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Research Article

The clinical value of Stimulated Thyroglobulin/TSH ratio in patients with differentiated thyroid cancer for successful initial ablation after total thyroidectomy

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Abstract

Objective

This study aim to using thyroid stimulating hormone(TSH) to correct Thyroglobulin(Tg) and analyzing Tg/TSH ratio to predict the value of successful radioactive iodine remnant ablation（RIRA）, and assess whether Tg/TSH ratio can be used as a good predictor and compared with stimulated thyroglobulin.

Methods

One hundred and ninety DTC patients with total thyroidectomy were retrospectively analyzed to compare the ability of Tg level and the Tg/TSH ratio to predict successful RIRA.

Results

One hundred and twenty-eight (67.37%) patients were successful ablation. Patients' gender, age, pathological types and cervical lymph node metastasis did not difference between successful and unsuccessful group(all $P > 0.05$). There were significance statistically difference between successful and unsuccessful group about Tg level and Tg/TSH ratio ($t=6.85$, 9.46, respectively, all $P < 0.01$). The optimum cutoff value for Tg to predict ablation curative effect was 38.18 ng/ml and the sensitivity and specificity was 87.50% and 58.06%, respectively. And for the Tg/TSH ratio optimum cutoff value was 0.969 and the sensitivity and specificity was 93.75% and 56.45%, respectively. According multivariate regression analysis showed only initial ablation (131)iodine doses, Tg level and Tg/TSH ratio remained significantly associated with successful ablation. The correlation for Tg/TSH ratio with OR 9.43(3.45-25.64) was more stronger than alone Tg with OR 3.14(1.25-7.87).

Conclusions

This study conclude that the Tg/TSH ratio has more stronger than alone Tg in predicting successful RIRA in patients of DTC.

Key Words

Differentiated thyroid carcinoma, thyroglobulin, thyroid stimulating hormone, predictive valve, treatment effect .

Introduction

Thyroid cancer is a common malignant tumor in the endocrine system, and the incidence is different in the various ethnic groups and regions（1). Differentiated thyroid cancer (DTC) accounted for the vast majority of all thyroid cancer(90%)（2). In recent years, surgical resection of lesions and radioactive iodine remnant ablation（RIRA）and suppression therapy for thyroid stimulating hormone(TSH) with thyroxine have became the optimal treatment mode for DTC (3), but there isn't still an unified and effective prediction index of risk stratification for the patients before RIRA. Thyroglobulin(Tg) is usually regarded as an important reference index in follow-up for postsurgical thyroid removal of DTC（4). Stimulated thyroglobulin is a good predictor in the predicting factors for success RIRA, but its result was restricted by the tumor staging, the level of TSH and other factors（5).

Therefore, this study aimed to using TSH to correct Tg and analyzing Tg/TSH ratio to predict the value of successful RIRA, and assess whether Tg/TSH ratio can be used as a good predictor and compared with stimulated thyroglobulin.

Materials and methods

Patients

We retrospectively analyzed the patients with DTC after total thyroidectomy treated at the department of nuclear, First Affiliated Hospital of Guangxi Medical University, from January 2014 to November 2015. We authorized an approval from Ethical Review Committee First Affiliated Hospital of Guangxi Medical University for this study. Only 190 patients with DTC met according to the inclusion and exclusion criteria.

Inclusion criteria

(1)all patients with DTC were adults ;(2) all patients were underwent total thyroidectomy; (3)those who postoperative pathology confirmed thyroid papillary carcinoma and follicular carcinoma;(4) those who accepted RIRA after 3-4 weeks with total thyroidectomy; (5)those who having thyroxinere placement should be discontinued about 3-4 weeks;(6)those who underwent treatment whole body iodine scan (WBIS) after RIRA a week.

Exclusion criteria

(1) the patients with thyroglobulin antibody (TgAb) were positive; (2)TgAb, TSH, and Tg levels measured from different time or different samples; (3)the patients underwent contrast-enhanced CT within one-month preablation; (4)The patients were followed-up for lost;(5)the patients were without total thyroidectomy; (6) the patients have done diagnostic WBIS before RIRA because of possible stunning effect.

Variables and definitions

Serum index's determination: TSH, Tg, and TgAb levels of all patients were measured by a fully automatic chemiluminescence apparatus(DXI 800, Beckman, USA) at a clinical laboratory before RIRA. Reportable range of TSH is 0.34 to 5.60 uIU/mL Reportable range of Tg is 5 to 40 μg/L. Reportable range of TgAb is no less 30%.

