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Prevalence and determinants of misclassification of the risk of recurrence of differentiated thyroid cancer after the first ^{131}I post-therapeutic scintigraphy

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Abstract

^{131}I total body scintigraphy has long been used for imaging the extent of disease in differentiated thyroid cancer (DTC). Currently, the risk of recurrence of DTC is stratified into low-, intermediate-, and high-risk based on pathological findings. In practice, ^{131}I post-therapeutic scintigraphy after the first ^{131}I treatment tends to detect additional cervical lymph node metastasis and/or distant functioning metastasis, which can guide the treatment, hence having a high impact on clinical outcome. The aim of our study is, therefore, to explore the prevalence of misclassification of the risk stratification system after the first dose of ^{131}I therapy and to determine the factors associate with it. Misclassification was defined as the difference of the risk stratification between the one based on pathological findings and the other based on ^{131}I post-therapeutic scintigraphy. Total of 360 patients was included. Of these, 57 patients were misclassified (15.8%). That is, 39 (10.8%) in the low-risk group should be in the intermediate group, 2 (0.6%) patients in the low-risk group should be in the high risk, and 16 (4.4%) patients in the intermediate group should be in the high-risk group. The baseline stimulated thyroglobulin (Tg) level of ≥ 10 ng/mL showed a strong association with the misclassification (OR=3.2, 95%CI: 1.4 to 7.5; p=0.007). In conclusion**,** detection of considerable number of misclassification in risk stratification of DTC has raised awareness of the under-prescription of ^{131}I doses. Attention should be paid to patients with a high baseline stimulated Tg level of greater than 10 ng/mL.

Keywords: Differentiated thyroid cancer, Radioiodine, ^{131}I scintigraphy, Risk of recurrence, Misclassification

1. Introduction

Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer, having the ability to concentrate iodide. Radioiodine (^{131}I); a radionuclide emits beta particles which can destroy cells by their high energy and gamma ray, which have an excellent penetrating property to image. Therefore, targeted radioiodine therapy (^{131}I therapy) and ^{131}I total body scintigraphy have long been used for the therapy and imaging of the DTC. The 2015 American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [1] proposed the use of ^{131}I dose depending on the risk of recurrence classified by pathological results after thyroid operation followed by the post-therapeutic total body scan obtained 2-10 days after ^{131}I therapy for re-staging and re-classification of the risk of recurrence. Thus, the DTC risk classification system depends primarily on the pathological results [1]. On the other hand, ^{131}I scintigraphy can detect functioning thyroid tissue throughout the body. Two possibilities found from ^{131}I scintigraphy that might change risks are 1) clinical cervical lymph node metastasis and 2) functioning distant metastasis.

Metastasis is the main factor that affects clinical outcomes. Data from the National Cancer Institute of United States on Surveillance, Epidemiology, and End Results Program (SEER 2010-2015) [2] showed the incidence of cervical lymph node metastasis is about 30-80% of DTC patients with the predominance of the

papillary subtype whereas that of functioning distant metastasis is about 4% of the patients. According to the new AJCC staging 8th edition [3], the overall survival of stage I without metastasis is 98-100%, stage II 85-95%, stage III 60-70%, and stage IV is less than 50%. Although the overall survival of DTC is satisfactory, still the recurrence of the disease has often been found. The risk stratification system proposed by ATA 2015 [1] has been used for predicting the survival of the DTC patients. In the aspect of ^{131}I therapy, Thies et al, 2014 [4] suggest the importance of choosing the right dose of ^{131}I from the first episode of treatment. Thus, overall survival will be shorter in the DTC patients who need more than one episode of ^{131}I therapy. This point of view makes the consideration of choosing the right dose which main affects patient outcome.

In the clinical practice nowadays, DTC patients are stratified based on the risk of recurrence by pathological results, and then, the activity of ^{131}I are chosen according to their risk of recurrence. In some literature, clinically N positive (cN1) patients were found often, which affects clinical outcome [5,6], and the functioning metastasis was found in about 5-30% of the patients by ^{131}I planar scintigraphy only [7-12]. Thus, some patients were prescribed under-estimated dose of ^{131}I according to their misclassification of the risk of recurrence from the pathological report resulting in poor clinical outcome. Verburg et al. (2014) reported the worse outcome after prescribed the under-dose of ^{131}I in both low and high-risk DTC [13] 3). Besides, a new technology of ^{131}I total body scintigraphy with the single photon computed tomography (SPECT/CT) can give high accuracy to detect metastatic sites with structural details, leading up-staging and re-classification of the risk of recurrence of the disease.

