Success Rate of Radioactive Iodine Ablation in Low-Risk of Recurrence Well-Differentiated Thyroid Carcinoma Patients

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ABSTRACT

Objective: To evaluate success rate and factors affecting the success of radioactive iodine (RAI) ablation in low-risk of recurrence well-differentiated thyroid carcinoma patients.

Methods: Retrospective review of medical records was done in 132 low-risk of recurrence well-differentiated thyroid cancer (WDTC) patients between January 2007 and December 2013. All patients underwent 1) total thyroidectomy or equal surgery and 2) pre-ablative evaluationwith ^{99m}Tc-pertechnetate thyroid scan and 24-hour ^{131}I thyroid uptake. RAI ablation using low activity (30 mCi: n = 17) or high activity (80 or 100 mCi: n = 115) were given. Success rate of each activity and a comparison of success rates between 2 doses were analyzed. Criteria of successful ablation were composed of 1) no palpable neck mass 2) no demonstrable thyroid and tumor uptake on the follow up 6-12 months diagnostic whole body scan (WBS) and 3) stimulated thyroglobulin (Tg) lower than 2 ng/mL in the absence of interfering thyroglobulin antibodies (TgAb <40 IU/mL). Factors that may affect success of radioactive iodine ablation were studied; age, gender, tumor size, stage, pathological result, number of lesions, pre-ablation 24-hour ^{131}I thyroid uptake, serum T4, TSH, Tg and TgAb at time of ablation.

Results: Overall success rate of RAI ablation was achieved in 95 patients out of 132 patients (72%). Low and high dose RAI ablation were completed in 9/17 patients (52.9%) and in 86/115 patients (74.8%), respectively (p-value = 0.082). Baseline Tg at time of ablation was a factor related to the success of ablation. Median Tg in success and failure group was 2.61 and 7.18 ng/mL, respectively (p = 0.023).

Conclusion: Success of ^{131}I ablation in low-risk of recurrence well-differentiated thyroid cancer patients was 72%. The factor relating to ablative success was Tg level at time of ablation.

Keywords: Well-differentiated thyroid cancer, low risk of recurrence, radioactive iodine ablation

Siriraj Med J 2016;68:229-234
E-journal: http://www.tci-thaijo.org/index.php/sirirajmedj

INTRODUCTION

Treatment of low-risk of recurrence WDTC is usually based on Revised American thyroid association (ATA) management guidelines.[1] However, clinical practices may vary due to a physician's experience, patients, and protocol of each institute i.e. pre-ablative evaluation, dosage of RAI used for ablation and criteria defining successful ablation. Consequently, a study done in one institute may not represent the outcome of others. With this reason, this study was performed to evaluate success rate and factors affecting the success of RAI ablation in low-risk of recurrence WDTC patients based on Siriraj Hospital's protocol.

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Received 18 February 2016
Revised 28 March 2016
Accepted 30 March 2016

MATERIALS AND METHODS

Retrospective review of medical records from January, 2007 until December, 2013 was done following approval from the institute ethical committee. Inclusion criteria were low-risk of recurrence WDTC patients who were sent for first RAI ablation. Low-risk of recurrence WDTC was defined as 1) no local or distant metastases, 2) all macroscopic tumor has been resected, 3) no tumor invasion of loco-regional tissues or structures, 4) no aggressive histology or vascular invasion, and 5) there was ^{131}I uptake only at thyroid bed on post-Tx WBS. Exclusion criteria were patients with an age under 18 years old and whose pre-ablative evaluation or post-Tx WBS revealed loco-regional or distant metastasis. Risk of recurrence and staging were based on revised ATA management guidelines and the AJCC Cancer staging manual, 6th ed.,[2] respectively.

Treatment followed our institute's protocol. Total thyroidectomy or equal surgery was done and followed by pre-ablative evaluation within 2-4 weeks. In patients who received thyroid hormone, withdrawal for at least 2 weeks was required. Pre-ablative evaluation was performed with 1) thyroid scan (intravenous administration of 2 mCi ^{99m}Tc-pertechnetate), and 2) 24-hour ^{131}I thyroid uptake (oral administration of 100 μCi ^{131}I).

