

Clinical Outcomes and influence factors of differentiated thyroid carcinoma with negative preablative stimulated thyroglobulin and iodine-positive lymph nodes: A retrospective analysis

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Abstract

Background To investigate the clinical outcome of postoperative differentiated thyroid carcinoma (DTC) patients with negative preablative-stimulated thyroglobulin (ps-Tg) and iodine-positive lymph node after the first radioablation. **Methods** A total of 136 DTC patients with ps-Tg < 2 ng/ml and iodine-positive lymph nodes who were initially treated by ¹³¹I at our hospital from May 2015 to February 2018 were enrolled. These patients were followed up for 6-36 months, and then were classified into 3 groups according to the clinical outcomes as follows: excellent response (ER) group, indeterminate response (IDR) group, and structural incomplete response (SIR) group. Univariate and multivariate analyses were performed to assess the differences of factors (e.g. age, gender, extraglandular infiltration) between 3 groups. **Results** The N stage (P=0.001), sizes of the displayed lymph nodes (P<0.001), ps-Tg level (P=0.002), and TgAb level (P=0.001) were significantly different among the 3 groups. The gender (P=0.615), age (P=0.332), the primary tumor size (P=0.311), extrathyroidal invasion (P=0.549), T stage (P=0.944), rate of lymph node metastasis (P=0.170), locations of the displayed lymph nodes (P=0.099), and degree of recurrence risk (P=0.783) were not significantly different among the 3 groups. The corresponding sensitivity, specificity, positive predictive value, and negative predictive values were 93.3%, 82.6%, 86.4%, and 91.3% respectively when the cut-off value of the lymph node size was 7.25 mm. **Conclusion** For the DTC patients with negative ps-Tg and iodine-positive lymph nodes, postoperative N stage, size of the displayed lymph nodes, and ps-Tg and TgAb levels could be used as sensitive indicators for predicting clinical outcomes.

Background

Serum thyroglobulin (Tg) measurement and ¹³¹I-whole body scan (¹³¹I-WBS) are important indexes for the postoperative follow up of the patients with differentiated thyroid carcinoma (DTC). Elevated serum Tg level and positive results in ¹³¹I-WBS generally suggest tumor recurrence or metastasis. Nevertheless, negative serum Tg and ¹³¹I-WBS results suggest that disease conditions of the patients are stable, and no recurrence or metastasis are expected to be found in such patients. However, inconsistencies between the Tg and ¹³¹I-WBS findings are very common in clinical practice. Over recent years, many studies have investigated the clinical outcomes, as well as the diagnosis and treatment strategies in patients with positive Tg and negative ¹³¹I-WBS results [1, 2]. However, few studies have focused on the patients with negative Tg and positive ¹³¹I-WBS results. Several previous studies have shown that negative Tg and positive ¹³¹I-WBS results could be found in 4.4% - 28.6% of the patients [3-6]. However, consensus on the clinical significances and management strategies has not yet been reached. The aim of this study was to postoperatively investigate the clinical outcomes and the influencing factors in DTC patients with negative preablative stimulating Tg (ps-Tg) and lymph node metastasis as shown by posttreatment ¹³¹I whole-body scan (Rx-WBS), and to explore the influencing factors. The reported findings could be used for the development of precise strategies for the diagnosis and treatment.

Methods

Patients and Data Collection

Data from the 892 DTC patients who received total thyroidectomy followed by radioactive iodine (RAI) remnant ablation at our hospital between May 2015 and February 2018 were retrospectively analyzed. The inclusion criteria were as follows: 1) negative ps-Tg (<2ng/ml) regardless of TgAb level[7]. and 2) ¹³¹I-SPECT/CT scan examinations at 5-6 days after ¹³¹I showed cervical lymph nodes, and ultrasound examinations showed cervical lymph nodes enlargement, suggesting high possibility of metastasis. The patients who had the ps-Tg ³ 2 ng/ml, and/or for whom ¹³¹I scanning only showed the residual thyroid tissues, while the ultrasound examinations did not suggest specific cervical changes, were excluded from the study. Finally, 136 patients including 30 males and 106 females were included. The mean age of the patients was 45.6±12.1 years. The doses of the ¹³¹I treatment were decided according to the following criteria: for the patients in whom the extrathyroidal invasion was found during the operation, and ultrasound examinations before ¹³¹I treatment suggested high possibility of lymph node metastasis, the dose of ¹³¹I was 150 mCi; while for the other patients, the dose of ¹³¹I was 100 mCi. Afterwards, TSH inhibition therapy was conducted, and the patients were regularly followed up. In the follow up, the three items of the thyroid function test, serum Tg, TgAb, and cervical ultrasound examination were routinely measured. Diagnostic ¹³¹I scanning was also conducted if necessary. According to the guidelines for DTC diagnosis issued by the American Thyroid Association in 2015[7], the clinical outcomes for the patients at 6-36 months after the initial ¹³¹I treatment were classified as excellent response (ER, n=90), indeterminate response (IDR, n=26), and structural incomplete response (SIR, n=20). There were no patients with the biochemical incomplete response (BIR). During the follow up, the Tg of the patients in the ER group were all <0.2 ng/ml or gradually decreased; the ultrasound examinations showed negative results; diagnostic ¹³¹I scanning did not show positive lesions, and thus no further ¹³¹I treatment or surgical treatment was conducted. While in the IDR group, three patients were confirmed with lymph node metastasis by lymph node biopsy, and surgical treatments were conducted for them; while the other 19 patients were continued to be followed up. For the patients in the SIR group, seven received surgical treatments after lymph node biopsy, and 13 received secondary ¹³¹I treatment.

