested that additional I-131 treatment was not recommended in patients with thyroid bed uptake but st-Tg levels <2 ng/mL and negative neck ultrasonogram since <1% of these patients had clinical recurrence in the subsequent follow-up and minimal visible remnants in the thyroid bed had no clinical importance and did not affect the subsequent follow-up and outcome[36,37]. Moreover, st-Tg levels measurement and neck ultrasonogram had been reported by several groups as best indicators of complete remission/ persistent disease in the follow-up patients after RRA. The present study was retrospectively analyzed data in the past time, so unnecessary additional I-131 treatment was given in these 11 patients. All 12 patients in this group revealed no clinical evidence of disease with median follow-up of 8 years.

Ten of 44 (22.7%) patients with unsuccessful ablation (6 patients from WBS-ve st-Tg levels ≥2 ng/mL group and 4 patients from WBS+ve st-Tg levels ≥2 ng/mL group, Table 4) had high st-Tg levels (13.6-440 ng/mL, median 40.9 ng/mL) after RRA. Two patients required two doses and eight patients required more than four doses of additional I-131 treatment. Subsequently, persistent diseases with tumor in cervical or mediastinal lymph nodes were detected with other adjunctive investigation such as US, CT or PET-CT during follow-up. These verify that unsuccessful ablation is an adverse event in the follow-up of DTC patients and carries higher risk of recurrence as described by Verburg FA et al[30]. Follow-up of patients with unsuccessful ablation in first dose of I-131 particularly patients with high st-Tg levels should be more intensive than those with successful ablation in one dose and it was necessary to treat DTC patients early and intensively to achieve the best possible prognosis.

Study limitation

One of the limitations of the presented study is the evaluation of stunning effect, which is known by various factors such as the doses used for diagnostic WBS, the interval time between diagnostic WBS and ablation or treatment, the therapeutic doses and the definition of stunning itself. Cervical thyroid bed uptake was not performed in the present study so comparison between diagnostic WBS and 72 hours post ablative WBS could be from only visualization with inaccurate results. Only 1-3 mCi (37-111 MBq) is used in diagnostic WBS in this study, so less effect of stunning is suggested. However, Pedro WS[21] provided that RRA with high dose 100 mCi (3.7 GBq) had high efficacy in treatment and might have minimized the stunning effects as well as in the present study.

Conclusion

The presented study verifies that 100 mCi of I-131 is effective in RRA of low-risk DTC patients after surgery. Additional I-131 treatment to achieve non-visualized thyroid bed activity should be individualized depending on clinical characteristics. The two factors influencing ablation success are st-Tg levels at time of ablation and tumor size. Clinical outcome of these low-risk patients should be assessed during an optimal follow-up time. St-Tg levels have more specificity than WBS as a criterion in assessment of successful ablation and have better efficiency in differentiate patients with and without disease than follow-up WBS. Follow-up diagnostic WBS in low-risk patients with undetectable st-Tg levels after ablation is not recommended. However, the management of DTC is still lack of prospective data with various debates. Up to date, the effectiveness of rhTSH rather than hormone withdrawal RRA and long term follow-up has several advantages for low-risk DTC patients and is widely used in the DTC management guidelines in European and US countries.

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Potential conflicts of interest

None.

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การรักษาผู้ป่วยมะเร็งไทรอยด์ชนิด differentiated ที่มีความเสี่ยงต่ำด้วยไอโอดีนรังสี

ยุทธนา แสงสุดา

วัตถุประสงค์: เพื่อประเมินอัตราผลสำเร็จและปัจจัยที่มีผลต่อความสำเร็จของการรักษาผู้ป่วยมะเร็งไทรอยด์ที่มีความเสี่ยงต่ำชนิด differentiated หลังการผ่าตัดด้วยไอโอดีนรังสีปริมาณสูง 100 มิลลิคูรี (3.7 กิกะเบคเคอเรล) ครั้งแรก

