Factors Influencing the Success of the First Radioiodine Therapy for Differentiated Thyroid Carcinoma

Apichaya Claimon MD*,
Pawana Pusuwan MD*, Benjapa Khiewvan MD*

** Division of Nuclear Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Objective: *Differentiated thyroid cancer (DTC) has a favorable prognosis following treatment by thyroidectomy and subsequent post-operative radioactive iodine therapy (RAIT). However, prognostic factors for the success of the first RAIT remain inconclusive. The aim of the present study was to evaluate prognostic factors for the success of the first RAIT in DTC patients.*

Material and Method: *We retrospectively studied 401 DTC patients who underwent total, near-total and subtotal thyroidectomy followed by high dose RAIT from 1994 to 2004. Successful RAIT was assessed using the following criteria: (a) stimulated serum thyroglobulin (sTg) < 10 ng/ml; (b) negative diagnostic ^{131}I total body scan (DxTBS); and (c) no serial increase in thyroglobulin antibody (TgAb) levels. Factors influencing successful first RAIT were evaluated.*

Results: *In total, 401 patients were enrolled into the present study. Most patients were female (81.5%) and had papillary cell type cancer (74.3%). Median tumor size was 2.55 cm. (range, 0–11 cm). Metastases at cervical node and distant sites were found prior to RAIT in 167 and 26 patients, respectively. The first RAIT doses of 2.96–3.7, 5.5 and 7.4 GBq were administered to 133, 262 and 6 patients, respectively. Overall success rate of the first RAIT was 32.9%. From univariate analysis, female sex, age of <45 years, underwent thyroidectomy without cervical lymph node dissection, no multifocality, free surgical margin, no metastasis and sTg of <20 ng/dl at ablation were prognostic factors. Age of <45 years and sTg of <20 ng/dl at ablation were independent significant prognostic factors (both $p<0.001$) from multivariate analysis.*

Conclusion: *Age below 45 years and sTg below 20 ng/dl at ablation are independent prognostic factors for the success of the first RAIT.*

Keywords: *Differentiated thyroid cancer, prognostic factors, radioiodine therapy, treatment outcome*

J Med Assoc Thai 2017; 100 (2): 207-218
Full text. e-Journal : *http://www.jmatonline.com*

Thyroid carcinoma is a common endocrine cancer with a worldwide incidence of 12.9/100,000 per year, as reported by the Surveillance, Epidemiology and End-Results (SEER) program[1]. Differentiated thyroid cancer (DTC) constitutes approximately 90% of thyroid carcinoma cases[2]. The major type of DTC is papillary thyroid cancer (PTC), followed by follicular thyroid cancer (FTC). With proper treatment, patients have favorable prognosis. In general, treatment includes thyroid surgery followed by radioactive iodine treatment (RAIT), which can ablate both residual thyroid tissue and metastasis.

Correspondence to:
Khiewvan B, Division of Nuclear Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Prannok Road, Siriraj, Bangkok Noi, Bangkok 10700, Thailand.
Phone: +66-2-4196220-1, Fax: +66-2-4127165
E-mail: benjapa.khi@mahidol.ac.th

Successful RAIT improves recurrence-free survival and cancer-specific survival[3]. Moreover, it allows serum thyroglobulin (Tg) to be used as a specific marker for recurrent disease during follow-up[4]. Successful RAIT on the first attempt may improve quality of life and also reduce costs. However, not every patient is successfully treated by the first RAIT. Knowing the factors for successful treatment will guide the clinician to give the most appropriate management of each patient. Treatment and follow-up strategies can be modified for each patient based on risk factors, to minimize radiation toxicity but maintain success rates[5], and is known as risk-modulated therapy. Standard risk factors for disease progression and patient outcome include age, sex, previous exposure to ionizing radiation, tumor size, histology, invasive properties, multifoci tumor, metastasis[2] and successful ablation[6]. Of these, age appeared to be one of the most important prognostic factors[7]. To date, risk factors and stratification have differed, causing controversy, and there has been no consensus[8]. For example, adverse prognosis of regional lymph node metastasis was found in some studies[9,10] but not in others[11,12]. Three and four stages were determined from quantitative TNM[13] and AJCC TNM[14], respectively, due to different criteria and risk factors. Multifoci microcarcinoma is also an example of the controversy for RAI ablation between ATA and EANM guidelines. While the ATA recommends not to treat multifoci microcarcinoma with RAI[15], there is no such exception in the EANM guideline[16]. A variety of risk factors in the literature may have resulted from different subject inclusion criteria, doses of RAI, and diagnostic criteria for the success of RAIT. Examples of different ablation success criteria are sTg cut-off level, which could be as high as 10 ng/dl[17] or undetectable[3]. The objective of the present study was to evaluate factors influencing the success of the first standard high dose RAIT in DTC.

Material and Method

Study population

We retrospectively analyzed data from every patient underwent the first RAIT at the Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine Siriraj Hospital, a tertiary care center, from 1994 to 2004. The study protocol was approved by the Siriraj Institutional Review Board (ethics approval number SI 624/2009). During this period, 870 patients were treated at our institution. No data were available regarding the total number of patients who underwent thyroid surgery or thyroid surgery followed by RAIT during this 10-year period.

Inclusion criteria were patients with histological confirmation of DTC and who underwent at least subtotal thyroidectomy and then received the first high dose RAIT ($\geq$2.96 GBq). Exclusion criteria were inadequate or loss of important data records, such as type of thyroid surgery, pathological report, result of total-body scan (TBS), serum thyroid stimulating hormone (TSH) or Tg. According to these criteria, 469 patients were excluded, and the remaining 401 patients were enrolled in the present study.

