Endocrine (2019) 65:149–154
https://doi.org/10.1007/s12020-019-01914-z

ORIGINAL ARTICLE

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Is TSH suppression still necessary in intermediate- and high-risk papillary thyroid cancer patients with pre-ablation stimulated thyroglobulin <1 ng/mL before the first disease assessment?

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Received: 26 February 2019 / Accepted: 19 March 2019 / Published online: 28 March 2019

Abstract

Objective Since papillary thyroid cancer (PTC) patients with pre-ablation stimulated thyroglobulin (s-Tg) < 1 ng/mL generally have a favorable prognosis, is TSH suppression still necessary in intermediate- and high-risk PTC patients with pre-ablation s-Tg < 1 ng/mL after initial therapy? The aim of this study was to assess the rate of disease recurrence in intermediate- and high-risk PTC patients with pre-ablation s-Tg < 1 ng/mL according to TSH levels measured 1 year after initial therapy.

Methods A retrospective series of intermediate- and high-risk PTC patients with pre-ablation s-Tg < 1 ng/mL was analyzed. Disease status was defined as the presence or absence of structural disease during late follow-up. Patients were grouped according to TSH level at 1 year: group 1, TSH < 0.1 mIU/L; group 2, TSH 0.1–0.5 mIU/L; group 3, 0.5–2 mIU/L; group 4, >2 mIU/L.

Results This study included 166 patients (78.3% females, median age 44 years) of whom the risk of recurrence was intermediate in 97 (58.4%) and high in 69 (41.6%). The response to initial therapy at 1 year was excellent in 163 patients (98.2%) and indeterminate in 3 (1.8%). Group 1 consisted of 63 patients (38%), group 2 of 47 (28%), group 3 of 28 (17%), and group 4 of 28 (17%). During a median follow-up duration of 5.8 years, disease recurrence was observed in only 4 patients (2.4%). The rate of disease recurrence was not significantly different between the TSH groups.

Conclusion TSH suppression before the first response to treatment assessment does not seem to influence the rate of disease recurrence after initial therapy in intermediate- and high-risk PTC patients with pre-ablation s-Tg < 1 ng/mL.

Key Terms Thyroid cancer · Pre-ablation stimulated thyroglobulin · 1ng/mL · ^{131}I · TSH suppression

Introduction

Thyrotropin (TSH) suppression therapy has been commonly used for papillary thyroid cancer (PTC) patients after total thyroidectomy [1, 2]. The goal of TSH suppression varies dependent on the risk of disease recurrence and response to treatment. Current concept is that TSH suppression should be done before the first response to treatment assessment in intermediate- and high-risk PTC patients [3, 4]. The 2015 American Thyroid Association (ATA) guidelines recommend keeping TSH <0.1 mIU/L in high-risk patients and 0.1–0.5 mIU/L in intermediate-risk patients after total thyroidectomy and ^{131}I ablation. Once an excellent response to initial therapy is achieved, a lesser degree of TSH suppression is employed with a recommended range of 0.5–2.0 mIU/L.

There is emerging literature that has noted the presence of pre-ablation stimulated thyroglobulin (s-Tg) < 1 ng/mL after total thyroidectomy in a non-negligible number of PTC patients [5–8]. Owing to different study populations and cutoff values for anti-Tg antibodies (anti-TgAb) positivity, the reported prevalence varied from 9% to 65%. Despite of varying cutoff values defined among various studies, a high negative predictive value of pre-ablation s-Tg for persistent and recurrent disease has been documented unanimously, regardless of the disease staging. In a meta-analysis involving nearly 4000 thyroid cancer patients, the overall

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negative predictive value of pre-ablation s-Tg was reported to be as high as 94% with a cutoff value of 10 ng/mL [5].

Since PTC patients with pre-ablation s-Tg < 1 ng/mL generally have a favorable prognosis, is TSH suppression still necessary in intermediate- and high-risk PTC patients with pre-ablation s-Tg < 1 ng/mL after initial therapy? Like the low-risk PTC patients, TSH-suppression therapy is not recommended after initial therapy [9]. The aim of the present study was to investigate the rate of tumor persistence and recurrence in intermediate- and high-risk PTC patients with pre-ablation s-Tg < 1 ng/mL stratified according to TSH levels measured at 9–12 months from initial therapy. Our hypothesis was that TSH suppression may be unnecessary during this period in this group of patients.