Iodine dose activities

(131)iodine was produced by Chengdu in nuclear isotope co., LTD(CNNC). All patients signed the inform consent form before RIRA. Therapeutic dose activities of (131)iodine were administrated by two physicians depend on thyroid residues status and whether had distant metastasis. In general, the dose activities were as follows: 1.11～3.7 GBq（30~100 mCi）of (131)iodine for low-risk cases; 3.7 ~5.55 GBq (100~150 mCi) for intermediate-risk cases (26); and 150~200 mCi (5.55~7.40 GBq) for high-risk cases. In order to enhance the effect of intestinal absorption for (131)iodine, we suggested patients having a abrosia two hours before and after taking (131)iodine. And physicians also suggested patients having a good rest and scaling up nutrition in hospital. Post-treatment WBIS was curried out 5~7 days after giving therapeutic dose activities of (131)iodine, including the whole body, regional imaging of cervical region and chest imaging .We used dual head digital gamma camera(Infinia Hawkeye 4, GE, USA) for both Post-treatment and diagnostic WBIS. The apparatus has high-powered parallel aperture collimator, and the set up parameters for energy peaks with 364 keV, window width with 20% , matrix with 64×64 and enlargement factor with 2 times, respectively.

Therapeutic evaluation

All patients have underwent neck ultrasound and diagnostic WBIS after taking (131)iodine 4~6 months and measured serum indexes. Successful ablation judgment standard is defined as no evidence of lesions on diagnostic WBIS, Tg < 1ng/mL with negative TgAb（6）.

Statistical analysis

SPSS version 20.0 was used to analyzing our data. Normally distributed continuous data were analyzed using unpaired Student's t-test, and were showed as mean ± standard deviation. Non-normally distributed data were showed median(M) and inter-quartile range(IQR), and data compared were analyzed using Mann–Whitney's U test. We have used receiver operating characteristic (ROC) analysis to generating ROC curves and getting the optimum cutoff values of Tg and Tg/TSH ratio. Univariate and multivariate logistic regression analysis was performed to assess the predictors of successful RIRA. The significance level was 0.05 of the P analysis values.

Results

Baseline characteristics

A total of 190 patients who were accepted RIRA and assessed in this study. Baseline characteristics of the study population successful ablations are summarized in Table I.

The study most were female (137; 72.1%) .The patients' age range 18 to 77 years(39.98±0.88). One hundred and seventy-one patients (90.0%) were papillary carcinomas, and another patient (19; 10.0%) were follicular carcinomas. Nineteen patients (65; 34.2%) were cervical lymph node metastases and 33 patients (17.4%) had distant metastasis. One hundred and twenty-eight (67.37%) patients were successful ablation, and another patient (62; 32.63%) were unsuccessful ablation. Patients' gender, age, pathological types and cervical lymph node metastasis did not difference between successful and unsuccessful group(all P＞0.05). However, there was significance statistically difference between successful and unsuccessful group about whether had distant metastasis or not(F=4.57, P ＜ 0.05). There were significance statistically difference between successful and unsuccessful group about Tg and Tg/TSH ratio (t=6.85, 9.46, respectively, all P＜0.01). The group of successful has hold 51.61% when the Tg levels more than 38.18 ng/ml, however, the unsuccessful just 6.92%. The group of successful has hold 58.06% when the Tg/TSH ratio more than 0.969, however, the unsuccessful just 12.5%.

Table I. Comparison of characteristics of patients with successful and unsuccessful ablation.

characteristics	successful ablation n=128（67.37%）	unsuccessful ablation n=62（32.63%）	t /X^2 value	P value
Gender				
male	37（28.91%）	16（25.81%）		
female	91（71.09%）	46（74.19%）	X^2=0.200	0.655
Age				
45 or less	88（68.75%）	42（67.74%）		
More than 45	40（31.25%）	20（32.26%）	X^2=0.020	0.889
Pathological types				
papillary carcinoma	114（89.06%）	57（91.94%）		
Follicular carcinoma	14（10.94%）	5（8.06%）	X^2=0.383	0.536
Lymphatic metastasis				
Yes	47（36.72%）	18（29.03%）		
No	81（63.28%）	44（70.97%）	X^2=1.096	0.295
Distant metastasis				
Yes	17（13.28%）	16（25.81%）		
No	111（86.72%）	46（74.19%）	X^2=4.566	0.033
Ablation dose (mCi)				
130 or less	27(21.09%)	43(69.35%)		
More than 130	101(78.91%)	19(30.65%)	X^2=41.809	0.001
TSH（mIU/L）				
M（IQR）	8.72(19.70.88.13)	24.09(2.34.79.85)	t=8.373	0.002
50 or less	46（35.94%）	37（59.68%）		
More than 50	82（64.06%）	25（40.32%）	X^2=9.569	0.002
Tg（ng/ml）				
M（IQR）	6.54（0.19-21.65）	26.32（18.28-42.93）	t=6.846	0.001
38.18 or less	121（93.08%）	30（48.39%）		
More than 38.18	9（6.92%）	32（51.61%）	X^2=49.22	0.001
Tg/TSH ratio				
M（IQR）	0.19（0.04-1.07）	1.61（0.27-2.54）	t=9.465	0.001
0.969 or less	112（87.50%）	26（41.94%）		
More than 0.969	16（12.50%）	36（58.06%）	X^2=43.62	0.001