Many studies reported the overall re-classification prevalence in all risk of DTC is about 5-30% [7-12], and the high frequency of misclassification caused under-prescription of ^{131}I therapy, which directly affects clinical outcome. Thus, exploration of the prevalence of misclassification care is important to mirror our patients. Moreover, the factors which may indicate misclassification remains unclear. Therefore, the primary objective of this study is to determine the prevalence of misclassification in the risk stratification system of DTC patients who underwent post-therapeutic ^{131}I scintigraphy after the first dose of ^{131}I therapy. The secondary objective of this study is to explore factors related to misclassification.

2. Materials and methods

2.1 Patients

DTC patients who underwent the first ^{131}I Post-therapeutic scintigraphy at the Division of Nuclear Medicine, Department of Radiology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University from January 1, 2012, to December 30, 2019, were included. All patients who meet all the inclusion criteria and does not meet any exclusion criterion were consecutively enrolled.

2.2 Inclusion and exclusion criteria

Patients were included in the study if all of the following criteria were met- 1) pathological confirmed of low or intermediate risk of differentiated thyroid cancer, 2) underwent near-total or total thyroidectomy, 3) treated with the first episode of ^{131}I, 4) blood test for TSH $\geq$ 25 μIU/L at the day before ^{131}I orally administration, and 5) the first post-therapeutic ^{131}I scan was obtained 2-10 days after the first dose of ^{131}I. Patients who received an injection of thyrotropin alfa, who had previous treatment for thyroid cancer except for surgery, and whose medical record was incomplete were excluded.

Clinical data including age, sex, pathological report, ^{131}I scintigraphy report and radiographic reports, and the results of blood test of tumor markers (stimulated serum thyroglobulin and anti-thyroglobulin levels) were obtained from the medical record and PACs system of Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand.

2.3 ^{131}I post-therapeutic scintigraphy

At first, all DTC patients were defined and stratified for their risk of recurrence according to their pathological reports. The dose of ^{131}I was prescribed based on the patient's risk of recurrence: 30 mCi for low risk, 150 mCi for intermediate risk, and 200 mCi for high risk. The post-therapeutic scintigraphy by both planar and SPECT/CT techniques was obtained at 2-10 days after ^{131}I administration.

Anterior and posterior whole-body planar scintigraphy images were obtained using the Discovery NM/CT 670 (GE Healthcare, IL, USA) equipped with a high energy parallel hole collimator, with an energy peak set at 364 keV ± 10%, 256x256 imaging matrix, using continuous acquisition mode with detector speed of 4 cm/min. The SPECT/CT images were acquired using the same machine with an energy peak set at 364 keV ± 10%, 256x256 imaging matrix, using continuous acquisition mode with low dose CT scan of 16 slides.

