

Outcome of Radioactive Iodine Ablation/ Treatment in Pathologically-Defined Low Risk of Recurrence Well-Differentiated Thyroid Carcinoma Patients

Ajalaya Teyateeti, M.D., Achiraya Teyateeti, M.D., Pawana Pusuwan, M.D.*

Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To evaluate outcome of radioactive iodine (RAI) ablation/treatment in pathologically defined low risk of recurrence well-differentiated thyroid carcinoma (WDTC) patients.

Methods: A 7-year retrospective review of medical records was done in 155 pathologically defined low risk of recurrence (LRR) WDTC patients. Total thyroidectomy or equal surgery and pre-ablative evaluation were done in all patients. The 1st dose of RAI ablation was either 30 or 80/100 mCi. The following doses of RAI ablation/treatment were adjusted by patients' risk of recurrence and treatment response. Criteria of successful ablation/treatment were 1) no evidence of clinical disease 2) no demonstrable abnormal uptake on the follow-up 6-12 months diagnostic whole body scan (Dx-WBS) and 3) stimulated thyroglobulin (Tg) lower than 2 ng/mL and thyroglobulin antibodies (TgAb) lower than 40 IU/mL. Patients received RAI ablation/treatment until they achieved disease remission or there was evidence of treatment failure.

Results: Cumulative success rate after the 1st, 2nd and 3rd RAI ablation/treatments were 61.3%, 75.5% and 82.6%, respectively. The risk of recurrence among 155 patients were 83.2% low risk (n=129), 11.6% intermediate risk (n=18), and 5.2% high risk (n=8). Of 129 true LRR patients, the success rates of 1st, 2nd and 3rd RAI ablation were 73.6% (n=95), 10.1% (n=13) and 6.2% (n=8), respectively. After RAI treatment for 3 sessions, disease remission was observed in 10 of 18 intermediate risk of recurrence (IRR) patients and only 1 of 8 high-risk of recurrence (HRR) patients. Between success and failure group, there was statistically significant difference in risk of recurrence (p-value = 0.000), baseline Tg (2.61 vs 7.17 ng/mL, p-value = 0.015) and TgAb (16.8 vs 33.7 IU/mL, p-value = 0.004).

Conclusion: Disease remission in pathologically defined LRR patients after the 1st, 2nd and 3rd sessions of RAI ablation/treatment were 61.3%, 75.5% and 82.6%, respectively. IRR and HRR were found in 16.8% of pathologically defined LRR patients. Risk of recurrence, baseline Tg and TgAb strongly correlated with RAI ablation/treatment outcome. Highest success rate was observed in true LRR (89.9%). None of the IRR and HRR patients had disease remission following the 1st RAI ablation and remission rate was only 43.2% following 3 sessions of RAI treatment.

Keywords: Low risk of recurrence well-differentiated thyroid cancer; radioactive iodine ablation; radioactive iodine treatment; thyroid neoplasm

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Correspondence to: Pawana Pusuwan

E-mail: pawana.pus@mahidol.ac.th

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INTRODUCTION

Outcome of RAI ablation/treatment in LRR WDTC patients has been studied for many years. However, most of the existing studies were exclusively done in LRR patients and excluded those with pathologically LRR who later discovered functioning metastasis. In fact, activity of 1st RAI ablation/treatment given to patients in many institutes, including our institute was determined by pathological findings. Therefore, unexpected loco-regional or distant metastasis representing non-low risk of recurrence is probably discovered on post-therapeutic WBS in few patients. Additionally, these patients might be cured despite lower activity of RAI treatment. With this reason, evaluation of RAI ablation/treatment outcome based on pathological criteria is more useful to reflect our current practices.

