The importance in diagnosing patients with conflicting observational data for post surgery radioiodinated ablation of thyroid remnants

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Abstract

Objective: There is a special group of patients, according to 2015 American Thyroid Association guidelines. This group is defined as "the patients with conflicting observational data for post-surgery radioiodine ablation (COD for PSRIA)". For this special group of patients RIA is applied after a thorough reassessment of histopathological, clinical and biochemical features, including thyroglobulin (Tg). However, there is no consensus on what is the suitable cut-off value for the radioiodine ablation (RIA) decision or for therapy prediction. Moreover, is also unclear which Tg parameters should be used for these purposes. If we can determine useful and practical cut-off values for excellent response (ER) and non-structural incomplete response (non-SIR) response categories, this will facilitate our therapy response prediction before RIA and may allow us to categorize the group of "COD for PSRIA" based on a higher risk of recurrence/relapse or disease specific mortality rates according to serum thyroglobulin (Tg). This categorization may also enable us to plan the follow-up frequency of patients more scientifically. Consequently, it may provide the more efficient use of medical facility and healthcare system resources. **Subjects and Methods:** Two hundred forty-nine patients (out of 577 examined) with "COD for PSRIA" were included in this study. Firstly, patients with indeterminate, biochemical incomplete and structural incomplete responses were considered as the non-ER group and compared to the ER group. Secondly, patients with excellent, indeterminate, and biochemically incomplete responses were considered as the non-SIR group and compared to the SIR group. The data were evaluated by MedCalc Statistical Software version 18.9. **Results:** The cut-off value for ER patients was calculated as ≤6.57 ng/mL. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 67.9%, 75.4%, 55.6% and 83.8%, respectively. The cut-off value for non-SIR patients was calculated as ≤12.7 ng/mL. Sensitivity, specificity, PPV and NPV were 78.5%, 91.7%, 35.5% and 98.6%, respectively. **Conclusion:** If a patient has ≤6.57ng/mL pre-ablative Tg, follow-up intervals of patients with "COD for PSRIA" may be extended due to lower recurrence/relapse rates. However, if a patient has >12.7ng/mL pre-ablative Tg, these patients should be followed-up more frequently in order to determine SIR earlier. This approach may enable more efficient use of medical facility and healthcare system resources and a more scientific planning of their follow-up treatment. This approach seems to have the potential to contribute significantly to cost-effectiveness.

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Introduction

Differentiated thyroid carcinomas (DTC) are the most common endocrine malignancy. They comprise 3.3% of all cancer cases and their prevalence has been increasing. Due to the widespread use of imaging modalities and particularly neck ultrasonography (US), most patients are diagnosed at low or intermediate risk stages and the rate of their high-risk category has been decreasing [1-3]. If a tumor is ≤1.0cm and is limited to the thyroid gland, post-surgery radioiodine ablation (RIA) is not recommended according to the American Thyroid Association (ATA) 2015 guidelines, which are the last updated guidelines [4]. Contrary, RIA is recommended for tumors in the high-risk category. For the remaining categories, there is an ongoing debate about postoperative RIA. This group was determined as conflicting observational data for post-surgery radioiodine ablation (COD for PSRIA) by the 2015 ATA guidelines. This category of patients is diagnosed after a thorough reassessment of lots of histopathological, such as tumor size, subtype of the tumor, extrathyroidal extension, surgical margin positivity, in addition to other clinical and biochemical features, including serum thyroglobulin (Tg). However, there is no consensus on what is the suitable Tg cut-off value for the RIA patients or for their therapy prediction. [5-7]. Moreover, it is also unclear which Tg parameters (stimulated or sup-

pressed) should be used for these purposes. It is clear that, if Tg antibody is present, TG measurement is not reliable. In addition, Tg has approximately 65 hours of half-life [8], and it can be detected after the surgery for several weeks in the venous blood sample. Although it has abovementioned disadvantages, it can be beneficial for decision of therapy or prediction, if used properly.