Electro-chemiluminescence immunoassay (ECLIA, E170, Roche, USA) was used for the measurement of Tg and TgAb levels; the detection range of this method is 0.100-500.000 ng/ml and 10-4000 IU/ml, respectively. CLIA method (ADVIA CENTAVRXP, Bayer, Germany) was used for the measurement of TSH level. The detection range of CLIA method is 0.04-100.00uIU/ml. L-T4 inhibition therapy (2.0-2.5ug/kg/d) was adopted for all the patients at 48-72 h after ¹³¹I treatment, according to the ATA guidelines. SPECT/CT imaging (Symbia T16, Simens, Germany) was conducted for patients 5-6 days after ¹³¹I treatment. The ¹³¹I scanning in all patients was conducted independently by 3 experienced radiologists/technicians, and the agreement about the display of local lymph nodes was made among them.

Statistical analysis

SPSS 23.0 software was used for the statistical analysis. One-way analysis of variance, χ^2 test, and Kruskal-Wallis rank-sum test were used for the comparisons of gender, age, size of primary tumor, extrathyroidal invasion, T stage, postoperative N stage, rate of lymph node metastasis, sizes and locations of the displayed lymph nodes, degree of recurrence risks, ps-Tg, and TgAb among the 3 groups. LSD test was used for the comparison between two groups. Multi-factor logistic regression was used to assess the effect of the factors on the treatment responses. Mann-Whitney rank-sum test was used to analyze the differences in the size of the displayed lymph nodes between the ER group and non-ER group (including EDR and SIR groups), and to establish the receiver operating characteristic (ROC) curve of the association between lymph node sizes and ER. The optimal cut-off value was identified, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the size of the displayed lymph nodes for prediction of the clinical outcomes were calculated. $P < 0.05$ was considered statistically significant.

Results

General characteristics

The postoperative N stage ($H=13.157$, $P=0.001$), size of the displayed lymph nodes ($H=73.602$, $P < 0.001$), ps-Tg level ($H=12.234$, $P=0.002$), and TgAb level ($H=14.772$, $P=0.001$) were significantly different among the 3 groups. However, the gender ($\chi^2=0.971$, $P=0.615$), age ($F=1.111$, $P=0.332$), size of primary tumor ($H=2.335$, $P=0.311$), extrathyroidal invasion ($\chi^2=1.201$, $P=0.549$), T stage ($H=0.116$, $P=0.944$), rate of lymph node metastasis ($H=3.540$, $P=0.170$), location of the displayed lymph nodes ($\chi^2=4.619$, $P=0.099$), and degree of recurrence risk ($H=0.490$, $P=0.783$) were not significantly different among the 3 groups (**Table 1**). In addition, a multi-factor logistic regression analysis showed that postoperative N stage (OR:0.750, 95%CI: 0.161-3.500, $P=0.714$), ps-Tg (OR: 2.002, 95%CI: 0.856-4.679, $P=0.109$), and TgAb (OR: 1.001, 95%CI: 1.000-1.001, $P=0.052$) were not significantly associated with the treatment responses of the patients. However, the size of the displayed lymph nodes was significantly associated with the treatment responses of the patients in the 3 groups (OR:2.252, 95% CI: 1.761-2.878, $P < 0.001$).