Before each RAIT session, a thyroid scan with 74 MBq of ^{99m}Tc-pertechnetate and 24-h ^{131}I uptake using 3.7 Bq were obtained to estimate the amount of residual thyroid tissue after surgery[18]. All patients were prepared by thyroid hormone withdrawal (THW) to obtain optimal stimulated serum TSH, because TSH stimulation increases the ability of thyroid cells to accumulate iodine. Patients were advised to avoid iodine in their diets for about 10 days prior to the RAIT. On the same day of RAI administration, serum T4, TSH, sTg and TgAb levels were measured. Standard fixed doses of RAI were given to all patients, with doses adjusted based on pathological results and evidence of metastasis. An ^{131}I dose of 2.96–3.7 GBq was administered to patients exhibiting no invasive pathological properties or evidence of metastasis (n = 133), while 5.55 GBq was given to patients with invasive properties (such as angiolymphatic, perineural, and extrathyroidal invasion), multifoci tumor or presence of lymph node and/or pulmonary metastasis (n = 262). For patients with osseous metastasis, 7.4 GBq was administered (n = 6)[15]. Post-treatment total body scans (RxTBS) were obtained after 72 h using a gamma camera equipped with a high energy, general purpose collimator to obtain anterior and posterior planar views from head to proximal thighs, as well as static images of the anterior neck, both with and without sternal notch marker. Additional images at areas of interest were acquired as needed. After discharge, all patients were prescribed thyroxine (LT4) at the suppressive therapy dose to repress TSH levels and inhibit tumor growth.

Evaluation of RAIT success

All patients were classified into two groups: successful and unsuccessful. Criteria for successful treatment were defined by all of the following: negative DxTBS; sTg <10 ng/ml; no rising of TgAb in serial measurement; no evidence of residual thyroid remnant or metastasis from clinical, pathological or other imaging investigation (if any); and no death from thyroid cancer.

After 6 months to 1 year post RAIT, serum Tg during TSH suppression (suppressed Tg) was measured. If the levels were $\geq$10 ng/ml, patients were classified into the unsuccessful group and received a second RAIT session. Patients with suppressed Tg levels below 10 ng/ml underwent DxTBS with 74–185 MBq of ^{131}I, after preparation by THW. Again, serum T4, TSH, sTg and TgAb levels were measured. Serum T4, TSH, Tg and TgAb were evaluated by the same laboratory by immunoradiometric assay (IRMA). The cut-off point for positive sTg was at 10 ng/ml. Even though the relatively high cut-off value of sTg using in the present study, the sTg cut-off level at 10 ng/ml was also used in a recent study in Thailand for determination of ablation failure(17). Patients were also considered as ablation failures or exhibiting recurrence if increasing TgAb levels were detected by serial measurement.

The DxTBS images were interpreted without knowledge of any clinical information by two nuclear medicine physicians independently. For conflicting results, a third physician interpreted the data and a consensus among the three nuclear medicine physicians was obtained. Diagnostic criteria for negative DxTBS included no evidence of abnormal ^{131}I uptake at the thyroid bed or elsewhere (Fig. 1), otherwise findings were considered positive(17).

Long-term follow-up

Patients in the unsuccessful group received repeated RAIT until remission, lost follow-up or death. The median follow-up time was 87.98 months (range, 6.14–207.08 months). Treatment with re-surgery or external radiotherapy was given to patients with gross tumor masses or non-RAI avid tumors. Patients in the successful group did not require further RAIT, except for some who developed recurrence. Recurrence was defined as measured by at least one of the following criteria: cytological or pathological confirmed of recurrence; DxTBS; and sTg or suppressed Tg $\geq$ 10 ng/dl or increased TgAb. During follow-up, all patients received a suppressive dose of LT4 as previously described. Serum T4, TSH and LT4 compliance were also recorded. Suppressed Tg and TgAb levels were regularly measured every 6 months and DxTBS was imaged every 5 to 10 years. All patients were followed up until death or lost follow-up. Recurrence-free survival was determined from time of negative DxTBS to time of definite evidence of recurrence. Overall survival was measured from time of the first RAIT until death or lost follow-up (censor date)(3).

Statistical analysis

Both standard and controversial factors for prognosis were evaluated for their significance. Standard risk factors are sex, age at diagnosis (cut-off at 45 years), types of thyroidectomy (total-, near-total-, subtotal-thyroidectomy), histology (papillary, follicular, mixed papillary-follicular, Hurthle cell), variant (follicular, columnar, trabecular), tumor size, multifocality, extrathyroidal extension, invasive properties (none, capsular-, vascular-, lymphatic-, perineural-invasion), surgical margin, known metastasis prior to the first RAIT, serum TSH at ablation (cut off at 30 mIU/L), serum sTg at ablation and dose of the first RAIT. Controversial risk factors include presenting symptoms (thyroid nodule, cervical node enlargement, occult tumor, hoarseness, tracheal obstruction, distant metastasis), cervical or mediastinal lymph node dissection prior to RAIT, hospital undertaking the surgery (Siriraj or other hospitals), how many session(s) of thyroid surgery, 24-h ^{131}I uptake (%), duration from thyroidectomy to RAIT (cut off at 6 weeks), serum T4 and TgAb (cut off at 10 IU/ml) at ablation, amount of thyroid hormone replacement, drug compliance, and duration between the first RAIT and DxTBS.

For statistical analysis, we used SPSS for Windows software package, version 17.0 (SPSS Inc., Chicago, IL, USA). Analysis was performed using Pearson-Chi square test and unpaired t-test for categorical and continuous data, respectively. Statistical significance was attributed to p-values of less than 0.05. Multiple logistic regression analysis was carried out to identify independent prognostic factors for the first RAIT. A receiver operating characteristic (ROC) curve was used to describe the performance of the diagnostic value of sTg at the optimal cut-off level. The

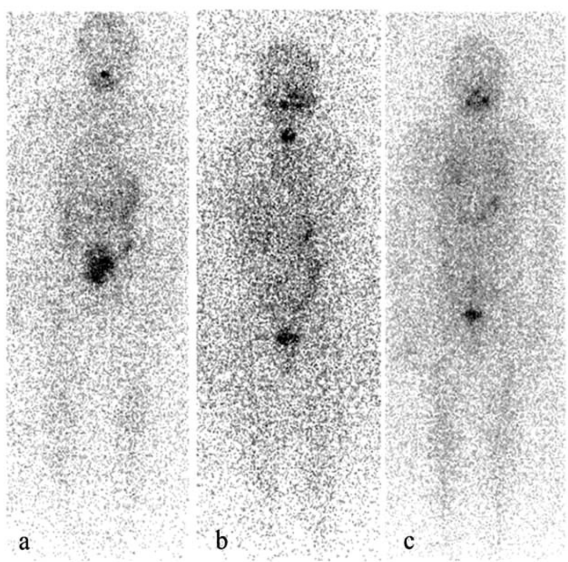

Fig. 1 Interpretation of DxTBS images. Negative study (a), positive uptake at thyroid bed (b) and lungs (c).