MATERIALS AND METHODS

Retrospective chart review of medical records of 155 patients from January, 2007 until December, 2013 was done following approval of the ethical committee of the faculty (Si.742/2013). Inclusion criteria were patients with pathologically proved LRR WDTC according to the revised American Thyroid Association (ATA) management guidelines¹ which were 1) no local metastases, 2) all macroscopic tumor has been resected, 3) no tumor invasion of locoregional tissues or structures, and 4) tumor does not have aggressive histology or vascular invasion. Exclusion criteria were patients with age under 18 years old. Staging were based on the AJCC Cancer staging manual 6th ed.²

All patients underwent total thyroidectomy or equal procedures followed by pre-ablative evaluation with thyroid scan using 2 mCi ^{99m}Tc-pertechnetate and 24-hour ¹³¹I thyroid uptake using 100 uCi. Prior to RAI ablation/treatment, patients had low-iodine diet for 2 weeks and withdrew from thyroid hormone until TSH was over 30 mU/L. The 1st RAI ablation was either 30 or 100 mCi and may be reduced to 80 mCi in patients with marked residual thyroid tissue. The consequent RAI ablation/treatment was adjusted

by risk of recurrence and treatment response; 30 and 100 mCi for LRR with persistent residual thyroid tissue or tumor, 150 mCi for cervical lymph node (CLN) metastasis, pulmonary metastasis, LRR with marked residual thyroid tissue and LRR with poor response to prior RAI, and 200 mCi for bone metastasis and high serum Tg with negative WBS. Baseline T4, TSH, Tg and TgAb were collected on the day of ablation. Post-therapeutic WBS (post-Tx WBS) was obtained in 2-5 days after RAI ablation. Additional SPECT/CT imaging was performed as indicated.

After RAI ablation/treatment, thyroid hormone suppression was given. Serum TSH was periodically checked to keep in appropriate level according to revised ATA management guidelines¹. Dx-WBS with Tg and TgAb were done within 12 months after each session of RAI ablation/treatment, except when previous WBS showed no definite abnormal uptake and serum Tg was higher than 10 ng/ml. Dx-WBS was obtained 3 days following oral administration of 5 mCi ¹³¹I.

Successful RAI ablation/treatment or disease remission was composed of 3 criteria; 1) no clinical evidence of disease, 2) no imaging evidence of disease which were no abnormal ¹³¹I uptake at thyroid bed or elsewhere, insignificant ¹³¹I uptake that did not require further RAI ablation/treatment and there was no evidence of disease (NED) in long-term clinical follow up or ultrasonography, or focal ¹³¹I uptake at upper midline neck representing thyroglossal duct remnant, and 3) undetectable serum Tg (stimulated Tg less than 2 ng/mL) in absence of interfering TgAb (TgAb level less than 40 IU/mL³ or decrease of TgAb more than 50% from initial level at 3 years in case TgAb was higher than 40 IU/mL⁴).

Further RAI ablation/treatment was considered when 1) there was residual thyroid tissue/tumor or functioning metastasis on Dx-WBS, or 2) there was no significant abnormal ¹³¹I uptake on Dx-WBS, but stimulated Tg level was over 10 ng/mL.

Following each session of RAI ablation/treatment, risk of recurrence was re-stratified based on the revised ATA management guidelines¹. Patients were considered as true LRR when ¹³¹I uptake on post-Tx WBS was only within the thyroid bed. Patients were categorized as IRR

when there was evidence of CLN metastasis by imaging or pathological report and HRR when there was distant metastasis or high serum Tg.

Factors that may predict outcome of RAI ablation/treatment included age, gender, tumor size, staging, histology, number of tumors, pre-ablative 24-hour ¹³¹I thyroid uptake, baseline Tg, TgAb and risk of recurrence were reported in the form of percentage, mean ± SD or median. Comparison between groups was done by t-test, Mann-Whitney test, Pearson Chi-square and Fischer's exact test. P-value less than 0.05 was considered as statistically significant. Cut-off values of baseline Tg and TgAb to discriminate between LRR and non-LRR patients using receiver operating characteristic analysis was also performed. The SPSS program version 13.0 was used for analysis of all data.

RESULTS

Among 155 patients, 139 patients were female (89.7%). Age range was 19-83 years.