2.4 Classification of risk of recurrence based on ^{131}I post-therapeutic scintigraphy report

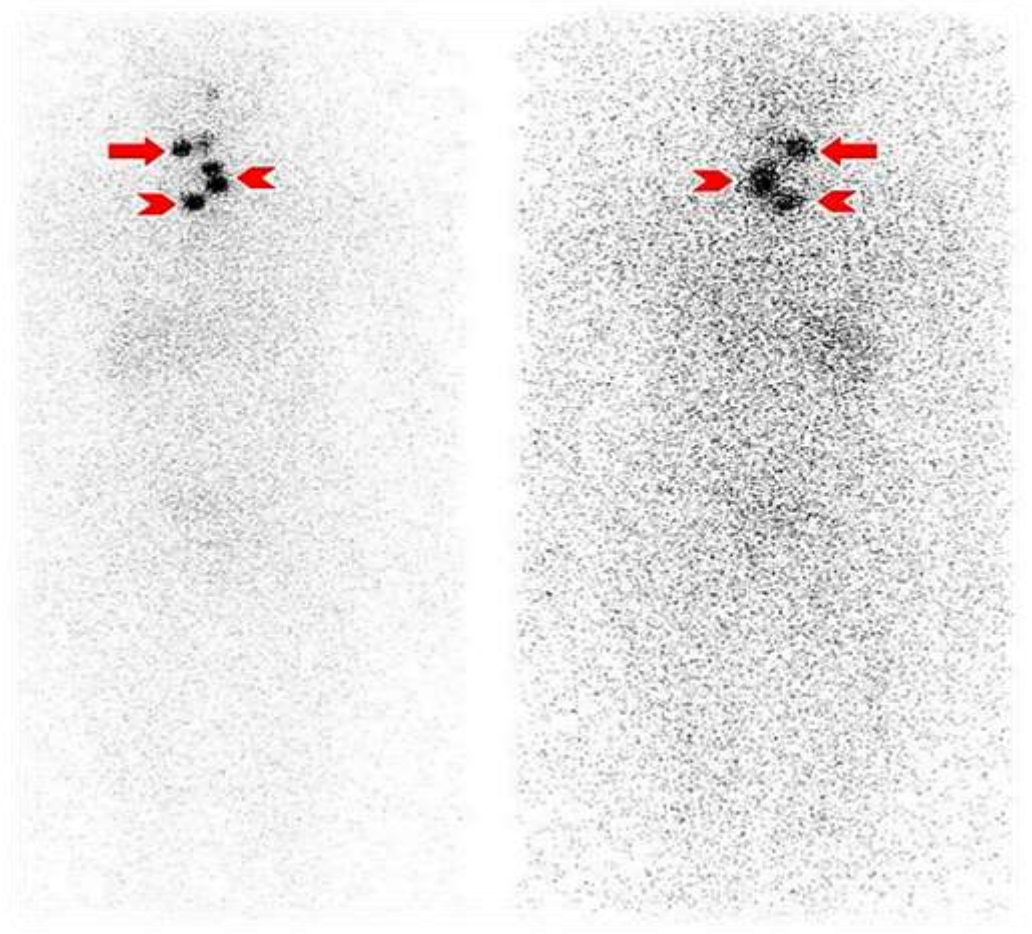
Planar and SPECT/CT images at the working station, including stimulated serum thyroglobulin and serum anti-thyroglobulin level, were reviewed and reported by experienced nuclear medicine physicians in our department. The authors reviewed the pathological reports to classify the patients into three groups, low, intermediate, and high-risk groups, according to the 2015 ATA criteria [1]. Then, ^{131}I post-therapeutic scintigraphy of both planar and SPECT/CT images of the patients in the PACS system was reviewed for re-classification by two nuclear medicine physicians. In case of discordant impression between two nuclear medicine physicians, the third nuclear medicine physician gave a consensus.

2.5 Misclassification of the risk of recurrence

Re-classification was based on the first ^{131}I post-therapeutic scintigraphy with or without SPECT/CT images, then reviewed by two experienced nuclear medicine physicians. In the first classification, patients could be classified as either "intermediate risk" if the ^{131}I avid lymph node metastasis without ^{131}I avid distant metastasis was found (Figure 1) or "high risk" if the ^{131}I avid distant metastasis was found (Figure 2).

Misclassification was then defined as having the change of risk assessment based on pathology based on the radiology at the first post-therapeutic ^{131}I scintigraphy with or without SPECT/CT images.

In case of discordant impression between two nuclear medicine physicians, the third nuclear medicine physician gave a consensus.



Anterior Posterior

Figure 1 DTC with low risk changing to intermediate-risk after the first ^{131}I post-therapeutic scintigraphy. The planar whole-body images revealed thyroid remnants (red arrows) and multiple functioning cervical lymph node metastases (red arrows heads).