วัสดุและวิธีการ: ศึกษาแบบย้อนหลังในช่วงเวลาตั้งแต่ พ.ศ. 2537 ถึง พ.ศ. 2554 ในผู้ป่วยมะเร็งไทรอยด์ที่มีความเสี่ยงต่ำชนิด differentiated หลังการผ่าตัด จำนวน 166 ราย อายุเฉลี่ย 38 ปี (18-76 ปี) เป็นผู้หญิง 147 ราย ผู้ชาย 19 ราย ซึ่งมีขนาดของก้อนมะเร็งมากกว่า 1 เซนติเมตร โดยมีระยะของโรคเป็น pT1pN0 53 ราย pT2pN0 81 ราย pT3pN0 15 ราย และ pTxpN0 17 ราย ที่รักษาด้วยไอโอดีนรังสีครั้งแรกปริมาณสูง 100 มิลลิคูรี (3.7 กิกะเบคเคอเรล) เกณฑ์ผลสำเร็จของการรักษาด้วยไอโอดีนรังสีครั้งแรก หมายถึงการไม่เห็นสารรังสีอยู่ที่บริเวณต่อมไทรอยด์และที่อื่น ๆ ของร่างกายจากการตรวจสแกนทั่วร่างกายหลังจากให้การรักษาด้วยไอโอดีนรังสีครั้งแรกเป็นระยะเวลา 6-12 เดือน ร่วมกับการตรวจหาค่าไทโรโกลบูลินขณะได้รับการกระตุ้นมีค่า <2 นาโนกรัม/มิลลิลิตร โดยไม่มีการรบกวนค่าการตรวจจากไทโรโกลบูลินแอนติบอดี การรักษาเพิ่มเติมด้วยไอโอดีนรังสีในปริมาณ 100-150 มิลลิคูรี (3.7-5.5 กิกะเบคเคอเรล) ทุก 6-12 เดือน ขึ้นอยู่กับลักษณะทางคลินิกของผู้ป่วยเพื่อไม่ให้เนื้อเยื่อไทรอยด์เหลืออยู่

ผลการศึกษา: ผู้ป่วย 122/166 รายประสบความสำเร็จของการรักษาด้วยไอโอดีนรังสีครั้งแรกคิดเป็น 73.5% มีผู้ป่วย 9 ราย (5.4%) ไม่ประสบความสำเร็จจากทั้ง 2 เกณฑ์ ผู้ป่วย 26/44 ราย (59.1%) ที่ไม่ประสบความสำเร็จได้รับการรักษาเพิ่มเติมด้วยไอโอดีนรังสี 100-150 มิลลิคูรี (3.7-5.5 กิกะเบคเคอเรล) ในระยะเวลาทุก 6-12 เดือน ปัจจัยที่มีความสำคัญทางสถิติต่อการรักษาได้สำเร็จในครั้งแรกได้แก่ ระดับไทโรโกลบูลิน ขณะได้รับการกระตุ้นในเวลาที่ได้รับการรักษาด้วยไอโอดีนรังสีครั้งแรกและขนาดของก้อนมะเร็ง โดยในกลุ่มผู้ป่วยที่ประสบความสำเร็จจากการให้ไอโอดีนรังสี มีระดับไทโรโกลบูลินขณะได้รับการกระตุ้นดังกล่าว 7.52±11.50 นาโนกรัม/มิลลิลิตร (0.1-80.3) ซึ่งมีค่าต่ำกว่าอย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับกลุ่มผู้ป่วยที่ไม่ประสบความสำเร็จจากการให้ไอโอดีนรังสีซึ่งมีค่า 24.05±24.90 นาโนกรัม/มิลลิลิตร (1.3-97), p-value < 0.001 กลุ่มผู้ป่วยที่ไม่ประสบความสำเร็จจากการให้ไอโอดีนรังสีมีขนาดก้อนมะเร็งใหญ่กว่ากลุ่มผู้ป่วยที่ประสบความสำเร็จอย่างมีนัยสำคัญทางสถิติ (3.2±1.1 และ 2.7±1.1 เซนติเมตร) p-value = 0.012

สรุป: อัตราความสำเร็จของการรักษาผู้ป่วยมะเร็งไทรอยด์ชนิด differentiated ที่มีความเสี่ยงต่ำหลังการผ่าตัดด้วยไอโอดีนรังสีครั้งแรกได้ผลดีและสอดคล้องกับผลงานวิจัยที่ผ่านมา ปัจจัยที่มีความสำคัญทางสถิติต่อการรักษาได้สำเร็จในครั้งแรกได้แก่ ระดับไทโรโกลบูลินขณะได้รับการกระตุ้นในเวลาที่ได้รับการรักษาด้วยไอโอดีนรังสีครั้งแรก และขนาดของก้อนมะเร็ง