Prior to RAI ablation, low-iodine diet for 2 weeks and thyroid hormone withdrawal until serum TSH level was equal or above 30 mU/L were required. Serum T4, TSH, baseline Tg during thyroid hormone withdrawal (stimulated Tg) and TgAb were measured on the day of ablation. Patients received RAI ablation of 30 mCi were treated as out-patients and those who received dosage more than 30 mCi were admitted for at least 2 days in a radiation isolation ward. Post-therapeutic whole body scan (post-Tx WBS) was obtained 2-5 days following the RAI ablation. Additional SPECT/CT imaging was performed in selected cases as indicated.

After RAI ablation, patients received levothyroxine 2 μg/kg. Evaluation of serum TSH level was performed at 2-3 months to keep TSH in range of 0.1-0.5 mU/L. Evaluation of treatment response was done at 6 months by measuring serum T4, TSH and Tg during thyroid hormone suppression (suppressed Tg) and TgAb. Diagnostic whole body scan (Dx-WBS) and stimulated Tg with TgAb were done within 12 months after ablation. Dx-WBS was obtained 3 days following oral administration of 5 mCi ^{131}I.

Interpretation of ^{131}I whole body scan was derived from consensus of 3 nuclear medicine physicians. For Dx-WBS performed 6-12 months after RAI ablation, ^{131}I uptake at thyroid bed was considered as imaging evidence of either remnant or tumor. No imaging evidence of tumor was defined as; 1) there was no abnormal ^{131}I uptake at thyroid bed or elsewhere, 2) there was insignificant ^{131}I uptake at thyroid bed on Dx-WBS which did not require 2nd RAI ablation and there was no evidence of disease in long-term follow up, or 3) there was focal uptake at upper midline neck representing thyroglossal duct remnant.

Criteria of success ablation were 1) no clinical evidence of disease, 2) no imaging evidence of disease on the follow up 6-12 months Dx-WBS and negative neck ultrasound, if available, and 3) stimulated Tg lower than 2 ng/mL in the absence of interfering TgAb (Fig 1). Cut-off level of interfering TgAb in this study was 40 IU/mL according to reference value of Roche Elecsys method[3]. In a patient whose TgAb was higher than 40 IU/mL, TgAb level should decrease more than 50% from initial level at 3 years.[4]

Success rate of RAI ablation was reported as percentage. Comparison of success rate between low and high dose RAI was done by Chi-square or Fischer's exact test. Factors that may affect success of RAI ablation - age, gender, tumor size, stage, pathological result, number of lesions, pre-ablation 24-hour ^{131}I thyroid uptake, serum T4, TSH, Tg and TgAb at time of ablation were reported in form of mean ± SD or median. Comparison between success and failure groups was done by t-test or Mann-Whitney test. P-value less than 0.05 was considered as statistically significant. The SPSS program version 13.0 was used for analysis of all data.