Table 1. Patient characteristics

Clinical characteristic	Successful (n = 132) (%)	Unsuccessful (n = 269) (%)	*p*-value
Median age (range, years)	36.5 (18-73)	42 (10-89)	< 0.001*[b]
Age (<45/>45 years)	98/34	149/120	< 0.001*[a]
Gender (female/male)	115/17	212/57	0.044*[a]
Pathology (PTC/FTC/mixed/Hurthle)[c]	93/34/3/2	205/49/11/3	0.287[a]
Median tumor size (range, cm.)[c]	2.7 (0.2-7.5)	2.5 (0-11)	0.549[b]
Thyroidectomy (total/near-total/ subtotal)	105/21/6	202/43/24	0.287[a]
Cervical LN dissection[c]	(n = 131)	(n = 264)	0.023*[a]
	45 (34.3)	138 (52.3)	
Multifocality[c]	(n = 106)	(n = 207)	0.043*[a]
	43 (52.3)	109 (63.6)	
Extrathyroidal extension[c]	(n = 104)	(n = 207)	0.051[a]
	23 (22.1)	68 (32.9)	
Free resection margin[c]	(n = 84)	(n = 168)	0.039*[a]
	60 (71.43)	103 (61.31)	
Metastasis prior to first RAIT	44 (33.3)	149 (55.4)	<0.001*[a]
Stim Tg at time of ablation[c,d]	(n = 88)	(n = 165)	
Median (range), (ng/dl)	3.6 (0-191.8)	35.3 (0-63,800)	0.114[b]
STg (<20/>20 ng/dl)	70/8	61/104	<0.001*[a]
Median first RAI dose, mCi	150 (80-150)	150 (80-200)	0.289[b]

* Significant *p*-values <0.05
[a] Chi-square test
[b] Unpaired t-test
[c] Data missing in some patients
[d] Analyzed after exclude patients with TgAb >10 IU/ml

curve was constructed by computing sensitivity and specificity of the sTg cut-off in predicting successful first RAIT. Recurrence-free survival of the successful group was evaluated by a Kaplan–Meier curve. Overall survival was evaluated and compared between groups. Cohen's kappa (square kappa) statistics were used for the calculation of inter-observer agreement regarding the DxTBS interpretation between two observers. The kappa values were interpreted as follows: <0.20 poor agreement; 0.21–0.40 fair agreement; 0.41–0.60 moderate agreement, 0.61–0.80, good agreement; and 0.81–1.00 excellent agreement[18].

Results

From 1994 to 2004, 870 patients received the first RAIT at our institution. Of these, 469 patients were excluded owing to incomplete data (n = 304), receiving RAIT doses of less than 2.96 GBq (n = 137), receiving prior RAIT from other hospital (n = 16), underwent external radiotherapy at neck before DxTBS (n = 10) and coexistent medullary thyroid cancer (n = 2). A total of 401 patients were included to the analysis.

The mean age at diagnosis was 41.9 years (range, 10–89 years), and 81.5% of patients were women. The most common presenting symptom was

Table 2. Prognostic factors for the success of the first RAIT

Factors	Univariate, *p*-value	Crude OR [95% CI]	Multivariate, *p*-value	Adjusted OR [95% CI]
Sex, female	0.044*	1.82 [1.01 to 3.27]	0.316	1.40 [0.73 to 2.71]
Age, < 45 years	<0.001*	2.31 [1.47 to 3.67]	0.005*	2.11 [1.26 to 3.54]
Lymph node dissection, no	0.023*	2.04 [1.32 to 3.14]	0.704	0.85 [0.36 to 2.00]
Multifocality, no	0.043*	1.63 [1.01 to 2.62]	0.877	0.89 [0.37 to 2.16]
Resection margin, free	0.039*		0.434	
Free		2.85 [1.30 to 6.24]		1.80 [0.58 to 5.61]
Close or very close		3.49 [1.32 to 9.27]		2.66 [0.81 to 8.75]
Metastasis, no	<0.001*	2.48 [1.61 to 3.83]	0.221	1.70 [0.73 to 3.98]
Stim-Tg at 1st RAIT, < 20 ng/dl	<0.001*	14.92 [6.72 to 33.10]	<0.001*	12.08 [5.25 to 27.80]

**p*-values < 0.05.

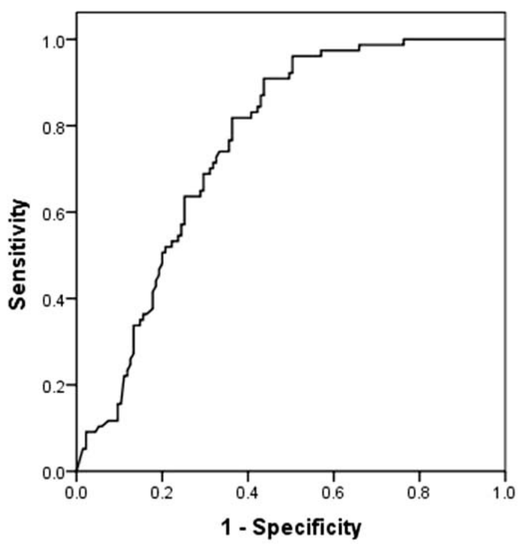

Fig. 2 ROC curve of sTg at the first RAIT in discriminating patients who achieved successful and unsuccessful from the first RAIT. The area under the curve for a perfect discriminatory test would be 1.0; which gave a value of 0.759 in this curve. The sTg cut-off at 20 ng/ml produced the highest sensitivity and specificity for prediction of the first RAIT outcome.