Subgroup analysis

Association between N stages and clinical outcomes

There were 14 patients in the N0 subgroup, and all of them (14/14, 100%) achieved ER; 22 patients in the N1a subgroup, where 81.82% (18/22) of them achieved ER, and 18.18% (4/22) of them achieved IDR. In addition, 100 patients were in the N1b subgroup, 58.00% (58/100) of them achieved ER, 22.00% (22/100) achieved IDR, and 20% (20/100%) of them achieved SIR. The percentage of patients who achieved ER was lower in the N1b subgroup than the other two subgroups, while more patients in the N1b subgroup were with IDR and SIR; where all the SIR were found in the N1b subgroup.

Associations of ps-Tg and TgAb levels with clinical outcomes

The median ps-Tg level in the IDR subgroup was 1.85ng/ml (0.795-1.893ng/ml), which was significantly higher than the 1.09 ng/ml in the ER subgroup ($t=3.183, P=0.004$) and 0.34ng/ml in the SIR subgroup ($t=3.029, P=0.007$). However, the ps-Tg levels in the ER and SIR subgroups were not significantly different ($t=0.778, P=1.000$). The median TgAb level in the SIR subgroup was 900.05IU/ml(60.58-2738 IU/ml), which was significantly higher than the 40.42 IU/ml in the ER subgroup ($t=3.808, P<0.001$) and 39.02IU/ml in the IDR subgroup ($t=2.971, P=0.009$). However, the TgAb levels in the ER and IDR subgroups were not significantly different ($t=0.259, P=1.000$).

Association between lymph node sizes and clinical outcomes

The patients were further divided into the ER subgroup and non-ER subgroup (including the patients of IDR and SIR), according to the status of disease-free survival 6-36 months after the initial ^{131}I treatment. The analysis showed that the median size of the lymph nodes in the ER subgroup was 5.0mm(4.0-5.0mm), which was significantly lower than in the non-ER subgroup (10.0mm, 8.0-13.0mm; $U=298.00, P=0.000$). The ROC analysis of the association between lymph node sizes and disease-free survival (**Figure 1**) showed that the area under the ROC was 0.928 (95%CI: 0.877-0.979). Analysis of the ROC showed that when 7.25 mm was used as the cut-off diameter of the lymph nodes for the prediction of poor prognosis, the Youden index was the highest (0.759), and the corresponding sensitivity and specificity were 93.3% and 82.6, respectively. Among the 136 patients included in this study, true positive, false positive, true negative, and false negative were found in 38, 6, 84, and 8 patients, respectively. The accuracy of this cut-off value for the prediction of disease-free status in patients was 89.7% (122/136), and the corresponding PPV and NPV were 86.4% (38/44) and 91.3% (84/92), respectively. When the diameter of the lymph node was >7.25 mm, 45.45% (20/45) of patients achieved SIR, 40.91% (18/44) of patients achieved IDR, and 13.64% (6/44) of patients achieved ER. However, when the lymph node diameter was <7.25 mm, 91.3% (84/92) of patients achieved ER, 8.70% (8/92) of patients achieved IDR, and there was no patient with SIR.

Discussion

The change of the serum Tg after total thyroidectomy is an important indicator of residual tumor status and recurrence monitoring during the follow up. Over recent years, the predictive values of ps-Tg for disease remission, recurrence, persistence, or distant metastasis after ^{131}I treatment have received more and more attentions[8-10]. Lee *et al.*[11] have used 2 ng/ml as the cut-off ps-Tg level to predict the disease-free survival of DTC patients, and the NPV was as high as 94.9%. Yet, in our own clinical practice, we found that a lot of DTC patients with the ps-Tg <2 ng/ml also experienced local recurrence or metastasis, which could be explained by the following reasons: 1) Tg has already been synthesized by the lesions, but has not been released to the circulation[12]. For instance, in the present study, one patient had the ps-Tg of 1.68ng/ml, but the Tg level in the lymph node aspiration fluid was 20.56 ng/ml, which was evidently higher than the serum Tg level, which supported our hypothesis. 2) The level of the Tg produced by the lymph nodes with metastasis is too low, and is difficult to be detected by the monoclonal antibody assay[12]. 3) The conformation of the Tg changes, and it rapidly clears after entering the

blood[13] . 4) High level of Tg could lead to hook effect[14]. 5) TaAb could influence the measurement of Tg[15] ; 6) serum TSH level could influence the measurement of Tg. 7) DTC is poorly differentiated, and thus the synthesis and release of Tg are relatively low. However, the clinical outcomes of these patients after ^{131}I treatment still remain unclear.