TABLE 1. Demographic data of patients

Factors		Total number Number	(n=155) Percent
Gender	Female	139	89.7
Surgery	Total thyroidectomy	74	47.7
	Completion thyroidectomy	68	43.9
	Thyroidectomy with CLN dissection	9	5.8
	Others	4	2.6
Histology	Papillary carcinoma	144	92.9
	Follicular carcinoma	10	6.5
	Mixed papillary and follicular carcinoma	1	0.6
Number of tumor	Unifocal	130	83.9
	Multifoci	25	16.1
Tumor size ²	Tx	1	0.6
	T1	75	48.4
	T2	61	39.4
	T3	18	11.6
Stage ²	Unknown	1	0.6
	I	120	77.4
	II	24	15.5
	III	10	6.5
Risk of recurrence ¹	Low	129	83.2
	Intermediate	18	11.6
	High	8	5.2

Total or completion thyroidectomy without CLN dissection was performed in 142 patients (91.6%). Major histology was papillary thyroid carcinoma in 144 patients (92.9%). T1 tumor staging and stage I were found in 75 patients (48.4%) and 120 patients (77.4%), respectively. (Table 1). Pre-ablative evaluation with 24-hour ¹³¹I uptake ranged from 0.9-16.7%; median 2.0%. Baseline Tg and TgAb were less than 0.1 to 124.3 ng/mL with median of 3.02 ng/mL and 6.2 - 4000 IU/mL with median 18.7 IU/mL, respectively.

Outcome of RAI ablation/treatment

Of 155 patients, 135 patients received 80 or 100 mCi RAI ablation (87.1%). Only 20 patients received 30 mCi RAI ablation (12.9%). Overall success rate of 1st RAI ablation regardless of RAI activity was 95 of 155 patients (61.3%).

Of 60 patients who failed 1st RAI ablation/treatment, 55 patients received the 2nd RAI ablation/treatment. Five patients who did not receive 2nd RAI activity had negative WBS with slightly high Tg or TgAb. RAI activity of 30 or 100 mCi RAI

TABLE 2. Outcome of RAI ablation/treatment

RAI activity	Outcome of RAI ablation/treatment		
	Success, n (%)	Failure, n (%)	Inconclusive ⁺ , n (%)
1st dose (n=155)			
80* or 100	86 (63.7%)	49 (36.3%)	
30	9 (45%)	11 (55%)	
Total	95 (61.3%)	60 (38.7%)	
2nd dose (n=55 [#])			
30	0 (0%)	1 (100.0%)	0 (0%)
100**	10 (58.8%)	1 (5.9%)	6 (35.3%)
150***	12 (33.3%)	21 (58.3%)	3 (8.3%)
200****	0 (0%)	1 (100%)	0 (0%)
Total	22 (40%)	24 (43.6%)	9 (16.4%)
3rd dose (n=17 ^{##})			
100	2 (66.7%)	0 (0%)	1 (33.3%)
150	8 [§] (66.7%)	3 (25%)	1 (8.3%)
200	1 [§] (50%)	1 ^{§§} (50%)	0 (0%)
Total	11 (64.7%)	4 (23.5%)	2 (11.8%)
Total (after 3 sessions of RAI ablation/treatment)	128 (82.6%)	4 (2.6%) ^α	23 (14.8%) ^{###}

⁺ Inconclusive due to short follow-up period or unavailable data

* Two patients received 80 mCi RAI ablation due to marked residual thyroid tissue. The 1st RAI ablation was success in patient with 24-hour ¹³¹I uptake of 15.63%. Another patient with 24-hour ¹³¹I uptake of 11.56% received 2nd 150 mCi RAI treatment due to evidence of CLN metastasis on post-Tx WBS and disease was in remission after 3rd RAI treatment (cumulative dose 380 mCi)

** 8/17 patients received 1st 30 mCi RAI ablation.

*** Increase to 150 mCi due to 1) functioning metastasis detected on post-Tx WBS; pulmonary - 1 patient and CLN - 18 patients, 2) marked residual thyroid uptake - 8 patients, 3) poor response to 1st RAI ablation i.e. increasing or stable serum Tg level - 6 patients, or 4) negative Dx-WBS with high stimulated Tg - 3 patients.

**** Increase to 200 mCi due to bone metastasis

§ Increase RAI activity 1) Patient received 3rd 150 mCi RAI ablation/treatment owing to marked residual thyroid uptake after two sessions of 30 mCi RAI. 2) Patient received 3 sessions (100, 150 and 200 mCi) of RAI treatment due to poor response as evidence by rising Tg.