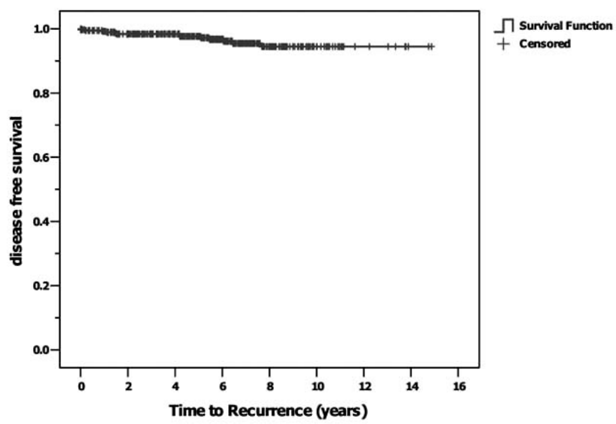

Fig. 3 Cumulative disease-free survival curve in 132 patients after the success of the first RAIT. One patient was lost to follow-up just after performing DxTBS.

thyroid nodule (78.1%). The majority of histology was papillary cell type (74.3%), and non-aggressive variant (97.5%). Total thyroidectomy was performed in 76.6% of patients. Fifty-two percent of patients underwent thyroidectomy at Siriraj Hospital. Most patients (62.1%) underwent only one session of thyroid surgery before receiving the first RAIT (range, 1–4 sessions). Cervical lymph node dissection was performed in 46.3% of patients and 89.1% were positive for cervical node metastasis. The most common type of cervical node surgery was node excision (48.6%), followed by unilateral radical neck dissection (36.1%). Only two patients underwent mediastinal node dissection. Median tumor size was 2.55 cm. (range, 0–11 cm.). Lack of pathological invasive properties such as multifocality, extrathyroidal-, thyroid capsular-, vascular-, lymphatic-, nerve-invasion, and tumor at the surgical margin were noted in 51.4%, 70.7%, 62.5%, 81.4%, 92.7%, 97.0% and 64.7% of patients, respectively. Two hundred and eight patients (51.9%) had no evidence of metastasis. Established metastases were noted prior to first RAIT at cervical nodes (n = 167), lung (n = 8), bone (n = 8), mediastinal node (n=1), and mixed regions (n = 9). Most patients (65.3%) received 5.55 GBq, followed by 2.96–3.7 GBq (33.2%) and 7.4 GBq (1.5%) for the first RAIT.

Two physicians agreed on DxTBS interpretation in 353 patients; the resulting kappa value of 0.752 was consistent with good agreement between the two observers[18].

According to the criteria used in the present study, successful first RAIT was achieved in 132 patients (32.9%). The successful group was composed of 66.67% of patients without metastasis, 32.58% with cervical node metastasis and 0.75% with mediastinal node metastasis. The unsuccessful group was composed of 269 from 401 (67%) patients, determined by positive DxTBS (36.4%), positivity for both DxTBS and sTg (19.2%), positive sTg (11.2%) and rising of TgAb (0.2%). In the unsuccessful group, 46.1% of patients had cervical node metastasis, followed by 44.6% without metastasis, 3% with lung metastasis, 3% with bone metastases and 3.3% with multiple regions metastases. The baseline characteristics of patients in the two groups were compared in Table 1.

Characteristic data of both groups were analyzed to evaluate prognostic factors. From logistic regression (univariate) analysis, seven factors were significant for success of the first RAIT as follows: female sex, age of < 45 years, underwent thyroidectomy without cervical lymph node dissection, no multifocality, free surgical margin, no metastasis and sTg < 20 ng/dl. Other parameters such as presenting symptoms, age (without cut-off), pathology, types of thyroidectomy, hospital of thyroid surgery, number of thyroid surgery prior to the first RAIT, 24-hr ^{131}I uptake, duration from thyroidectomy to RAIT, tumor size, extrathyroidal extension, invasive property, serum T4, TSH and TgAb at ablation, sTg (without cut-off), doses of the first RAIT, amount of thyroid hormone replacement and drug compliance and duration between the first RAIT and DxTBS were not significant.

We further evaluated the 7 significant prognostic factors by multiple logistic regression analysis for their independency. The result showed that age of <45 years and sTg <20 ng/dl at ablation were independent significant prognostic factors (both $p<0.001$). The 5 other tested factors were not significant, (Table 2).

The mentioned sTg cut-off value at 20 ng/dl was derived after exclusion of patients with negative sTg but positive TgAb (TgAb >10 IU/ml) and then receiver operating characteristic (ROC) analysis was performed. After exclusion, there were 88 and 165 patients in the successful and unsuccessful groups, respectively. The sTg cut-off value at 20 ng/dl was the best cut-off level to predict ablation outcome, giving sensitivity and specificity values of 90.90% and 45.29%, respectively, (Fig 2).

To evaluate long term outcome, all of the enrolled patients were followed up with a median follow-up time of 87.98 months (range 6.14–207.08 months). In total, 240 patients were followed up for longer than 5 years; of these, 26 patients were followed for more than 10 years. Mean disease-free survival time of the successful group (n = 132), as calculated by the Kaplan–Meier method, was 14.3 years, (Fig 3). Sixteen of patients with treatment success (12.1%) developed recurrence, with a mean time of recurrence at 3.20±2.54 years. The baseline characteristics of patients who developed recurrence were non-metastasis (10/16 patients) and cervical node metastasis (6/16 patients). Sites of recurrence were at the thyroid bed (68.8%), cervical node (12.5%), mediastinum (6.3%) and multiples of these areas (12.5%). All patients with recurrence received repeat RAIT for 1.88±1.20 sessions (range 1–5 sessions). Mean accumulative dose was 15.21±7.19 GBq (range 6.66–33.30 GBq). One of these patients received external radiation at neck after the fourth RAIT showed non-iodine-avid metastatic lymph nodes.

In the unsuccessful group (269 patients), there were 46.1% with cervical node metastasis, 44.6% without metastasis, 3% with lung metastasis, 3% with bone metastases and 3.3% with multiple regions metastases. Repeat RAIT were given to 238 patients until they became free of disease. Sixty-eight patients were lost during the follow-up, thus 170 patients were available for evaluation of repeated RAIT success. The success was eventually achieved in 89/170 patients (52.4%); however, two of these patients had recurrence at the thyroid bed later on. The median number of repeat RAIT sessions given to this group was 1 session (range 0–10 sessions), with median cumulative doses of 11.1 GBq (range 6.66–33.30 GBq). Eighteen patients received an accumulative dose of ≥37 GBq, but none developed serious adverse effects or complications. Two patients needed external radiotherapy for the treatment of metastasis at the brain and neck. Causes of RAIT cessation included no ^{131}I avidity (n = 17), transfer to another hospital (n = 14), poor performance status (n = 10), death (n = 2) and poor response to RAIT (n = 1). Five patients in the unsuccessful group died during the follow-up period with mean duration from ablation to censor of 43.99±21.29 months (range, 8.51–63.21 months).