Patients and methods

The study protocol was approved by our Institutional Review Board. The committee waived patient consent because this study was of retrospective design and used only deidentified clinicopathologic information.

Patients

In order to have follow-up period of at least 5 years for each case, all PTC patients seeking postoperative ^{131}I therapy at our department from May 2008 to Dec 2013 were retrospectively reviewed. All patients underwent post hoc stratification according to 2015 ATA criteria, and intermediate- and high-risk patients were first selected. Only patients with a pre-ablation s-Tg < 1 ng/mL and negative TgAb were finally analyzed.

According to the 2015 ATA risk stratification system, follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion) was considered as high risk. This criterion was not present in the 2009 risk stratification system. The extensive vascular invasion was identified and reported by our pathologists but the exact numbers of vascular invasion was not available for every case before 2016. As such, patients with follicular thyroid cancer were not considered in the study.

Treatment protocol

All patients underwent total thyroidectomy. Central compartment neck dissection was performed in patients when either biopsy-proven lymph node metastases or suspicious findings were preoperatively found on neck ultrasound (US) or when advanced primary tumors (T3 or T4) were noted. Lateral compartment neck dissection was performed in cases with biopsy-proven metastatic lateral neck lymphadenopathy.

Adjuvant ^{131}I therapy was initiated 1–4 months after surgery. All patients were routinely prepared with a low-iodine diet and levothyroxine (L-T4) withdrawal. At the time of ^{131}I administration, serum TSH levels were >30 mIU/L in all patients. We adopted an empiric activity dosing protocol to determine the prescribed activity of ^{131}I. Activity administered for adjuvant therapy ranged from 1.1 to 5.5 GBq.

All pre-ablation s-Tg and TgAb levels were measured with the high-sensitive electrochemiluminescence immunoassay during hypothyroidism just before the adjuvant ^{131}I administration at the same laboratory in our hospital. The assay used was the Roche Elecsys 2010 system (Roche Diagnostics GmbH, Mannheim, Germany), which was calibrated against the CRM-457 standard. This method provided a sensitivity of 0.04 ng/mL and a reference range of 0.5–55 ng/mL. Sera showing TgAb levels >40 IU/mL were excluded from the study. Quality control was ensured by assaying two levels of control sera in each series and by reassessing all sera showing a coefficient of variation exceeding 10%. A full description of s-Tg and TgAb measurements and the quality control has been published previously [6, 10].

Initial evaluation after ^{131}I therapy

All patients were evaluated 9–12 months after initial therapy by neck ultrasound (US) and s-Tg and TgAb measurements. Diagnostic whole-body ^{131}I scintigraphy was obtained in all high-risk patients and in selected cases with intermediate risk. The newly proposed response-to-therapy criteria were used to assess the clinical outcome after initial therapy.

Late follow-up

Patients without apparent disease at the initial evaluation were followed up by annual measurement of Tg during L-T4 therapy (Tg/T4) and TgAb and neck US. Imaging methods other than US (chest and mediastinal computed tomography (CT), fluorine-18 fluorodeoxyglucose-positron emission tomography/CT) were performed when Tg/T4 converted to levels >1 ng/mL. Diagnosis of a tumor in lesions detected by the imaging methods was made by cytology or histology and/or unequivocal ectopic uptake (excluding false-positive results) on whole-body ^{131}I scintigraphy or fluorine-18 fluorodeoxyglucose-positron emission tomography/CT.

The patients were grouped as follows according to the TSH level measured at the 9–12-month assessment (the first response to treatment assessment): group 1, TSH<0.1 mIU/L; group 2, 0.1–0.5 mIU/L; group 3, 0.5–2 mIU/L; group 4, >2 mIU/L. For patients (51/166, 30.7%) who had TSH

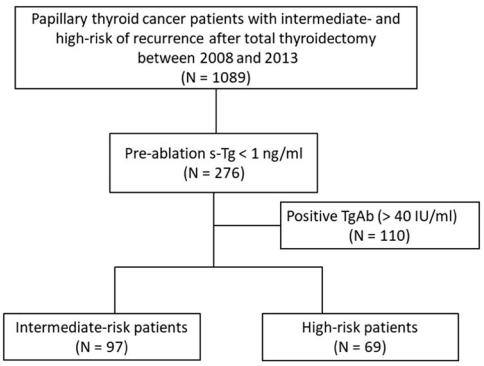

Fig. 1 Flow chart summarizing patients' inclusion at the study

measurements during LT4 therapy more than once on record, the mean value was calculated.