§§ Patient with bone metastasis with stimulated Tg 2.73 ng/mL and negative Dx-WBS.

Five patients did not receive 2nd RAI ablation. Four patients had negative Dx-WBS, but stimulated Tg was higher than 2 ng/mL. NED on neck US or neck and chest CT scan and serum Tg decreased overtime. Another patient had negative Dx-WBS and stimulated Tg less than 2 ng/mL, however, baseline TgAb was high and follow-up period was too short.

Seven patients did not receive 3rd RAI ablation. Six patients had negative Dx-WBS, but stimulated Tg was higher than 2 ng/mL. Another patient refused further treatment

^α One patient had persistent CLN metastasis even after the 4th RAI treatment. Another two had high serum Tg level with negative post-Tx WBS, and the last one had pulmonary and bone metastases.

Include 12 patients who did not receive further treatment

TABLE 3. Factors that may predict outcome of RAI ablation/treatment

Clinical characteristics		Success	Failure	p-value
Age, years ⁺		46.97±13.4	44.63±13.117	0.288*
Gender, n (%)	Female	85 (61.2%)	54 (38.8%)	0.916 ^α
Histology, n (%)	Papillary CA	89 (61.8%)	55 (38.2%)	0.582 [#]
	Follicular CA	6 (60%)	4 (40%)	
	Mixed CA	0 (0%)	1 (100%)	
No. of lesion, n (%)	Unifocal	82 (63.1%)	48 (36.9%)	0.298 ^α
	Multifoci	13 (52%)	12 (48%)	
Tumor size, cm. ⁺⁺		2.1 (1.2,3.0)	2.5 (1.5,3.5)	0.957 [§]
Staging, n (%)	I	71 (59.2%)	49 (40.8%)	0.369 ^α
	II	16 (66.7%)	8 (33.3%)	
	III	8 (80%)	2 (20%)	
24-hr. uptake, (%) ⁺⁺		1.78 (1.15,4.51)	2.96 (0.96,5.60)	0.750 [§]
Tg, ng/mL ⁺⁺		2.61 (1.0,7.26)	7.17 (1.0,22.99)	0.015 [§]
TgAb, IU/mL ⁺⁺		16.8 (10.0,53.4)	33.7 (13.33,233,68)	0.004 [§]
Risk of recurrence	Low	95 (73.5%)	34 (26.4%)	0.000 [#]
	Intermediate	0 (0%)	18 (100%)	
	High	0 (0%)	8 (100%)	

⁺Data are means ± SD, ⁺⁺Data are median (Interquartile range), * t-test, ^α Pearson Chi-square, [#] Fischer's Exact test, [§] Mann-Whitney test, &Interquartile range

ablation was given to 18 LRR patients. RAI activity of 150 mCi was given to 36 patients and 200 mCi was given to a patient with bony metastases. Overall success rate regardless of RAI activity was only 22 from 55 patients (40%). Among the remaining 33 patients, 24 patients were considered as failure group and there were inconclusive results in 9 patients due to short follow-up period or unavailable data.

Of 24 patients who failed 2nd RAI ablation/treatment, 17 patients received the 3rd ablation/treatment. Of seven patients who did not receive 3rd RAI activity, 6 of them had negative WBS with high Tg and the last one refused further treatment. RAI activity of 100 mCi was given to 3 LRR patients and 150 mCi was given to 6 LRR patients, 3 patients with CLN metastasis and 3 patients with poor response to RAI treatment. The 200 mCi RAI treatment was given to a bone metastatic patient and a patient who had poor response to 2 previous sessions of RAI treatment.