Overall survival time was determined by time to death or time to censor (lost follow-up). Six patients (five from the unsuccessful group) died during follow-up; however, the exact causes of death were unknown. The successful group had a mean overall survival time of 99.09 months (range, 6.14–207.08 months). Conversely, the unsuccessful group had a shorter mean overall survival time of 85.91 months (range, 8.51–202.84 months), but there was no statistically significant difference in mean survival time between the groups ($p = 0.467$). Fig 4 summarizesd the treatment outcome and follow-up in all 401 patients.

Owing to the relatively low overall success rate, the authors attempted to evaluate the success of the first RAIT in the subgroup of low risk patients. Patients with metastasis, aggressive variants, invasion of tumor to vascular or extrathyroidal structures, and incomplete tumor resection were excluded. Moreover, patients who had received subtotal thyroidectomy were also excluded, owing to suboptimal surgery. There were 139 patients remaining after the exclusion. The success rate of the low risk subgroup was 47.5%.

Discussion

It is known that DTC has favorable prognosis after proper treatment with adequate thyroid surgery follow by RAIT. There are multiple prognostic stratification schemes for DTC, the most popular one is the latest edition (seventh) of the AJCC TNM (tumor/node/metastasis) staging system that classified patients into four stages (stages I–IV). The newly developed quantitative TNM (QTNM) method that is used to categorize patients into three risk stages (low-, intermediate-, and high-risk) is more simple and correlates with disease-free survival (DFS) and cancer-specific survival (CSS)[13]. These two staging systems were developed from many prognostic factors, such as histology, age (with 45 years of age being the cut-off), tumor size, extrathyroidal extension and regional lymph node metastasis. The MACIS staging system is another staging system from the Mayo Clinic that has added factors of completeness of resection and invasion[19]. Thus far, these staging systems relate to recurrence and death from thyroid cancer; but none can predict the first RAIT outcome because the relevant prognostic factors remain inconclusive.

Previous studies showed age, sex, cell type[20], staging[21], tumor size[20,22], node metastasis[3,10], distant metastasis[3], ablation dose[9] and sTg at ablation[3,22] as significant prognostic factors for the successful ablation; however, these results were discrepant and underwent no systematic analysis. Moreover, prognostic factors may differ if different criteria for the successful treatment were applied. Successful treatment or remission criteria were recently changed. STg cut-off to determine remission varied in the literature from 10 ng/dl[17], 2 ng/dl[20,23], 1 ng/dl[21] to undetectable[3]. Historically, DxTBS was almost always performed in every patient; but currently, neck ultrasonography is substituted for DxTBS[21]. In the present study, we used rather conservative criteria for successful RAIT composed of negative DxTBS and sTg levels below 10 ng/dl, as it harmonized with our real clinical practice at that time. We also categorized patients with rising serial TgAb into unsuccessful or recurrence groups because there is evidence that increased TgAb can be used as a surrogate for persistent/recurrent disease[24].

The present study demonstrated the seven significant prognostic factors for the success of the first RAIT, which were female sex, age of <45 years, underwent thyroidectomy without cervical lymph node dissection, no multifocality, free surgical margin, no metastasis and sTg <20 ng/dl at ablation. Two of these (age <45 years and sTg <20 ng/dl at ablation) are independent prognostic factors.

It is well-recognized that advanced age at diagnosis strongly correlates with poorer prognosis for recurrence and CSS. The age factor complemented various staging and prognostic systems for DTC[25]. The AJCC TNM staging system categorizes patient age <45 years into stages I and II, and >45 years into stages I–IV[15]. The mortality rate increases 5.4 times for age >45 years compared with the lower age group[26]. However, the study of Mazurat et al. showed that using the threshold at 55 year-old was better than at 45 year-old[11]. The cut-off at 45 years was still applied in the majority of studies and staging systems. The present study showed the significance of age at diagnosis with the threshold at 45 years to the first RAIT outcome. Without applying an age cut-off, there was no significance of age to the success of ablation, which was compatible with the study of Verburg et al[24]. However, Haymart et al reported confounding factors that may relate to age, such as nutritional status, DNA repair ability, function of sodium-iodide symporter, TSH receptors, immune function and variation of genetic mutation[25]. These factors should be considered as they may influence and alter the significance of the age factor.

Baseline sTg at ablation may reflect the amount of residual thyroid tissue/tumor and metastasis, and may correlate with the outcome of ablation. A previous study confirmed the significance of sTg at ablation to ablation outcome[3], but the cut-off point of sTg was not evaluated. A recent study showed sTg at the time of ablation as well as tumor size, as the predictive factors for remnant ablation[22]. Our study confirmed the significant relationship between the cut-off value of sTg and the outcome of the first RAIT. We found the most suitable cut-off at 20 ng/ml, which was close to a recent study that indicated the best cut-off sTg at 18 ng/dl[23] and 28 ng/dl[27]. STg cut-off at 20 ng/ml gives a high sensitivity of 90.90% but a low specificity of 45.29% for predicting the first ablation success. Conditions that may interfere with the accuracy of sTg cut-off include level of TSH, methods to stimulate TSH (by thyroid hormone withdrawal or rhTSH administration) and presence of TgAb. Another study using rhTSH as a method of TSH stimulation found the significance of sTg to the ablation outcome at a lower cut-off point of 5 ng/dl[21].

In the present study, the successful group had a DFS of 14.3 years with a recurrence rate of 12.2%. However, the unsuccessful group that was able to achieve remission after repeated RAIT sessions had only 2.2% (2/89 patients) recurrence rate. Recurrence in the two patients was found within 2 years, and the thyroid bed was the site of recurrence. Our result did not correlate with the study of Verburg et al that reported the significantly higher 10-year DFS in the ablation success group compared with the ablation failure group (95% vs. 78%, $p = 0.007$)[3]. Mazzaferri et al[28] showed a higher recurrence rate during longer follow-up time. The 40-year recurrence rate was around 35%, and a 23.5% recurrence rate was shown at 16.6 years follow-up. The majority of recurrence was observed within the first decade after treatment. The lower recurrence rate of our study could have resulted from the relatively high cut-off level of sTg (to indicate remission) and shorter follow-up time. A further study using an optimal sTg cut-off for remission following many guidelines (ATA, etc.) may be warranted to evaluate the recurrence rate after the successful first RAIT. Additionally, recurrent cancer can be detected until 40 years after treatment, thus a longer follow-up time is necessary.