This study used the DTC patients with the ps-Tg<2ng/ml, and lymph node metastasis detected by scanning after ^{131}I treatment, as the subjects. The patients were followed up for 6-36 months after the initial ^{131}I treatment. The obtained results showed that there were no patients with BIR, which was in agreement with the findings reported by Han *et al.*[12]The gender, age, size of primary tumor, extrathyroidal invasion, T stage, rate of lymph node metastasis, and degree of recurrence risk were not significantly different among the ER, IDR, and SIR groups. However, the N stage, sizes of the displayed lymph nodes, ps-Tg, and TgAb were significantly different among the 3 groups, suggesting that these factors could be the risk factors for poor prognosis.

The patients whose postoperative N stage was N0 were all combined with extrathyroidal invasion, and their T stages were T3 or T4. The preoperative ultrasound examinations and intraoperative exploration did not reveal any abnormal lymph nodes. ^{131}I -WBS after the operation showed that the size of the metastatic lymph nodes that with iodine uptake was generally small. ER were achieved in all these patients during the follow up, suggesting that for the ps-Tg negative patients with lymph node metastasis and the postoperative stage N0, the treatment responses were generally good despite the relatively advanced T stage. In addition, one ^{131}I treatment with the dose of 100-150mCi could achieve ER. SIR were only found in the N1b subgroup in this study, suggesting that compared with the patients in the N0 and N1a subgroups, the response to ^{131}I treatment in the N1b subgroup was relatively poor, although there were lymph nodes with iodine uptake. Therefore, early interventions, close monitoring, and timely treatments should be applied for the patients with N1b stage to reduce the rate of recurrence and improve the prognosis.

Previous studies[16]have shown that in DTC patients who had positive TgAb before the operation, TgAb level should be monitored during the follow up, since the continuous decrease of serum TgAb level indicates disease remission. On the contrary, continuous increase of serum TgAb levels may suggest the possibility of disease remission. Subgroup analysis of the ps-Tg and TgAb levels showed that the ps-Tg level was significantly higher in the IDR subgroup compared to ER and SIR subgroups, while the TgAb level in the SIR subgroup was significantly higher compared to ER and IDR subgroups. These findings suggest that in the cases of ps-Tg < 2 ng/ml, the increase of TgAb level is significant for poor prognosis. Therefore, close follow up, dynamic TgAb level monitoring, and timely interventions should be adopted for such patients, since they could help optimize the treatment strategies.

The multi-factor regression analysis employed in this study showed that the size of the displayed lymph nodes could be an independent factor affecting the clinical outcomes of the patients after ^{131}I treatment. When the sizes of the lymph nodes were lower than a certain cut-off value, the possibility of disease-free survival in the patients was the highest. The further ROC analysis showed that using 7.25 mm as the cut-

off value of the lymph node size could obtain the sensitivity and NPV of 93.3% and 91.3%, respectively. However, the specificity and accuracy were relatively low, which could be associated with the relatively small sample size in this study. Consequently, prospective studies with larger sample sizes are needed to verify the cut-off value of the lymph node size. In the patients whose displayed lymph node sizes were <7.25mm, 91.30% of them achieved satisfactory treatment efficacies at 6-36 months after the ¹³¹I treatment; in addition, no recurrence or disease persistence were found in this group. Therefore, for the DTC patients with the size of the displayed lymph nodes <7.25 mm, the longer interval of the follow up examinations could eliminate the over-examination, and could relief the mental and financial burdens of patients, thus improving their life quality. In contrast, for DTC patients with the size of the displayed lymph nodes >7.25 mm, satisfactory treatment efficacy was found in only 13.64% of them, while the lesions persisted in 45.45% of the patients during the follow up. Further treatments were suggested for these patients; 7 of them received secondary surgical treatment, and 13 of them received secondary ¹³¹I treatment. In addition, in 40.91% of patients the inhibitory Tg <0.2 ng/ml was observed during the follow up; the TgAb level was steady or tended to decrease, and ultrasound examinations suggested the abnormal structures of the cervical lymph nodes. However, diagnostic ¹³¹I SPECT/CT scanning did not show positive lesions. For these patients, biopsy was suggested since it can confirm the existence of metastatic lymph nodes. However, the ultrasound examinations showed that the lesions in most patients were steady and were not progressing, which is why TSH inhibition therapy was conducted, and the patients were further observed. However, no sufficient pathological evidence was obtained from these patients, which is one of the limitations in this study, and is also one of the reasons why the treatment response of these patients was IDR. As these patients continue to beat the risk of recurrence, they should be regularly followed up according to the ATA guidelines. The suspected metastatic lesions should be closely monitored, and further interventions should be timely provided for patients with the progressed disease.