In this study, we aimed to calculate two different cut-off values for stimulated Tg in the above-mentioned special group of patients. Due to lower recurrence/relapse rates among excellent response (ER) patients, the first cut-off value was calculated for them. Due to lower disease specific mortality rates among non-structural incomplete response (non-SIR) patients, the second cut-off value was calculated for these patients [4]. If we can determine useful and practical cut-off values for two different response categories, this will facilitate therapy response prediction before RIA. This may allow us to categorize the group of "COD for PSRIA" based on a higher risk of recurrence/relapse or disease specific mortality rates according to Tg and also to better plan their follow-up diagnosis and treatment.

To the best of our knowledge, this is the first study on this special group of patients according to above-mentioned context.

Subjects and Methods

Patients' selection

We retrospectively examined the data of 577 patients with DTC who received postoperative RIA after total thyroidectomy (TT) between April 2011 and July 2017. After January 2016, our clinic has started using the 2015 ATA guideline stratification system. For this reason, re-stratification was performed for patients who underwent risk stratification before January 2016.

Patient exclusion criteria were: a) Received the first RIA in different medical centers (n=61), b) Re-classified as high risk according to the 2015 ATA guidelines (n=20), c) Reached the ER criterion after the surgery, unless there was no lymph node (LN) metastases, minimal extra thyroidal invasion or a positive surgical margin (n=12), d) Intrathyroidal microcarcinomas (n=112), e) Lack of iodine-131 whole body imaging (^{131}I-WBI) at 6-12 months after RIA (n=86), f) Anti-Tg >20 U/mL (n=37).

Finally, 249 patients with "COD for PSRIA" were included in the study. We received the Ethics Committee approval, and this study was conducted according to the 1964 Declaration of Helsinki and subsequent amendments. Informed consent was signed by all patients before every procedure.

Surgery and histopathological examination

Thyroid surgery was performed by thyroid surgeons with at least 10 years experience. If a patient had biopsy-proven LN metastases before surgery, unilateral or bilateral cervical LN dissection was performed. If the patient had suspicious findings for LN metastases on the preoperative US, or during surgery, these nodes were examined by frozen section. A unilateral or bilateral cervical LN dissection was performed in cases of malignancy. All extracted tissues were examined histopathologically.

Radioiodine ablation therapy and the evaluation of therapy response

Before ablation therapy, thyroid hormone withdrawal (THW) and iodine-poor diet were applied according to the ATA guidelines [4, 9]. As a routine procedure of our clinic, pre-ablation US was performed at least 10 days before RIA and Tg, anti-Tg and TSH values were measured in venous blood sampled approximately 4 hours before therapy. Thyroid stimulating hormone two-site sandwich immunoassay was performed using direct chemiluminometric technology, which uses constant amounts of two antibodies. Its analytical sensitivity was 0.01μIU/mL (Siemens ADVIA Centaur Immunoassay System, Erlangen, Germany). Thyroglobulin assay was also performed with two-site sandwich immunoassay using direct chemiluminometric technology. Its analytical sensitivity was 0.2ng/mL and functional sensitivity was 0.9ng/mL (Siemens ADVIA Centaur Immunoassay System, Erlangen, Germany). Anti-Tg measurement was performed with solid-phase, enzyme-labeled, chemiluminescent sequential immunometric assay with analytical sensitivity <10kIU/L, functional sensitivity <20kIU/L (Siemens Immulyte 2000 Xpi Immunassay System, Erlangen, Germany). Low-risk and intermediate-risk patients received 3700MBq and 5450MBq of ^{131}I, respectively.

Six to twelve months after postoperative RIA, therapy response evaluation was performed with 185MBq of ^{131}I-WBI (two-headed single photon emission tomography (SPET) gamma camera Infinia 2; General Electric, Tel Aviv, Israel; Scan speed was 10cm/min) and Tg values. If there were any suspicious findings in ^{131}I-WBI, neck US/magnetic resonance imaging (MRI), or thorax computerized tomography was performed, according to lesion's localization.