The present study showed an insignificant difference in overall survival between groups, which was not consistent with the literature[3]. A possible explanation could be that numerous patients were lost to follow-up in a short period; thus, the survival curve reflects the censor date, not the true survival. Moreover, the exact cause of death in our six patients could not be obtained. Hence, the derived survival curve cannot

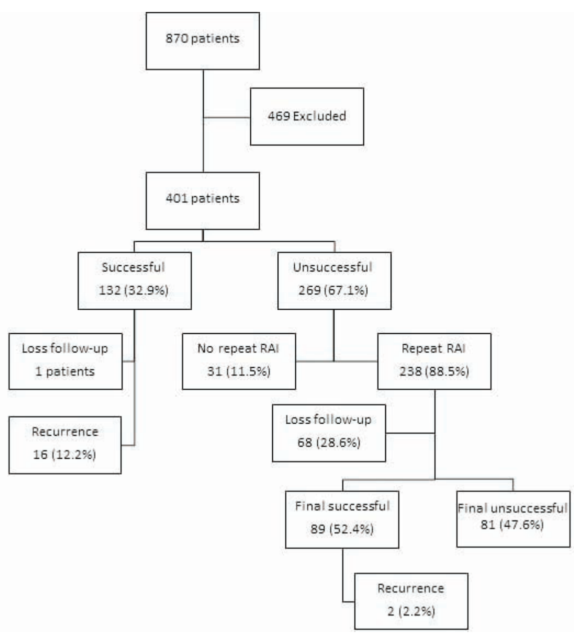

Fig. 4 Summary of the first RAIT outcome in 401 patients, result of repeated RAI treatment in unsuccessful group and recurrence of successfully treated patients.

imply thyroid cancer-specific survival. Further study may be needed to evaluate the impact of the successful first RAIT to disease specific recurrence and survival.

According to the result, we suggest modulation of treatment and follow-up strategies based on each patient's risk factors to achieve a higher success rate. Treatment modulation for high-risk patients should be more aggressive, such as thorough imaging investigations prior to the first RAIT to find any possible hidden metastasis, increased RAIT dose, and more frequent follow-up. Increasing RAIT doses in high risk patients who have potential for understaging may increase the success rate but should be traded-off with the adverse effects resulting from radiation. Serial blood sampling for calculation of maximal safe dose should be done in such cases. The safety and efficacy of this method was proved in patients with non-responsive residual disease[29]. Also, dosimetry-based RAIT may be used to achieve higher success rates by maximizing tumor absorbed dose[30]. Successful RAIT at the first attempt is important because it may improve quality of life, prevent additional radiation exposure from repeated RAIT, reduce costs, and shorten the waiting list of admission. Ablation failure patients need close follow-up or further investigations. About half of patients who failed from the first RAIT could not become free of disease from the repeat doses of RAIT[3]. Furthermore, some patients may develop radioiodine refractory disease and need re-surgery or external radiotherapy.

Remission criteria have an effect on treatment success rates. The present study used remission criteria of negative DxTBS and sTg with a cut-off at 10 ng/dl. Though most studies used a lower sTg cut-off, there were evidences that positive sTg below 10 ng/dl without evidence of structural disease resulted in a reluctance to administer repeat RAIT because it may be from minimal, non-pathological residual thyroid tissue or may decrease over time without any specific treatment[31]. Our study, using a criteria of sTg cut-off at 10 ng/dl, negative DxTBS and no increase in serial TgAb, gave a success rate from the first RAIT of 32.9%, which was quite unsatisfactory. While Verburg et al observed success from negative DxTBS and sTg < 1 ng/ml a higher successful ablation rate of 61%[3] in a group of patients with mixed risk. The successful ablation rate in a low-risk group using criteria of negative DxTBS and sTg < 2 ng/ml was increased to 73.5%[22]. The possible explanation for the inferior success rate in our study is patient selection bias. Low-risk patients were not included in the present study because they were treated with low-dose RAI (1.11 GBq); thus the patients enrolled in the study were generally in a higher risk group. The study of Tresoldi et al confirmed that the successful ablation rate was significantly lower in intermediate-risk patients, compared with the low-risk group studied (76.2% and 95.1%, respectively; $p = 0.025$)[21].

Many of the enrolled patients in our study had unfavorable prognostic factors, such as multifocality (48.6%), extrathyroidal extension (29.3%), positive resection margin (35.3%) and metastasis (48.1%). In the present study, none of the patients with lung or bone metastases achieved successful RAIT at the first attempt. Lymph node metastasis was found to be a predictor for treatment failure[32]. The high percentage of patients with unfavorable factors may be caused by delayed diagnosis and surgery resulting from low patient awareness or limited access to public health care at that time. In addition, approximately half of our patients were referred from other hospitals, causing a delay in the initiation of the first RAIT. Yu et al. compared the clinical outcome of patients treated a long time ago versus those who treated in recent years. They found a trend of progressively improved prognosis over a 15-year period, probably because of earlier diagnosis, lower staging and better diagnostic tools in the recent years[33].

According to the 2009 ATA guidelines, the initial surgical procedure should be near-total or total thyroidectomy[15]. However, the present study also included patients who received subtotal thyroidectomy (7.5%), which might have lowered the success rate. Moreover, we observed that many patients were under-staged due to un-identified metastasis at the ablation time. Thus, the given RAI doses were lower than they should have been, and this may have also lowered the success rate. Pre-ablation, low-dose TBS can be performed instead of ^{99m}Tc pertechnetate thyroid scans to prevent under-staging, and is currently being used in some centers in Thailand; however, this should be weighted with additional radiation exposure to patients, timing, work load, cost and possible stunning effect. Subgroup evaluation of low-risk patients who had received at least near-total thyroidectomy in the present study showed an increasing of the successful first RAIT rate to 47.5%.