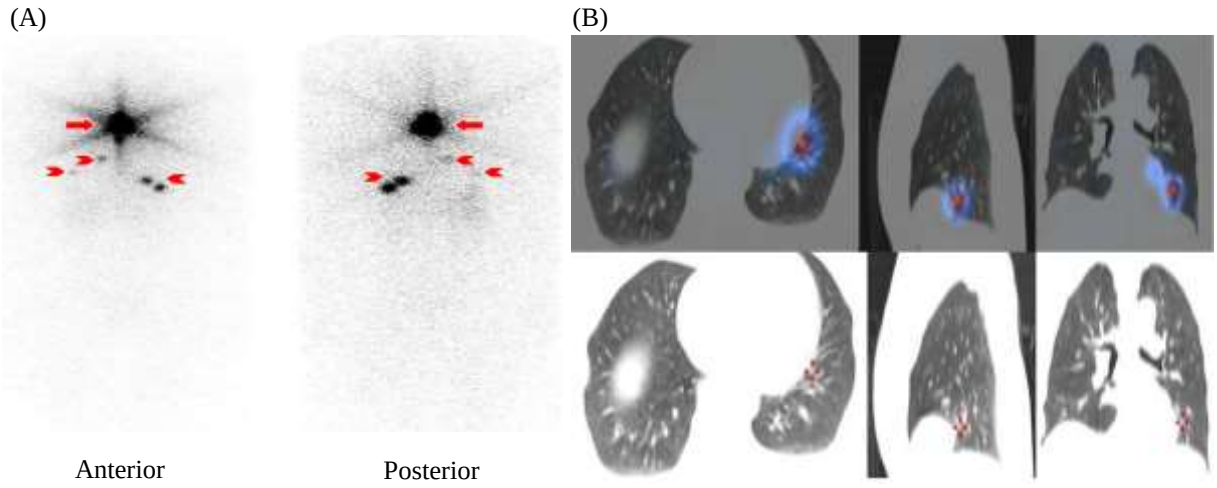


Figure 2 DTC with low risk of recurrence changing to high risk of recurrent after the first ^{131}I post-therapeutic scintigraphy. (A): The planar whole-body images revealed thyroid remnant (red arrows) and multiple functioning lung metastases at bilateral lung (red arrows heads), (B): The SPECT/CT images of the chest revealed multiple functioning lung metastases at the bilateral lung (red markers).

2.6 Statistical analysis

The sample size was calculated based on the formula of "sample size calculation for estimating the simple proportion (apparent prevalence)" [14]. The desired precision was ± 0.05 (5%), and the expected proportion of the misclassification was between 0.1 and 0.3, which were found from data explore in our center. The sample size was also estimated with 10% data loss. These led to the final number of 360 subjects.

Prevalence of misclassification and its 95% confidence interval (95%CI) was estimated based on normal approximation to binomial distribution. Logistic regression was used to assess the effects of various factors on misclassification. The factors included age, staging, tumor size, histology, serum stimulated thyroglobulin, and serum stimulated thyroglobulin test. We initially explored (bivariate analysis) their effects on the misclassification to obtain the unadjusted odds ratios with their 95%CI and p-value. The initial model for multivariable logistic regression contained all variables with the p-value obtained in bivariate analysis of 0.2 or less. Backward elimination was used as a method for variable selection to get the final best model. We then obtained adjusted odds ratios and their 95%CI.

The analysis was carried out using Statistical using Stata version 13.1 (StataCorp LLC, TX, USA). A *P*-value of less than 0.05 indicates statistical significance. The data management was done via REDcap.

3. Results and discussion

3.1 Patients

We selected a total of 360 DTC patients with low-to-intermediate risk of recurrence who received diagnostic ^{131}I post-therapeutic scintigraphy studies between January 1, 2012, and December 30, 2019. They consisted of 57 males and 303 females. The median age was 48 years, ranging from 17 to 82 years old. Among all 360 DTC patients, 130 patients were the low-risk group, and 230 patients were the intermediate-risk group. Papillary thyroid cancer was the most prevalent (312, 86.7%), including a few aggressive tumor subtypes (6, 1.9%), i.e., 4 patients of tall cell type and 2 patients of diffuse sclerosing type. The disease stage was mostly staged I (302, 83.9%), with the majority of patients having no cervical lymph node metastasis (N0) on the day before the first ^{131}I therapy. The patient's baseline pathology results show a median tumor size of 3 cm, ranging from 1 to 25 cm. The nodal size were available for 20 out of 95 patients with the mean size of 1.8 cm, ranging from 0.1 to 4 cm. Only one of 69 patients from 95 patients have the extranodal extension. Under the presence of TSH ≥ 25 µIU/mL, the median serum thyroglobulin level of all the patients was 3.8 ng/dL ranging from 0 to 3,563.1 ng/mL, and that of low-risk group was 3.9 ng/dL and of intermediate-risk group was 3.7 ng/dL. Likewise, the median serum anti-thyroglobulin of all the patients was 5.4 IU/mL ranging from 0 to 17,813 IU/mL, and that of low-risk group was 4.9 IU/mL and of intermediated-risk group was 5.7 IU/mL. Taken all those together, the proportion of clinical characteristics of low-risk and intermediate-risk groups were similar to each other and not different from those of the whole population group (Table 1).