M, Median, IQR, Interquartile range.

The result of ROC analysis for prediction efficacy of Tg and Tg/TSH ratio with RIRA

According to the ROC curve (Fig 1), the areas under the curve (AUC) for Tg level and Tg/TSH ratio were 0.772 [95% confidence interval(CI): 0.698-0.847] and 0.802 (95%CI: 0.728-0.876), respectively. The optimum cutoff value for Tg to predict ablation curative effect was 38.18 ng/ml and the sensitivity and specificity were 87.50% and 58.06%, respectively. And for the Tg/TSH ratio optimum cutoff value was 0.969, and the sensitivity and specificity was 93.75% and 56.45%, respectively. The other related statistical indicators with ROC analysis of cutoff values for Tg and Tg/TSH ratio are summarized in Table II.

Table II. ROC analysis of cutoff values for Tg and Tg/TSH ratio with related statistical indicators

Cutoff value	SEN (95% CI)	SPE (95% CI)	+LR (95% CI)	-LR (95% CI)	+PV (95% CI)	-PV (95% CI)
TTR ≤0.969	93.75 (88.1-97.3)	56.45 (43.3-69.0)	2.15 （1.7-2.7）	0.11 (0.05-0.2)	81.6 (74.4-87.5)	81.4 (66.6-91.6)
Tg ≤38.18	87.50 (80.5-92.7)	58.06 (44.8-70.5)	2.09 (1.7-2.6)	0.22 (0.1-0.4)	81.2 (73.6-87.3)	69.2 (54.9-81.3)

TTR, Tg/TSH ratio ;SEN, Sensitivity ; SPE, Specificity; +LR, positive likelihood ratio ; -LR, negative likelihood ratio; +PV, positive likelihood ratio; -PV, negative likelihood ratio; CI, confidence interval.

Outcomes of logistic regression analysis

In univariate logistic regression analysis, distant metastasis, initial ablation (131)iodine dose, TSH level, Tg level and Tg/TSH ratio were related predictor of successful RIRA(all $P < 0.05$), so they were performed with multivariate regression analysis(Table III). According multivariate regression analysis shows only initial ablation (131)iodine dose, Tg level and Tg/TSH ratio remained significantly associated with successful ablation. The more initial ablation (131)iodine dose is, the higher successful ablation rate will. The correlation for Tg/TSH ratio with OR 9.43(3.45-25.64) was more stronger than alone Tg with OR 3.14(1.25-7.87).

Table III. Multivariate analysis for Tg levels, Tg/TSH ratio of successful ablation.

Variable		OR（95% *CI*）	*P* value
Tg/TSH ratio	≤0.969:＞0.969	9.43（3.45-25.64）	＜0.01
Tg （ng/ml）	≤38.18:＞38.18	3.14（1.25-7.87）	0.014
Ablation dose(mCi)	＞130:≤130	2.38（1.09-5.18）	0.029

OR, odds ratio.

Discussion

Thyroglobulin is one of iodide glycoprotein of thyroid follicular cell produced, stored in the follicular cavity. Its plasma half-life is 29.9±2.8 hours and biological half-life is 3~4 days. Its secretory rate is 1.67 mg/kg/d under the stable state. The Tg stored follicular cavity will release into blood under the condition of TSH stimulated and lysosomal enzyme hydrolyzed（7）. In healthy people, only a few physiological dosage Tg release into blood(8). However, the half-life of Tg for patients with DTC will shorten and become no circadian and seasonal change. So measured Tg level is both sensitivity and specificity higher means, especially under the condition of TSH stimulated for patients of DTC after underwent total thyroidectomy（9,10）. But, levels of Tg measured will be restricted by some factors.Therefore, this study aim to use TSH to correct Tg and analyzing Tg/TSH ratio to predict value of RIRA for the patients with DTC. There is a very important significance to assess the outcome for DTC of RIRA, and it helps to guide making more appropriate individualized plan of diagnosis and treatment in the clinical work.