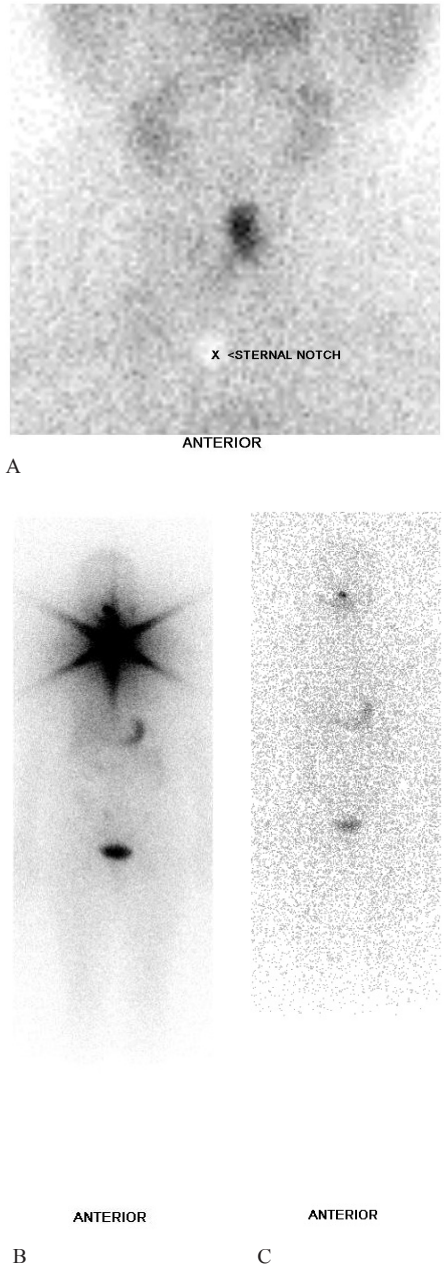

Fig 1. A) A 60-year-old woman with papillary thyroid carcinoma S/P total thyroidectomy whose pre-ablative ^{99m}Tc-pertechnetate revealed significant residual thyroid tissue, corresponding with 24-hour ^{131}I thyroid uptake of 10.97% (normal 15-45%) **B)** Post-Tx WBS (anterior view) of the same patient performed 3 days following 100 mCi RAI ablation showed intense radiotracer uptake at thyroid bed (star artifact) representing marked residual thyroid tissue. Baseline T4, TSH, Tg and TgAb were 2.3 µg/dL, 60 mU/L, 10.04 ng/mL and 53.4 IU/mL, respectively. **C)** Eight-month post-ablation Dx-WBS (anterior view) showed no evidence of residual thyroid tissue or functioning metastasis. T4, TSH, Tg and TgAb were 1.4 µg/dL, 76.23 mU/L, 0.1 ng/mL and 10 IU/mL, respectively. RAI ablation was successful in this patient.

RESULTS

Demographic data

Of 132 patients, 118 were female (89.4%). Age ranged from 19-83 years and 69 patients had age of 45 years or older (51.6%). Total and completion thyroidectomy were performed in 130 patients (98.5%). Major histology was papillary thyroid carcinoma (121 patients – 91.7%). Sixty patients had T1 tumor staging (45.5%) and 101 patients were stage I (76.5%) (Table 1).

Median of waiting time for RAI ablation after thyroidectomy of 132 patients was 69 days. Pre-ablative 24-hour ^{131}I uptake had median of 1.93%. Mean ± SD of serum T4 and TSH on the day of ablation were 2.39 ± 1.23 µg/dL and 82.8 ± 26.56 mU/L, respectively. Baseline Tg and TgAb had median of 2.91 ng/mL and 18.05 mU/L, respectively.

Outcome of RAI ablation

There were 115 patients who received high dose RAI; 100 mCi in 114 patients (99.1%) and 80 mCi in 1 patient (0.9 %). Only 17 of 132 patients (12.9%) received low dose RAI. Overall success rate regardless of RAI dosage was 95 from 132 patients (72%; 95% CI 63.8-78.9%). When using high and low dose, successful ablation was achieved in 86 of 115 patients (74.8%) and 9 of 17 patients (52.9%), respectively. The difference between success rate of low and high dose was not statistically significant (p-value = 0.082). (Table 2)

Factors that may affect success of RAI ablation

There were no statistically significant differences in age, gender, stage, histology number of lesions, baseline T4, TSH and TgAb between success and failure groups. Mean of tumor size and pre-ablation 24-hour ^{131}I thyroid uptake were higher in the failure group, but was not statistically significant. Median of baseline stimulated Tg and TgAb of success and failure groups were 2.61 versus 7.18 ng/mL (p-value = 0.023) and 17.3 versus 20.2 IU/mL (p-value = 0.292) (Table 3).

DISCUSSION

The success rate of radioactive iodine ablation in low-risk of recurrence well-differentiated

thyroid cancer patients has been studied for many years. However, a study done by one research group may not be adaptable to others. With this reason, the presented study followed the Siriraj Hospital institute's protocol and aimed to reveal outcome based on our practices.