Statistical analysis

The age, sex, lymphovascular/capsular/perineural invasions, tumor lymph nodes metastatic stages, presence of lymph node metastases and their relationships between the therapy response were examined. Then firstly, patients with indeterminate, biochemical incomplete, and structural incomplete responses were considered as the non-ER group and compared to the ER ones. Secondly, patients with excellent, indeterminate, and biochemically incomplete responses were considered as the non-SIR group and compared to the SIR ones.

Statistical analysis was performed by MedCalc Statistical Software version 18.9 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Descriptive statistics included numbers (n), percentages (%) and mean±standard deviation values. The relationship between categorical variables was examined by the chi-squared test and rxc tables. The receiver operating characteristic (ROC) curve method was used for diagnostic tests and for the calculation of cut-off values. A P-value <0.05 was considered as statistically significant.

Table 1. *The relationship between patient characteristics' and therapy response after first dose RIA*

Features	ER n=163	IR n=40	BIR n=15	SIR n=31	P-value
Histopathological type					**0.68**
Papillary	140	33	13	30	
Follicular	23	7	2	1	
Age	46.0	45.5	48.5	42.6	0.45
Gender					0.40
Male	33	13	3	6	
Female	130	27	12	25	
Lymph node metastasis					0.32
Present	37	13	6	9	
Not present	126	27	9	22	
ATA risk					0.10
Low	111	23	8	15	
Intermediate	52	17	7	16	
Tumor node metastasis stage					0.44
I	109	26	10	25	
II	24	4	0	2	
III	14	5	2	2	
IV	16	5	3	2	
Capsule invasion					0.11
Present	37	6	5	8	
Not present	59	16	4	4	
Lymphovascular invasion					0.37
Present	19	9	2	4	
Not present	75	18	11	8	
Perineural invasion					0.50
Present	7	0	0	1	
Not present	37	7	6	4	

American Thyroid Association; ATA, Excellent Response: ER, Indeterminate Response: IR, Biochemical Incomplete Response: (BIR), Structural Incomplete Response (SIR)

Results

In total, 194 of the 249 patients (77.9%) were female with mean age was 45.6±12.9 (18-86) years. Approximately 37.0% of the patients were intermediate-risk and 63.0% were low-risk. There were no significant relationships in terms of age, sex, lymphovascular/capsular/perineural invasions, tumor node metastases stages and 2015 ATA risk stratifications between the patients with different therapy responses. The presence of LN metastases was also insignificant when size was not considered (P=0.32). Findings are shown in Table 1. An example of a 36 years old male is shown in Figure 1.

The rate of excellent, indeterminate, biochemical incomplete, and structural incomplete responses within one year were 65.5%, 16.0%, 12.5%, and 6.0%, respectively. The mean and median Tg values of all response criterions are shown in Table 2. The median time interval between surgery to RRA was 73 days (12-745).

The cut-off value for ER patients was calculated as ≤6.57 ng/mL. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 67.9%, 75.4%, 55.6 % and 83.8%, respectively. The area under the ROC curve was 0.76 (95% confidence interval, 0.69-0.81, P=0.01, standard error, 0.03). The ROC curve is shown in Figure 2.

The cut-off value for non-SIR patients was calculated as

≤12.7ng/mL. Sensitivity, specificity, PPV and NPV were 78.5 %, 91.7%, 35.5% and 98.6%, respectively. The area under the ROC curve was 0.883 (95% confidence interval, 0.83-0.92, P< 0.01, standard error, 0.04). The ROC curve was shown in Figure 3.

Table 2. *Mean and median Tg values before the first dose of RIA and its*

	ER	IR	BIR	SIR
Tg mean	7.9	13.6	11.5	49.7
Tg median	2.5	7.1	12.6	27.0

Stimulated thyroglobulin: Tg, Excellent Response: ER, Indeterminate Response: IR, Biochemical Incomplete Response: (BIR), Structural Incomplete Response (SIR)