After 3 sessions of RAI ablation/treatment, 128 of 155 pathologically defined LRR patients had disease remission (82.6%). Outcome of RAI ablation/treatment was inconclusive in 11 patients

(7.1%) and there were 12 patients who did not receive further ablation or treatment (7.7%). Four patients who had persistent disease were non-LRR patients (2.6%). (Table 2)

Factors that may predict outcome of RAI ablation/treatment

Age, gender, tumor size, staging, histology, number of tumors and 24-hour ¹³¹I thyroid uptake had no statistically significant difference between success and failure groups. In contrast, risk of recurrence (p-value = 0.000), baseline Tg (2.61 vs 7.17 ng/mL, p-value = 0.015) and TgAb (16.8 vs 33.7 IU/mL, p-value = 0.004) of success and failure groups had statistically significant difference. (Table 3)

Initial characteristics that may predict risk of recurrence

As management of WDTC is based on risk of recurrence, we analyzed the initial characteristics that may predict risk of recurrence. Number of lesions, tumor size and staging showed no statistically significant difference between LRR and non-LRR groups. However, baseline Tg and

TgAb had statistically significant difference (2.87 vs 11.72 ng/mL, p-value = 0.044 and 18.1 vs 91.65 IU/mL, p-value = 0.015, respectively). (Table 4)

The area under the ROC curve of the baseline Tg and TgAb for discriminating LRR and non-LRR groups was 0.625 and 0.650, respectively. However, there was no appropriate cut-off value of baseline Tg and TgAb to discriminate between LRR and non-LRR patients. (Fig 1)

DISCUSSION

Cumulative success rate after 1, 2 and 3 sessions of RAI ablation/treatment were 61.3%, 75.5% and 82.6%, respectively. As aforementioned, there were 12 patients who did not receive further RAI ablation/treatment. Five of them were LRR patients whose 1st RAI ablation failed

by criteria. However, their long-term follow up showed NED and were likely to be in remission. In fact, these patients should be considered as indeterminate response according to the 2015 ATA management guidelines⁵ instead of failure RAI ablation. When they were included into the success group, the rate of success of 1st RAI ablation increased to 64.5%. On the contrary, of the remaining 7 patients; 2 – IRR and 5 HRR received 2 sessions of RAI treatment and ended up with negative WBS with high stimulated Tg or biochemical incomplete response⁵.

Of 155 pathologically defined LRR patients, true LRR, IRR and HRR were considered in 129 patients (83.2%), 18 patients (11.6%) and 8 patients (5.2%), respectively. Among 129 true LRR patients, cumulative success of 1st, 2nd and 3rd RAI ablation were observed in 95 patients (73.6%), 13 patients (83.7%) and 8 patients (89.9%), respectively. The remaining 13 patients were inconclusive. This means at least 116 LRR patients achieved RAI ablation/treatment in 3 sessions (89.9%) and only 21 patients (16.3%) had to receive more than one RAI ablation. The highest cumulative dose to achieve successful RAI ablation in true LRR was 450 mCi in a patient who had 24-hour ¹³¹I uptake of 6.7% and baseline Tg of 41.11 ng/mL. This patient had persistent radio-tracer uptake at thyroid bed and the dose of RAI ablation/treatment was increased dose by dose.

Success rate of the 1st 100 and 30 mCi RAI ablation after exclusion of non-LRR patients was 73.6% and 53%, respectively. This result was consistent with studies conducted in similar

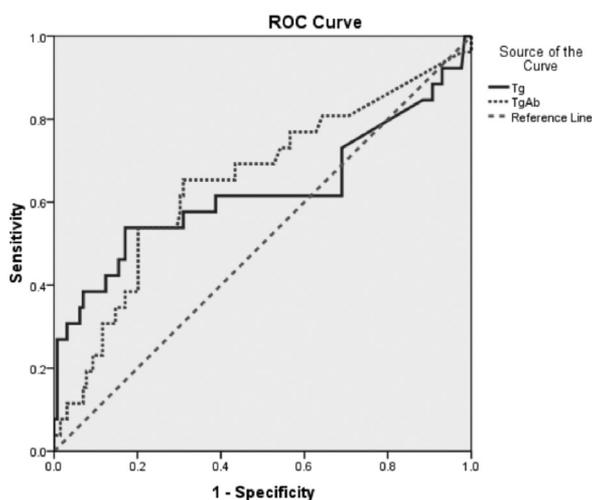


Fig 1. ROC curve of baseline Tg and TgAb for discriminating LRR and non-LRR groups