Overall success rate of RAI ablation in this study was 72%. High activity tended to provide higher success rate than low activity, but was not statistically significant (74.8% vs 52.9%; p-value = 0.082). Our success rate was quite different from many studies which claimed quite equal success rate of low and high activity RAI.[5-9] Nevertheless, this study was not designed to compare the success rate of low and high activity. Small number of patients received low activity and possible selective bias probably decreased reliability.

Success rate of high-activity in this study was comparable to that of 73.5% reported in a retrospective study by Saengsuda Y.[5] Moreover, population and methodology, especially criteria of successful ablation in this mentioned study were also similar to our study. However, results of large prospective randomized studies performed in European countries were different. Mallick et al.,[6] and Schlumberger et al.,[7] reported success rate of high dose RAI ablation as high as 88.9% and 94%, respectively. As in the prospective studies, variations of several factors which may affect the outcome of RAI ablation were minimized. For instance, all patients underwent thyroidectomy by experienced surgeons. Only 2.3% of patients had multiple foci of uptake or focal intense uptake representing marked residual thyroid remnant on pre-ablative scan.[6] In contrast to our study, thyroid operations in many patients were not performed by specialized thyroid surgeons resulting in marked residual thyroid remnant in 23.5% of patients. Therefore, the high success rate of prospective studies is understandable. Even so, another possibility of this inconsistent result, apart from different study design, may be ethnical difference of population which requires further studies to clarify.

Significantly high level of baseline stimulated Tg in the failure group as compared to the success group (7.18 vs 2.61 ng/mL; p-value = 0.023) led to the conclusion; baseline stimulated Tg level significantly correlated with success of ablation. Saengsuda Y., who reported mean ± SD of

TABLE 1. Demographic data of patients.

Factors		Total number (n=132)	
		Number	Percent
Gender	Female	118	89.4
Surgery	Total thyroidectomy	71	53.8
	Complete thyroidectomy	59	44.7
	Subtotal thyroidectomy	2	1.5
Histology	Papillary carcinoma	121	91.7
	Follicular carcinoma	10	7.6
	Mixed papillary and follicular carcinoma	1	0.8
Number of tumor	Unifocal	113	85.6
	Multifoci	19	14.4
Tumor size[2]	T1	60	45.5
	T2	54	40.9
	T3	18	13.6
Stage[2]	I	101	76.5
	II	21	15.9
	III (T3N0M0)	10	7.6
Dosage of ^{131}I ablation (mCi)	100	114	86.3
	80*	1	0.8
	30	17	12.9

*Reduced dosage due to significant residual thyroid tissue (24-hour ^{131}I thyroid uptake of 15.63%)

stimulated Tg in success and failure groups were 7.52 ± 11.5 vs 24.05 ± 24.9 ng/mL; p-value <0.001, respectively, also came to the same conclusion. In contrast, Mallick et al., found that baseline stimulated Tg did not strongly correlate to success rate. However, medians of baseline Tg among 4 population groups in the study by Mallick et al., were only 2.3, 1.6, 3.8 and 1.5 ng/mL. Thus, it is possible that baseline Tg would affect success rate only when its level is high enough.

Spencer CA[10] found a relationship between serum TgAb and Tg level, and suggested that TgAb could be used as surrogate marker in case Tg might be unreliable due to high TgAb. In this study, the median of TgAb in the success group was not statistically lower than failure group (17.3 vs 20.2 IU/ml; p-value = 0.292). Still, continuous decrease of serum TgAb level over time has been observed only in patients with successful ablation.

In our study, tumor size of failure group was larger than success group, but did not reach statistical significance (p-value = 0.057). Saengsuda Y. and Bal et al.[11] stated that tumor size significantly affected success of RAI ablation. Obviously, in the study by Saengsuda Y., 51.2% of patients were in T2 and Bal et al., reported an effect of tumor size on ablation based on cut-off size of 5 cm. In this presented study, 45.5% of patients had tumor size less than 2 cm. (T1). The greater size of tumor means higher likelihood of occult invasion and metastasis. Consequently, the relatively smaller tumor size of our study may be unable to demonstrate an effect of tumor size on success rate of RAI ablation.