The study is limited because of its retrospective method. The median follow-up time was shorter than that of the other studies because many patients (68/238 patients) were lost during follow-up even though they were not yet in remission. The prognostic consequence of the first RAIT success with respect to thyroid cancer-specific survival cannot be evaluated because causes of death could not be identified. To solve this problem, a prospective trial with long-term follow-up is required. Moreover, prognostic factors from this study may be not applicable to patients receiving low-dose RAIT because we included patients treated with high-dose RAIT. We suggest that prognostic factors of successful low-dose RAIT in low-risk patients should be studied separately. Finally, successful ablation criteria and mode of investigation changes rapidly, and this study used rather loose criteria for remission and recurrence. It should be noted that the significance of prognostic factors may also be affected by different criteria.

Conclusion

Age below 45 years and sTg below 20 ng/dl at ablation are significant independent prognostic factors for the success of the first RAIT. The success rate of the first RAIT in the present study was 32.9%. Of those patients who could not acquire the success from the first RAIT, 52.4% could achieve complete remission from the repeated RAIT sessions. Moreover, recurrent disease after complete remission is possible. Modification of treatment to a higher initial dose of RAIT and follow-up regimens are advised based on each patient's risk factors to ensure better ablation results and long-term outcome.

What is already known on this topic?

DTC has a favorable prognosis following treatment by thyroidectomy and subsequent RAIT. However, the risk factors for the success of RAIT within the first time is inconclusive.

What this study adds?

The result of the present study showed that age below 45 years and sTg below 20 ng/dl at ablation are independent prognostic factors for the success of the first RAIT.

Acknowledgment

The authors wish to acknowledge the assistance of Miss Julaporn Pooliam in the study design and statistical analysis. The authors have been supported by the "Chalermphrakiat Grant" at the Faculty of Medicine Siriraj Hospital, Mahidol University.

Potential conflicts of interest

None.

References

1. Surveillance, Epidemiology, and End Results (SEER) Program. SEER data, 1973-2011 [Internet]. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014 [cited 2015 Apr 20]. Available from: www.seer.cancer.gov
2. Aras G, Gultekin SS, Kucuk NO, Genc Y. Is thyroglobulin the stronger indicator for progressive disease than the other conventional factors in same age patient groups with differentiated thyroid cancer? Nucl Med Commun 2007; 28: 907-13.
3. Verburg FA, de Keizer B, Lips CJ, Zelissen PM, de Klerk JM. Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients. Eur J Endocrinol 2005; 152: 33-7.
4. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994; 97: 418-28.
5. Pryma DA, Mandel SJ. Radioiodine therapy for thyroid cancer in the era of risk stratification and alternative targeted therapies. J Nucl Med 2014; 55: 1485-91.
6. Doi SA, Woodhouse NJ, Thalib L, Onitilo A. Ablation of the thyroid remnant and I-131 dose in differentiated thyroid cancer: a meta-analysis revisited. Clin Med Res 2007; 5: 87-90.
7. Shah JP, Loree TR, Dharker D, Strong EW, Begg C, Vlamis V. Prognostic factors in differentiated carcinoma of the thyroid gland. Am J Surg 1992; 164: 658-61.
8. National Cancer Institute: PDQ thyroid cancer treatment [Internet]. Bethesda, MD: National Cancer Institute; 2015 [cited 2015 Apr 20]. Available from: http://cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional

9. Amin A, Badwey A, El Fatah S. Differentiated thyroid carcinoma: an analysis of 249 patients undergoing therapy and aftercare at a single institution. Clin Nucl Med 2014; 39: 142-6.
10. Sengöz T, Sürücü E, Demir Y, Derebek E. The effects of the factors related to the patient and the disease on the performance of ablation therapy in patients with differentiated thyroid cancer who have received I-131 ablation therapy. Mol Imaging Radionucl Ther 2012; 21: 103-9.
11. Mazurat A, Torroni A, Hendrickson-Rebizant J, Benning H, Nason RW, Pathak KA. The age factor in survival of a population cohort of well-differentiated thyroid cancer. Endocr Connect 2013; 2: 154-60.
12. Coburn MC, Wanebo HJ. Prognostic factors and management considerations in patients with cervical metastases of thyroid cancer. Am J Surg 1992; 164: 671-6.
13. Mankarios D, Baade P, Youl P, Mortimer RH, Onitilo AA, Russell A, et al. Validation of the QTNM staging system for cancer-specific survival in patients with differentiated thyroid cancer. Endocrine 2014; 46: 300-8.
14. Edge SB. American Joint Committee on Cancer: AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
15. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19: 1167-214.
16. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJ, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2008; 35: 1941-59.
17. Thientunyakit T, Pusuwan P, Tuchinda P, Khiewvan B. The correlation of post-operative radioiodine uptake and Tc-99m pertechnetate thyroid scintigraphy and the result of thyroid remnant ablation. J Med Assoc Thai 2013; 96: 1199-207.
18. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med 2005; 37: 360-3.
19. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993; 114: 1050-7.
20. Fatima N, uz ZM, Ikram M, Akhtar J, Islam N, Masood Q, et al. Baseline stimulated thyroglobulin level as a good predictor of successful ablation after adjuvant radioiodine treatment for differentiated thyroid cancers. Asian Pac J Cancer Prev 2014; 15: 6443-7.
21. Tresoldi AS, Sburlati LF, Rodari M, Schinkelshoek M, Perrino M, De Leo S, et al. Radioiodine ablation with 1,850 MBq in association with rhTSH in patients with differentiated thyroid cancer. J Endocrinol Invest 2014; 37: 709-14.
22. Saengsuda Y. Radioiodine remnant ablation in low-risk differentiated thyroid cancer. J Med Assoc Thai 2013; 96: 614-24.
23. Kendler DB, Vaisman F, Corbo R, Martins R, Vaisman M. Preablation stimulated thyroglobulin is a good predictor of successful ablation in patients with differentiated thyroid cancer. Clin Nucl Med 2012; 37: 545-9.
24. Verburg FA, Luster M, Cupini C, Chiovato L, Duntas L, Elisei R, et al. Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: a clinical position statement. Thyroid 2013; 23: 1211-25.
25. Haymart MR. Understanding the relationship between age and thyroid cancer. Oncologist 2009; 14: 216-21.
26. Sampson E, Brierley JD, Le LW, Rotstein L, Tsang RW. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. Cancer 2007; 110: 1451-6.
27. Ciappuccini R, Hardouin J, Heutte N, Vaur D, Quak E, Rame JP, et al. Stimulated thyroglobulin level at ablation in differentiated thyroid cancer: the impact of treatment preparation modalities and tumor burden. Eur J Endocrinol 2014; 171: 247-52.
28. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001; 86: 1447-63.
29. Lee JJ, Chung JK, Kim SE, Kang WJ, Park do J, Lee DS, et al. Maximal safe dose of I-131 after failure of standard fixed dose therapy in patients with differentiated thyroid carcinoma. Ann Nucl Med 2008; 22: 727-34.