Conclusions

In summary, for the DTC patients with negative ps-Tg, while ¹³¹I-SPECT/CT scan showed lymph node metastasis after the first ¹³¹I treatment, postoperative N stage, sizes of the displayed lymph nodes, and ps-Tg and TgAb levels resulted as more sensitive indicators for the prediction of the clinical outcomes. Most of the patients with the displayed lymph nodes in the size of <7.25 mm could achieve the disease-free survival status after ¹³¹I treatment.

Abbreviations

DTC=differentiated thyroid carcinoma

ps-Tg= preablative stimulating thyroglobulin

Rx-WBS= posttreatment ¹³¹I whole-body scan

ER =excellent response

IDR =indeterminate response

BIR =biochemical incomplete response

SIR =structural incomplete response

¹³¹I-WBS= ¹³¹I-whole body scan

RAI =radioactive iodine

ROC =receiver operating characteristic

PPV =positive predictive value

NPV =negative predictive value

Declarations

Ethics approval and consent to participate

The study ethics approval was granted from the local ethical committee of the Affiliated Hospital of Qingdao University, and the study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing of interests.

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Not applicable.

Authors' contributions

WZH designed the research; LXF,WGQ,XXT,ZYY and HN collected the data; LCH and LJ performed the data analysis and developed the model; WZH and LCH wrote the first draft of the manuscript; and WZH,

LCH and WXF critically edited and reviewed the final draft of the manuscript; LJ, WXF and WZH commented on and critically revised the manuscript. All the authors contributed to the conception of the study and approved the final manuscript.

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Table 1

Table 1 Comparisons of the general characteristics of patients in the 3 groups

	ER group	IDR group	SIR group	Statistics	P value
Gender (M/F)	18/72	6/20	6/14	0.971 (c ²)	0.615
Age (years)	46.0(38.7-53.0)	41(31.7-54.0)	47(37.0-59.0)	1.111 (F)	0.332
Size of the primary tumor (cm)	1.20(0.78-2.00)	1.50 (0.92-2.50)	1.40 (1.00-2.80)	2.335 (H)	0.311
Extrathyroidal invasion (Yes/No)	36/54	8/18	6/14	1.201 (c ²)	0.549
T stage					
T1/T2/T3/T4	24/8/36/22	8/0/12/6	4/2/12/2	0.116 (H)	0.944
Postoperative N stage					
N0/N1a/N1b	14/18/58	0/4/22	0/0/20	13.157 (H)	0.001
Rate of lymph node metastasis (%)	34.21 (13.71-50.00)	46.34 (28.57-50.00)	47.09 (28.00-68.75)	3.540 (H)	0.170
Recurrence stratification(n)					
Low /moderate /high risk	6/60/24	0/20/6	0/14/6	0.490 (H)	0.783
ps-Tg (ng/ml)					
TgAb (IU/ml)	1.09 (0.54-1.56)	1.85 (0.79-1.89)	0.34 (0.10-1.98)	12.234 (H)	0.002
	40.42 (21.64-184.83)	39.02 (19.88-270.17)	900.05 (60.58-2738.00)	14.772(H)	0.001

Figures

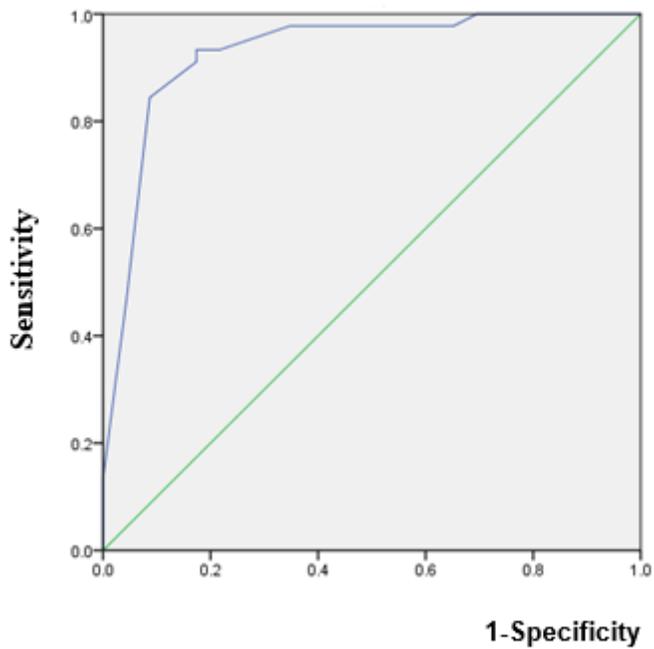


Figure 1

The ROC curve of lymph node size in predicting disease-free survival of the DTC patients (ROC curve, sensitivity, 1- specificity)

Supplementary Files

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- [Data.xlsx](#)