Continuous variables were expressed as median and range; categorical variables as number and percentage. Difference between categorical variables was evaluated with Pearson's chi-squared test.

Results

Characteristics of the patients

From May 2008 to June 2013, 1089 consecutive PTC patients with intermediate- and high-risk were referred to our department for adjuvant ^{131}I therapy after total thyroidectomy. Pre-ablation s-Tg was <1 ng/mL in 276 patients, among whom 110 had detectable TgAb (>40 IU/mL). The remaining 166 patients constituted our patient population (Fig. 1).

Total thyroidectomy was performed in all patients with apparently complete tumor resection and no signs of persistent disease after surgery. The initial risk of recurrence estimate was intermediate in 97 (58.4%) patients and high in 69 (41.6%). Of the 69 high-risk patients with pre-ablation s-Tg< 1 ng/mL, 55 patients (79.7%) had gross extra-thyroidal extension, 8 patients (11.6%) had metastatic lymph nodes <3 cm in largest dimension, 6 patients (8.7%) had both factors of high risk. The main characteristics of study cohort are indicated in Table 1.

Response

When evaluated 9–12 months after ^{131}I therapy, 3 patients (1.8%) were classified as indeterminate response. They had elevated s-Tg (1.1, 1.2, and 2.9 ng/mL), but no metastases were detected by US, chest CT, and diagnostic ^{131}I whole-body scintigraphy, and none of them received additional treatment. The remaining 163 patients (98.2%) were classified as excellent response.

Table 1 Patient characteristics

Parameter	Value
No. of patients	166
Gender, *n* (%)	
Women	130 (78.3)
Men	36 (21.7)
Age (years), median (range)	44 (16–77)
Surgery, *n* (%)	
TT	21 (12.7)
TT+central neck dissection	76 (45.8)
TT+central and lateral neck dissection	69 (41.6)
Histology, *n* (%)	
Classical papillary cancer	160
Follicular variant	6
Tumor size (cm), median (range)	2.6 (0.3–4.6)
Multi-centricity of the tumor, *n* (%)	74 (45.1)
Extra-thyroid invasion, *n* (%)	
No	62 (37.3)
Minimal extra-thyroid invasion	49 (29.5)
Gross extra-thyroid invasion	55 (33.1)
Number of lymph node resected, median (range)	8 (0–67)
Number of positive lymph nodes, median (range)	5 (0–35)
Presence of extra-nodal extension, *n* (%)	8 (4.8)
T[a], *n* (%)	
1a	57 (34.3)
1b	21 (12.7)
2	19 (11.4)
3a	9 (5.4)
3b	33 (19.9)
4	27 (16.2)
N[a], *n* (%)	
0	32 (19.3)
1a	77 (46.3)
1b	57 (34.3)
M[a], *n* (%)	
0	166 (100)
Staging [a], *n* (%)	
I	129 (77.7)
II	29 (17.5)
III	8 (4.8)
IV	0
Initial risk classification	
Intermediate risk	97 (58.4)
High risk	69 (41.6)
^{131}I-administered activity (GBq), median (range)	3.7 (1.1–5.5)
Follow-up (years), median (range)	5.8 (5.0–9.0)

TT total thyroidectomy

[a]Tumor–node–metastasis staging was determined according to the eighth edition of American Joint Committee on Cancer TNM staging system

Table 2 Characteristics of the patients with structural disease recurrence

Gender	F	M	F	F
Age at diagnosis (years)	23	42	25	51
Stage	I	I	I	I
Initial-risk classification	Intermediate	Intermediate	High	High
Interval between surgery and recurrence (years)	2.8	4.0	3.5	4.2
Non-stimulated Tg at time of recurrent disease (ng/mL)	0.43	0.34	0.87	0.72
Site of recurrence	Neck LN	Neck LN	Neck LN	Neck LN
Positive imaging method	US	US	US	US

F female, *M* male, *Tg* thyroglobulin, *LN* lymph node, *US* ultrasound

The patients were grouped according to the TSH levels measured at 9–12 months from initial therapy: 38% in group 1 ($N = 63$), 28% in group 2 ($N = 47$), 17% in group 3 ($N = 28$), and 17% in group 4 ($N = 28$).