30. Fatholahi L, Tabeie F, Pashazadeh AM, Javadi H, Assadi M, Asli IN. One size does not fit all: the merit of absorbed doses to the blood in 131I therapy for differentiated thyroid carcinoma. Health Phys 2015; 108: 53-8.
31. Frank RW, Middleton L, Stack BC Jr, Spencer HJ, Riggs AT, Bodenner DL. Conservative management of thyroglobulin-positive, nonlocalizable thyroid carcinoma. Head Neck 2014; 36: 155-7.
32. Lim I, Kim SK, Hwang SS, Kim SW, Chung KW, Kang HS, et al. Prognostic implication of thyroglobulin and quantified whole body scan after initial radioiodine therapy on early prediction of ablation and clinical response for the patients with differentiated thyroid cancer. Ann Nucl Med 2012; 26: 777-86.
33. Yu XF, Wang WB, Teng XD, Wang HY, Chen X, Wang HH, et al. Clinicopathological and prognostic analysis of follicular thyroid carcinoma in a single institute over a 15-year period. Eur J Surg Oncol 2014; 40: 869-74.

ปัจจัยที่ส่งผลต่อความสำเร็จของการรักษาโรคมะเร็งไทรอยด์ชนิด well-differentiate ด้วยไอโอดีนรังสีภายในครั้งแรก

อภิชญา คล้ายมนต์, ภาวนา ภูสุวรรณ, เบญจาภา เขียวหวาน

วัตถุประสงค์: *มะเร็งไทรอยด์ประเภท well-differentiated มีการพยากรณ์โรคที่ดีเมื่อได้รับการรักษาด้วยการผ่าตัดต่อมไทรอยด์และตามด้วยการรักษาด้วยไอโอดีนรังสี แต่ทั้งนี้ยังไม่เป็นที่แน่ชัดว่าปัจจัยใดบ้างที่ส่งผลต่อความสำเร็จในการรักษาด้วยไอโอดีนรังสีภายในครั้งแรก การศึกษานี้จึงมีวัตถุประสงค์เพื่อหาปัจจัยที่ส่งผลต่อความสำเร็จในการรักษาดังกล่าว*

วัสดุและวิธีการ: *ทำการศึกษาย้อนหลังผู้ป่วยมะเร็งไทรอยด์ประเภท well-differentiated จำนวน 401 ราย ที่ได้รับการผ่าตัดต่อมไทรอยด์ชนิด total, near-total หรือ subtotal และตามด้วยการรักษาด้วยไอโอดีนรังสีปริมาณสูงในช่วงระหว่างปี พ.ศ. 2537-2547 แล้วประเมินความสำเร็จของการรักษาโดยใช้เกณฑ์ดังนี้ (1) stimulated serum thyroglobulin (sTg) มีค่าน้อยกว่า 10 ng/ml; (2) diagnostic ^{131}I total body scan (DxTBS) มีผลเป็นลบ และ (3) ไม่มีการเพิ่มขึ้นของระดับ thyroglobulin antibody (TgAb) แล้วทำการวิเคราะห์หาปัจจัยที่ส่งผลต่อความสำเร็จของการรักษา*

ผลการศึกษา: *จากผู้ป่วยทั้งหมด 401 รายนั้น ส่วนใหญ่ของผู้ป่วยเป็นเพศหญิง (ร้อยละ 81.5) และเป็นมะเร็งไทรอยด์ชนิด papillary (ร้อยละ 74.3) ขนาดก้อนมะเร็งมีค่ามัธยฐาน 2.55 ซม. (ตั้งแต่ 0—11 ซม.) พบการแพร่กระจายไปที่ต่อมน้ำเหลืองบริเวณลำคอ และที่บริเวณห่างไกลก่อนการรักษาด้วยไอโอดีนรังสีในผู้ป่วย 167 และ 26 ราย ตามลำดับ ผู้ป่วยจำนวน 133, 262 และ 6 รายได้รับการรักษาด้วยไอโอดีนรังสีรังสีปริมาณ 2.96—3.7, 5.5 และ 7.4 GBq ตามลำดับ ร้อยละ 32.9 ของผู้ป่วยประสบผลสำเร็จจากการรักษาด้วยไอโอดีนรังสีภายในครั้งแรก จากการวิเคราะห์แบบ univariate นั้นพบว่าปัจจัยที่มีความสำคัญทางสถิติต่อความสำเร็จในการรักษาได้แก่ เพศหญิง, อายุต่ำกว่า 45 ปี, ผ่าตัดต่อมไทรอยด์แต่ไม่ได้รับการผ่าตัดต่อมน้ำเหลืองบริเวณคอร่วมด้วย, ไม่พบมะเร็งหลายจุดในต่อมไทรอยด์, ไม่พบมะเร็งที่ขอบชิ้นเนื้อที่ผ่าตัด, ไม่มีการแพร่กระจาย และระดับ sTg ที่ตรวจก่อนการรักษาด้วยไอโอดีนรังสีมีค่าต่ำกว่า 20 ng/dl และพบว่าอายุที่ต่ำกว่า 45 ปี และระดับ sTg ที่ตรวจก่อนการรักษาด้วยไอโอดีนรังสีมีค่าต่ำกว่า 20 ng/dl นั้นเป็นปัจจัยที่มีความสำคัญอย่างอิสระต่อปัจจัยอื่น (ค่า $p<0.001$) เมื่อวิเคราะห์แบบ multivariate*

สรุป: *อายุที่ต่ำกว่า 45 ปี และระดับ sTg ที่ตรวจก่อนการรักษาด้วยไอโอดีนรังสีมีค่าต่ำกว่า 20 ng/dl นั้นเป็นปัจจัยอิสระที่มีความสำคัญทางสถิติต่อความสำเร็จในการรักษาด้วยไอโอดีนรังสีภายในครั้งแรก*