Table 1 Characteristics of patients presented as number and percentage unless specified otherwise.

Characteristics	Total (n = 360) number (percent)	Low-risk (n = 130) number (percent)	Intermediate-risk (n = 230) number (percent)
Age at diagnosis (years)			
Mean (SD)	46.9	46.7	47.0
Median	48	49	48
Range	17 - 82	19 -70	17-82
Age group			
< 55 years	251 (69.7)	95 (73.1)	156 (67.8)
≥ 55 years	109 (30.3)	35 (26.9)	74 (32.2)
Sex			
Male	57 (15.8)	15 (11.5)	42 (18.3)
Female	303 (84.2)	115 (88.5)	188 (81.7)
Histology			
Papillary	312 (86.7)	101 (77.7)	211 (91.7)
Follicular	48 (13.3)	29 (22.3)	19 (8.3)
PTC with aggressive variant, Diffuse sclerosing (2, 0.6%), Tall cell (4, 1.3%)	6 (1.9)	0 (0)	6 (1.9)
TNM stage			
Stage 1	302 (83.9)	119 (91.6)	183 (79.6)
Stage 2	58 (16.1)	11 (8.5)	47 (20.4)
Stage 3	0 (0)	0 (0)	0 (0)
Stage 4	0 (0)	0 (0)	0 (0)
Pathological tumor staging (T)			
Tx	4 (1.1)	1 (0.8)	3 (1.3)
T1	127 (35.3)	56 (43.1)	71 (30.9)
T1a	50 (39.4)	29 (51.8)	21 (29.6)
T1b	77 (61.1)	27 (48.2)	50 (70.4)
T2	138 (38.3)	48 (36.9)	90 (39.1)
T3	91 (25.3)	25 (19.2)	66 (28.7)
T3a	77 (84.6)	25 (100)	52 (78.8)
T3b	14 (15.4)	0 (0.0)	14 (21.2)
T4	0 (0.0)	0 (0.0)	0 (0.0)
T4a	0 (0.0)	0 (0.0)	0 (0.0)
Tumor size (cm)			
The primary tumor cannot be evaluated	3 (0.8)	1 (0.8)	2 (0.9)
Micro -carcinoma (less than 1 cm)	48 (13.3)	27 (20.8)	21 (9.1)
Mean	3.5	3.6	3.5
Median	3	3.2	3
Range	1-25	1-25	1-10.5
Nodal size (cm) (n=20)			
Mean	1.8	0 (0)	1.8
Median	1.8	0 (0)	1.8
Range	0.1-4.0	0 (0)	0.1- 4.0
Extranodal extension (n=69)			
Negative	68 (98.5)	0 (0)	68 (98.5)
Positive	1 (1.5)	0 (0)	1 (1.5)
Thyroglobulin level (ng/mL)			
Mean	55.5	40.4	64.1
Median	3.8	3.9	3.7
Range	0-3,563.1	0-3,563.1	0-2,365.1
Anti-thyroglobulin level (IU/mL)			
Mean	193.1	38.6	280.3
Median	5.4	4.9	5.7
Range	0-17,813.0	0-2,528.5	0-17,813.0

3.2 Misclassification after the first ^{131}I post-therapeutic scintigraphy

Misclassification was defined as either "intermediate risk" if the ^{131}I avid lymph node metastasis without ^{131}I avid distant metastasis was found or "high risk" if the ^{131}I avid distant metastasis was found. Among 360 patients of ^{131}I post-therapeutic scintigraphy, 57 patients (15.8%, 95%CI 12.0-19.6) were identified to be misclassified. According to their initial risk stratification from pathology results, 130 low-risk patients were classified to 1.) changing from the low-to-intermediate group (39 patients, 10.8%), and 2.) changing for the low-to-high-risk group (2 patients, 0.6%). Among 230 intermediate-risk patients (16 patients, 4.4%) had distant metastasis, found on ^{131}I post-therapeutic scintigraphy; therefore, they were classified as changing from intermediate-to-high risk group (Table 2).

Table 2 Misclassification of DTC defined by risk of recurrence.