Rosario et al.,[12] showed correlation between amount of residual thyroid tissue and success rate of RAI ablation. When stimulated Tg less than 5 ng/mL was defined as successful ablation, Rosario et al., reported success rate of 95.8%, 94%, 83%, 70% and 50% for 24-hour ^{131}I uptake less than

TABLE 2. Outcome of 1st RAI ablation.

Dose of RAI ablation (mCi)	Outcome of 1st RAI ablation	
	Success, n (%)	Fail, n (%)
80* or 100	86 (74.8%)	29 (25.2%)
30	9 (52.9%)	8 (47.1%)
Total	95 (72%)	37 (28%)

*In the patient who received RAI ablation 80 mCi, the 1st ablation was successful

TABLE 3. Factors that may affect success of RAI ablation.

Clinical characteristics		Success	Fail	p-value
Age, years		46.86±13.4	42.35±12.9	0.081*
Gender, n (%)	Female	85 (72%)	33 (28%)	1.000#
Histology, n (%)	Papillary CA	89 (73.6%)	32 (26.4%)	0.180**
	Follicular CA	6 (60%)	4 (40%)	
	Mixed CA	0 (0%)	1 (100%)	
No. of lesion, n (%)	Unifocal	82 (72.6%)	31 (27.4%)	0.710**
	Multifoci	13 (68.4%)	6 (31.6%)	
Tumor size, cm.++		2.2	2.5	0.057##
Stage, n (%)	I	71 (70.3%)	30 (29.7%)	0.724**
	II	16 (76.2%)	5 (23.8%)	
	III	8 (80%)	2 (20%)	
24-hr. uptake, (%)++		1.75	3.19	0.504##
T4, µg/dL++		2.1	2.0	0.972##
TSH, mU/L++		98.72	97.25	0.777##
Tg, ng/mL++		2.61	7.18	0.023##
TgAb, IU/mL++		17.3	20.2	0.292##

+Data are means ± SD, ++Data are median, *t-test, **Pearson Chi-square, #Fischer's Exact test, ##Mann-Whitney test

1%, 1-2%, 2-5%, 5-10% and greater than 10%, respectively. However, in our study the amount of residual thyroid had no significant impact on success rate, probably because the residual thyroid was generally minimally evidenced by median of 24-hour ^{131}I uptake which was only 1.93%.

Several studies have shown relationships between amount of residual disease and success rate of ablation. However, the amounts of residual thyroid remnant were represented in different parameters – i.e. serum T4[13], TSH[13], Tg[5] and 24-hour ^{131}I uptake[12]. However, our study showed that only baseline Tg had a strong relationship to successful ablation. The main purpose of post-operative 24-hour ^{131}I uptake in our institute is to screen patients with significant amount of residual thyroid tissue, who may need additional surgery prior to RAI ablation. With this reason, extra-iodine pool was not strictly controlled and 24-hour ^{131}I uptake was probably interfered with. In addition, serum T4 and TSH of our study was collected on the day of ablation following thyroid hormone withdrawal for at least 3 weeks. Thus, serum T4 and TSH in this setting may not be well correlated to amount of residual thyroid remnant.

In conclusion, the success rate of RAI ablation in low-risk of recurrence well-differentiated thyroid cancer patients in this study was 72%, comparable to the retrospective study done in Thailand. High RAI activity tends to provide higher success rate, but does not reach statistical significance. Large tumor and advanced age potentially affect the success rate, but the only factor that strongly relates to success of ablation is Tg level at time of ablation.

ACKNOWLEDGMENTS

Authors would like to thank all of our colleagues in Division of Nuclear Medicine, Department of Radiology. This study was supported by a grant from the Siriraj Research Development Fund, Grant Number (IO) R015831022 and research authors also received a Chalermprakiat grant from the Faculty of Medicine Siriraj Hospital, Mahidol University.

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