In this study, we found age, gender, pathological types and cervical lymph node metastasis did not difference between successful and unsuccessful group, while the levels of Tg have significant correlation, and the view is consistent with other studies（5,11,12）. This study also found that the success rate for distant metastasis group is lower than non-distant metastasis group, which is perhaps the metastasis lesion have more stronger ability taking in (131)iodine than residual thyroid tissue while the later getting less under the same therapeutic (131)iodine dose. Besides, our results show the more initial therapeutic dose gives, the higher success rate will. The point is consistent with other studies（13,14). So the guides（3, 6） suggested that if the patients have distant metastasis, they should be increased the initial therapeutic dose activities（15.

In this study, optimum cutoff value is 38.18 ng/ml. Meanwhile, patients with Tg level < 38.18 ng/mL before RIRA had 3.4 times greater chance of successful ablation compared to those with Tg > 38.18 ng/mL with sensitivity of 87.50%, specificity of 58.06%, PPV of 81.2%, and NPV of 69.2%. This indicates that the lower Tg before RIRA is, the more chance for successful ablation will. Therefore, we can suggest that the surgeon as much as possible to eliminate the thyroid lesion and residual tissue for DTC patients. The cutoff value and the rate successful ablation of this study is slightly higher than Kendler' finding, who thought the Tg levels < 18 ng/mL before RIRA had 5.89 times greater chance of successful ablation compared to those with Tg > 18 ng/mL with sensitivity of 71.4%, specificity of 70.2%, PPV of 71.4%, and NPV of 70.2% （5）.As well, Nosheen's study also performed ROC analysis and found the higher sensitivity and specificity, and the rate of successful ablation was 89% with Tg ≤14.5 ng/ml, while it just was 33% with Tg ＞14.5 ng/ml（12）. Tg with optimum cutoff value of this study is different with other studies (11,16),it maybe due to the different laboratories and measurement kit and different intervals. Besides, the ability of thyroid intake iodine also is different because of regional differences, and our study analyzed the patients used higher (131) iodine therapeutic dose activities, which may affect the level of Tg.

Another retrospective study（17）had analyzed 133 patients with DTC of total thyroidectomy, and concluded that before RIRA the Tg＜8.55 ng/ml with sensitivity of 88%, specificity of 72%, PPV of 47%, and NPV of 95%. Above of these studies showing that the Tg has high sensitivity for predicting curative effect for initial ablation, and the lower the Tg is, the higher the effect will. However, the specificity of Tg is not high, it can't eliminate the situation of negative Tg.

What's more, our study also found the Tg/TSH having the more stronger correlation than alone Tg in the outcome of initial ablation. It is precisely because of this stronger correlation. Tg/TSH maybe helps to predict curative effect for initial ablation.

According to the ROC analysis, this study has got the optimum cutoff value of Tg and Tg/TSH. And we indicated that the optimum cutoff value of Tg/TSH with 0.969. The group of successful has held 58.06% when the Tg/TSH ratio more than 0.969, however, the unsuccessful just 12.5%. Besides, patients with Tg/TSH < 0.969 before RIRA had 9.43 times greater chance of successful ablation compared to those with Tg > 0.969 with sensitivity of 93.75%, specificity of 56.45%. Therefore, using Tg/TSH with higher sensitivity and PPV to evaluate the outcome of initial ablation has more advantages than alone Tg, that is 93.75% vs. 87.50% and 2.15 vs. 2.09. Zubair（5） similar studies analyzed the value of Tg and Tg/TSH for 75 patients with DTC, found the same success rate(60%) in our study. Lin's research indicated both Tg and Tg/TSH can be used as a predictor for distant metastasis in patients with DTC with total thyroidectomy（18).

Conclusions

In summary, our study concludes that the Tg/TSH ratio has stronger than alone Tg in predicting successful RIRA in patients with DTC. In order to provide more reliable theoretical foundation for clinical diagnosis and treatment, more clinical studies with larger samples and better tests with prospective designs are necessary to test and verify the real value of Tg/TSH ratio of DTC patients in the future.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This study was authorized an approval from Ethical Review Committee First Affiliated Hospital of Guangxi Medical University.

Consent for publication

The information to be published in this article is approved by the patients.

Publication of clinical datasets

The information to be published in this article is approved by the patients.

Competing interests

There are no conflicts of interests.

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