Risk of Recurrence	Total	Number of Misclassification	Percent of Misclassification	95% CI
All types of risk classification	360	57	15.8	12.0, 19.6
Low (n=130)				
to intermediate		39	10.8	
to high		2	0.6	
Intermediate (n=230)				
to high		16	4.4	

CI-confidence interval

3.3 Factors determine misclassification from pathological results

3.3.1 Age and gender

Among 360 patients, 109 patients were >55 years old at diagnosis of DTC, and among them, 15 (13.8%) misclassification patients were found. The proportion of misclassification among the patients <55 years (42/251, 16.7%) was similar to that of the older age group (OR 0.9, 95% CI 0.5-1.8, p-value 0.736) (Table 3). The majority of patients were female (303, 84.2%). The misclassification rate was similar in both males and females.

3.3.2 *Staging (tumor and nodal stage)*

Among 360 DTC patients, 57 patients were misclassified. Among 57 misclassified patients 23 (18.1%) patients were in T1 stage, 20 (14.5%) in T2 and 13 (14.3%) in T3 stages. The misclassification rate was not significantly different among the T1-T3 stages. In contrast, significant difference of misclassification rate was seen among nodal staging groups; misclassified patients were 52/265 (19.6%) in N0 and 5/95 (5.3%) in N1 (OR 0.2, 95% CI 0.07-0.5, p-value 0.001) (Table 3).

3.3.3 Tumor marker: thyroglobulin (Tg) and anti-thyroglobulin level (TgAb)

Based on the inclusion criteria of this study, all 360 participants had TSH ≥ 25 μIU/mL, so that serum Tg and TgAb levels before the 1st course of treatment are under-stimulated conditions. Of the 57 misclassified patients, stimulated serum Tg level of 12 patients were of <1 ng/dL, 21 were in the range of 1-10 ng/dL, and 24 in the range of 10-100 ng/dL. Thus, the proportion of misclassification is greater in the patients having baseline stimulated Tg level of >10 ng/mL. (OR 3.2, 95% CI 1.4-7.5, p-value 0.007). In our hospital, the positive TgAb result is defined as > 25 IU/mL. Among 57 misclassified patients, 8 had TgAb level of >25 IU/mL, and 49 had <25 IU/mL. The proportion of misclassified patients did not differ between the patient's group with TgAb levels of >25 IU/mL and < 25 IU/mL (OR 1.6, 95% CI 0.6-3.8, p-value 0.354) (Table 3).

Table 3 Factors associated with misclassification risk of recurrence.

Factors	Number of patients (n= 360)	Number of misclassification n =57 (%)	Crude OR	Adjusted OR	95%CI	*P*-Value
Age* (years)						
< 55	251	42 (16.7)	1	1		
≥ 55	109	15 (13.8)	0.8	0.9	0.5 – 1.8	0.736
T stage						
T1	127	23 (18.1)	1	1		
T2	138	20 (14.5)	0.8	0.7	0.4 – 1.4	0.348
T3	91	13 (14.3)	0.8	0.7	0.3 – 1.6	0.442
N stage						
N0	265	52 (19.6)	1	1		
N1	95	5 (5.3)	0.2	0.2	0.1 – 0.5	0.001
Thyroglobulin level** (ng/mL)						
< 1	109	12 (11.0)	1	1		
1 to <10	137	21 (15.3)	1.5	1.5	0.7 – 3.5	0.295
≥ 10	114	24 (21.1)	2.2	3.2	1.4 – 7.5	0.007
Anti-thyroglobulin level** (IU/mL)						
< 30	313	50 (16.0)	1	1		
≥ 30	47	7 (14.9)	0.9	1.4	0.6 – 3.4	0.487

Crude OR- crude odds ratio, Adjusted OR- adjusted odds ratio, CI-confidence interval.

*Age at the time of ^{131}I post-therapeutic scintigraphy.

**For the reference of thyroglobulin and anti-thyroglobulin levels, TSH levels of all participants were ≥ 25 μIU/L, and their thyroid hormone levels were within a normal range.

The primary aim of our study is to determine the prevalence of misclassification in DTC patients of the low-to-intermediate risk of recurrence who underwent post-therapeutic ^{131}I scintigraphy after the first ^{131}I therapy. Since ATA 2015 [1] proposed the idea of using low-dose ^{131}I therapy, which is effective enough to expect low risk of recurrence, the number of patients treated with low-dose has been accelerating increased. Thus, the baseline risk classification is made only by pathology, and patients of low risk of recurrence were treated with low-dose ^{131}I therapy, followed by the post-therapeutic scintigraphy to complete staging. Many patients with low risk by pathology have been changed to the intermediate or high-risk group who should receive high-dose ^{131}I therapy. Thus, the cure rate and prognosis of these misclassified patients may worse as compare to the patient who received the right ^{131}I therapeutic dose [13]. Therefore, this study was purposed to explore the magnitude of the misclassification problem among DTC patients treated with low-dose ^{131}I therapy.