TABLE 4. Initial characteristics that may predict the true risk of recurrence

Clinical characteristics		LRR	Non-LRR	p-value
No. of lesion, n (%)	Unifocal	110 (85.3%)	20 (76.9%)	0.378 [#]
	Multifoci	19 (14.7%)	6 (23.1%)	
Tumor size, cm. ⁺⁺		2.4 (1.5,3.25)	2.0 (0.65,2.75)	0.096 [§]
Staging, n (%)	I	99 (76.7%)	21 (84.0%)	0.922 [#]
	II	21 (16.3%)	3 (12.0%)	
	III	9 (7.0%)	1 (4.0%)	
24-hr. uptake, (%) ⁺⁺		1.83 (1.1,4.82)	2.41 (0.88,8.16)	0.801 [§]
Tg, ng/mL ⁺⁺		2.87 (1.0,8.46)	11.72 (1.0,46.36)	0.044 [§]
TgAb, IU/mL ⁺⁺		18.1 (10.0,63.0)	91.65 (14.95,293.9)	0.015 [§]

⁺⁺Data are median (Interquartile range), [#] Fischer's Exact test, [§] Mann-Whitney test

population and the same criteria of success ablation.⁶⁻⁷ Even so, success rate of the 2nd RAI ablation/treatment, regardless of RAI dosage was only 40%. The large group contributing to low success rate was patients who received 2nd 150 mCi RAI treatment due to functioning metastasis or poor response to 1st RAI ablation. Therefore, low success rate may partially relate to suboptimal treatment of the 1st dose of 100 mCi RAI for non-LRR patients.

Our previous study showed that the only influential factor of successful RAI ablation in LRR patients was baseline Tg (2.61 in success group and 7.18 ng/mL in failure group, p-value = 0.023)⁸. In this study, in which included both LRR and non-LRR patients with pathologically LRR, successful RAI ablation/treatment was still related to baseline Tg. However, the most influential factor was risk of recurrence. Obviously, none of the 26 non-LRR patients was successfully treated with the 1st ablative dose and only 11 patients had disease remission within 3 sessions of RAI treatment (42.3%). We found that baseline Tg and TgAb had potential to discriminate between LRR and non-LRR patients. However, there was no appropriate cut-off value. Yang et al.⁹ also conducted a study to find the cut-off value of post-operative stimulated Tg to distinguish risk of recurrence in 90 LRR, 283 IRR and 334 HRR patients. Nevertheless, they identified cut-off value of Tg of 2.95 ng/ml to distinguish LRR vs IRR, and 29.5 ng/ml to distinguish IRR vs HRR. We believe that our pathologically LRR patients had less disease burden, consequently, serum Tg may not be high enough to discriminate risk of recurrence.

Regarding presence of functioning metastases, there were 2 patients with distant metastases. A patient with CLN and lung metastases achieved remission after 2 sessions of RAI treatment (30 and 150 mCi) and a patient with bone metastasis had persistent disease after 3 sessions of RAI treatment (100, 200 and 200 mCi). Patients with CLN metastasis required at least 2 sessions of RAI treatment (cumulative dose 250 mCi or more) to be in remission as well. Prospective studies in European countries showed an excellent response of CLN metastases to ablative dose, either 30 or

100 mCi.¹⁰⁻¹¹ Possible explanation may be ethnical difference as outcomes of RAI ablation of studies in Eastern countries are generally lower than that in Western countries.¹²⁻¹⁴ Another possibility was status of BRAF mutation which probably has impact on treatment outcome.⁵ Unfortunately, BRAF mutation testing was not done in all patients.

The strength of this study is capability to reflect routine practice. However, limitation of this study is missing data of the outcome of 2nd and 3rd RAI ablation/treatment.

In conclusion, outcome of RAI ablation/treatment in pathologically defined LRR patients after 3 sessions of RAI is quite excellent (remission rate 82.6%), especially for true LRR patients (remission rate at least 89.9%). Non-LRR patients were found 16.8% and their remission rate was 43.2%. The influential factors of RAI ablation/treatment outcome were baseline Tg, TgAb and risk of recurrence.

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