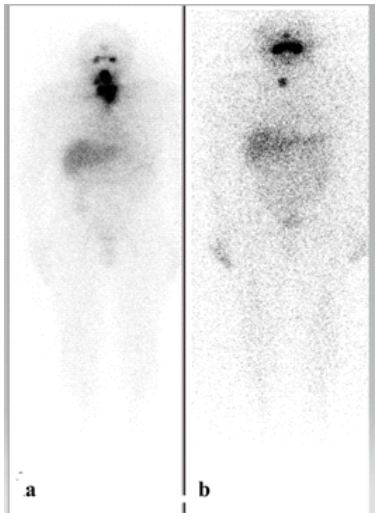

Figure 1. A 36 years old male patient diagnosed with a 45mm sized papillary thyroid carcinoma with extrathyroidal invasion, and negative surgical margin of the specimen. Before the 5450MBq RIA, the level of stimulated thyroglobulin was 26.7 ng/mL and anti Tg was <20U/mL. Residual tissue and lower cervical lymph nodes metastases were detected in post-ablative ^{131}I whole body image 1a. This lesion was also determined in pre-ablative ultrasonography had a size of approximately to 24mm. High ^{131}I uptake was detected in the lower cervical region at the 12th month follow-up in ^{131}I whole body image 1b. Stimulated Tg was 12.1ng/mL and anti-Tg was <20U/mL. The response was evaluated as a structurally incomplete response.

Discussion

Despite the high incidence of DTC, this disease accounts for a small portion of cancer-related deaths [1, 10]. Main causes of low mortality rates are less aggressive tumor behavior compared to most of other cancers and low incidence of high risk diagnosed patients. Banderia et al. (2017) reported that 85% of the patients who received 3700-5450MBq RIA were classified as low/intermediate risk [11]. Due to changes in the demographic features of patients, improvements of the imaging modalities and novel data about RIA therapy, the guidelines were updated by ATA, on 2015. According to these guidelines, if a tumor is ≤1.0cm and limited to the thyroid gland, postoperative RIA is not recommended. Of the remaining patients, those with low/intermediate risk are described as "COD for PS-RIA" [4]. Whether postoperative RIA therapy is required in these patients is still controversial. Zhang et al. reported that, RIA therapy was not related to cancer-specific death in intermediate risk DTC [12]. Despite that, there are many clinics treating these patients, because postoperative RIA increases the specificity of Tg, which is one of the most important parameters in detecting recurrence/relapse in these patients. In addition, if a patient does not receive postoperative RIA, he/she needs longer and more frequent monitoring. Moreover, according to some studies, these patients were more likely to undergo additional surgery [13-16]. Postoperative RIA is performed with a re-evaluation of lots of parameters for the group of patients with "COD for PSRIA". However, to the best of our knowledge, there are not any studies focusing on the relationship between pre-ablative Tg and these patients. We aimed to determine two different cut-off values for them. Due to lower recurrence/relapse rates among the ER patients, the first cut-off value was determined for them. The second cut-off value was determined for non-SIR patients due to the low disease specific mortality rates among them [4]. Useful and practical cut-off values for ER and non-SIR responses, may allow us to categorize this patient group on a higher relapse/recurrence rate or death risk, according to Tg.

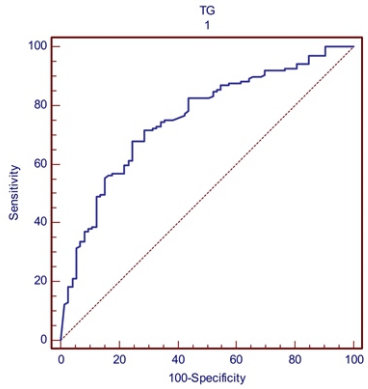

Figure 2. ROC analysis of stimulated Tg and excellent response.