The baseline characteristics of the DTC patients in this study were of low-to intermediate-risk features according to their pathological results (Table 1). When the post-therapeutic scintigraphy in 2-7 days after ^{131}I therapy were analyzed, about 16% of the patients were changed their classification of the risk of recurrence. Our results are similar to those in many works of literature, where the percentage of misclassification is ranging from about 5 to 30% [7-12]. The type of misclassification is mainly the change from low to intermediate-risk group because of the detection of functioning cervical lymph node metastasis in the post-therapeutic scintigraphy. The change of classification to high risk of recurrence was seen in 18 out of 57 misclassification patients. These patients identified as high risk of recurrence need additional therapy such as the second ^{131}I therapy, re-surgery, or radiation therapy. However, the patients who were changed from intermediate to high risk depending on the metastatic site have received insufficient ^{131}I dose by misclassification. For distant bone metastasis, the insufficient ^{131}I dose should be awared. The ^{131}I dose for distant lung metastasis should not be raised higher than the lung's critical radiation dose-the high-dose ^{131}I therapy for diffuse lung metastasis is prone to induce radiation-induced pulmonary fibrosis than for the solitary lung metastasis. For that reason, the typical ^{131}I dose in the intermediate risk of recurrence should not be raised for diffuse lung metastasis, although it should be considered for the misclassified patients who were changed from intermediate to high risk of recurrence. In summary, either low to intermediate or intermediate to high risk of recurrence may have received insufficient ^{131}I therapeutic dose. Consequently, the cure rate and prognosis in this misclassified group should be carefully considered and investigated further.

In this study, we aimed to explore the possible factors which may predict misclassification. We found that the proportion of misclassified patients was significantly higher in patients having the baseline stimulated serum Tg level of ≥ 10 ng/mL compared with those having Tg level of <10 ng/mL. The pre-operative imaging such as ultrasonography (US) or contrast-enhanced computerized tomography scan (CT) of the neck is recommended by ATA2015 guideline if possible, misclassification was clinically suspected [1]. The pathological nodal staging is an interesting factor. The patients with the pathological N1 stage had lower rate of misclassification than those in the pathological N0 stage. This may be due to the fact that once the N1 stage was diagnosed from physical examination or the pre-operative imaging, the attending surgeon perform a wider field of surgery for cervical node dissection, whereas the patients with pathological N0 stage usually receives only thyroidectomy. Other factors such as age and T stage are not associated with the proportion of misclassification. Although patients older than 55 years old were found to have a lower rate of misclassification. Older age than 55 years is one of the criteria to give higher staging in DTC from TNM staging according to poorer prognosis of disease as compare in the younger than 55 years old. Therefore, older than 55 years old may give awareness for pre-operative images which guided the surgeon to extend the operation field, results in more chance of lymph node removal than that the younger. Meaning of likewise to the tumor staging, the bigger tumor size tends to have a more aggressive operation, increasing the chance to remove the cervical lymph nodes.

The strength of our study is exploration of the prevalence of misclassification, which was found in the considerable number of patients, consequently affecting on therapeutic outcome in this group. The pre-operative imaging such as US or CT scan of the neck under clinical suspicion may reduce the number of misclassifications. As the limitations, only the strong factor in predicting misclassification was explored in this study. The magnitude of the effect of each factor needs a bigger sample size. Evaluation of the clinical outcome of misclassified cases and the factors associated to misclassification should be obtained in the further study.

4. Conclusion

Detection of considerable number of misclassification in risk stratification of DTC was emphasized in this study. This circumstance should raise awareness of the under-prescription of ^{131}I doses. Further study for evaluation of treatment outcome of these misclassified cases should be considered. Determinant factors predicting misclassification should be high baseline stimulated Tg level of greater than 10 ng/mL.

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6. Ethic approval

This retrospective chart review was conducted in a teaching hospital in northeastern Thailand and approved by the Khon Kaen University Ethics Committee for Human Research (Reference number: HE621346).

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