Banderia et al. (2017) studied the relationship between pre-ablative Tg and all risk groups as a whole. Authors found that the mean pre-ablative Tg values of excellent, indeterminate and incomplete responses were as 2.1ng/mL, 8.2ng/mL and 22.4ng/mL. The incomplete response group consisted of biochemical incomplete response and SIR patients, in that study. They also found a significant relationship between pre-ablative Tg level and excellent/incomplete responses. However, these authors did not find any relationship between Tg and indeterminate response and mentioned that this result may be due to the low number of patients studied [11]. Melo et al. (2010) studied patients with no metastases. Authors reported that

if pre-ablative Tg is ≤7.2ng/mL, the patient has a high probability of remission after the first year of RIA [6]. In a recent study, Piccardo et al. (2018) similarly focused on the patients without metastasis. However, the authors found that pre-ablative Tg levels were only related to biochemical incomplete response [17]. Despite a similar group of patients was studied, these results differ from the study of Melo et al. (2010). Unlike most other studies, Pitoia et al. (2017) examined the relationship between ER and three different patient groups. These groups were identified as low risk group, moderate and high risk group together, and all risk groups together. The authors determined 12ng/mL, 16ng/mL, 22ng/mL Tg cut-off values for these three groups, respectively [7]. Although TSH stimulation is performed by thyroid hormone withdrawal (THW) or recombinant TSH, it is noteworthy that the relationship between Tg and ER is still important, despite this different stimulation approaches. In this study, when increased TSH was only provided by THW, the Tg cut-off value was calculated as ≥25ng/mL for SIR. The sensitivity, specificity, PPV and NPV of this cut-off value were 91.4%, 63.4%, 39.5% and 97.7%, respectively [7].

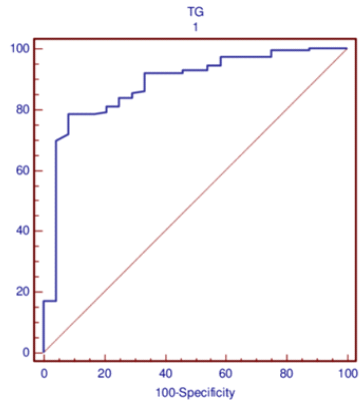

Figure 3. ROC analysis of the stimulated Tg and non-structurally incomplete response.

In the current study, we determined the cut-off value for ER as ≤6.57ng/mL. The sensitivity, specificity, PPV and NPV of this cut-off value were 67.9%, 75.4%, 55.6% and 83.8%, respectively. This means that, if a patient has ≤6.57ng/mL pre-ablative Tg, he/she will reach the ER criterion within one year with 83.8% likelihood. Therefore, we can conclude that such a patient will not experience recurrence/relapse with an 83.8% likelihood according to ATA 2015 guidelines. Because of that, the follow-up intervals of these patients may be extended. For non-SIR patients, the cut-off value was calculated as ≤12.7ng/mL. The sensitivity, specificity, PPV and NPV values were 78.5%, 91.7%, 35.5% and 98.6%, respectively. This means that, if a patient has 12.7ng/mL pre-ablative Tg, he/she will reach (the) non-SIR criterion within one year with 98.6% likelihood. Therefore, we can conclude that this patient will not die due to DTC with a 98.6% likelihood according to the ATA 2015 guidelines. However, if a patient's pre-ablative Tg is >12.7ng/mL, he/she has a higher risk of SIR. Due to this reason, we think that these patients should be followed more frequently after RIA.

An important advantage of our study was the high, and satisfactory number of RIA patients with COD of PSRIA studied. we evaluated all response criteria, contrary to most other studies. We believe, this advantage provided us with reliable statistical results. On the other hand, there were also some limitations. Firstly, this was a retrospective study and thus had some inherent limitations. Secondly, our patients received 3700-5450MBq of ^{131}I, and there were no patients who received 1100MBq. However, we think that our results can be also applied to patients receiving 1100MBq of RIA, because it has been reported that there is no significant difference between 1100 and 3700MBq therapy in low/intermediate risk patients [18].

In conclusion, if a DTC patient is in the COD for PSRIA group, and the anti-Tg level is <20U / mL, and if TSH stimulation is provided by THW, preablative sTg is a valuable parameter to predict therapy response. If such a patient has ≤6.57ng/mL pre-ablative Tg, follow-up intervals may be extended due to lower recurrence/relapse expected rates. However, if a patient has >12.7ng/mL pre-ablative Tg, should be followed up more frequently in order to determine SIR earlier. This may have the potential to contribute significantly to its cost-effectiveness. Multi-center, prospective studies are warranted.

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