Late follow-up

The time of follow-up ranged from 5.0 to 9.0 years (median 5.8 years). During follow-up, 4 patients (2.4%) were confirmed to have structural recurrent diseases, all of which were locoregional diseases and detected by neck US. In the initial evaluation after ^{131}I therapy, 4 patients were classified as excellent response. The characteristics of the four patients with recurrence are shown in Table 2. No preoperative or immediate postoperative clinicopathologic characteristics of patients associated with recurrence could be found. The three patients achieved remission after reoperation and ^{131}I therapy. The other patient refused reoperation and was still in observation status. The remaining 162 patients without tumor recurrence were not submitted to any additional therapy.

In the last assessment, all patients had a Tg/T4< 1 ng/mL. Specifically, 130 had an undetectable Tg/T4, 26 had a Tg/T4 between 0.05 and 0.2 ng/mL, and 10 had a Tg/T4 between 0.2 and 1 ng/mL. None of these 10 patients with a Tg/T4> 0.2 ng/mL showed an increase in Tg concentration. There was no case of death due to the disease.

The rate of structural disease was not significantly different between TSH groups (Pearson's chi-squared test, $p = 0.25$; Table 3).

Table 3 Structural disease at last assessment according to TSH range at 9–12 assessment

TSH range at 9–12 assessment	Structural disease, *n* (%)	
	Absent	Present
<0.1 mIU/L, $n = 63$	61 (96.8)	2 (3.2)
0.1–0.5 mIU/L, $n = 47$	46 (97.9)	1 (2.1)
0.5–2.0 mIU/L, $n = 28$	27 (96.4)	1 (3.6)
>2.0 mIU/L, $n = 28$	28 (100)	0

Pearson's chi squared test, $p = 0.25$

TSH thyrotropin

Discussion

Given its comparatively prolonged overall survival, the healthcare costs of thyroid cancer are expected to continue to rise and pose a great challenge to the society [11, 12]. Many authors [7, 13–17] and even the recently implemented eighth edition of the AJCC staging system [18] for thyroid cancer have opted to identify low-risk groups for disease recurrence and death and separate them from those with poor response to the initial therapy in order to move toward more cost-effective care and personalize the rhythm of follow-up. It is therefore important to identify independent biological parameters to predict disease status. A number of studies have noted that the presence of pre-ablation s-Tg < 1 ng/mL is not an uncommon clinical scenario in thyroid cancer patients after total thyroidectomy. Our study demonstrated the presence of pre-ablation s-Tg < 1 ng/mL and negative TgAb in 15.2% of intermediate- and high-risk PTC patients after total thyroidectomy. Although the exact reason for the prevalence of pre-ablation s-Tg < 1 ng/mL in certain thyroid cancer patients was unknown, the prognosis of this kind of patients was generally good with a recurrent rate of 2.4% observed in the present study. Very recently, Barres et al. [8] have investigated the prognostic value of pre-ablation s-Tg in terms of long-term remission in a large cohort of 1093 thyroid cancer patients. Of the 346 patients with pre-ablation s-Tg < 1 ng/mL and negative TgAb, only 17 patients (4.9%) experienced disease recurrence at a median follow-up of 5.6 years. In the subgroup analysis of local aggressive disease staged as T3 and T4, the pre-ablation s-Tg also demonstrated high negative predictive value. This interesting finding was in good agreement with ours.

TSH-suppression therapy has been the mainstay in the post-operative management of PTC [2]. However, even mild TSH-suppression therapy (TSH between 0.1 and 0.4 mIU/L) has been shown to impair, to a varying extent,

quality of life of thyroid cancer patients [19, 20]. Accordingly, a risk-adapted TSH-suppression strategy has been proposed in the recent ATA guidelines [3]. After initial therapy, TSH suppression is recommended only in intermediate- and high-risk patients while low-risk patients should maintain normal–low TSH levels. However, our study demonstrated that intermediate- and high-risk PTC patients with pre-ablation s-Tg < 1 ng/mL generally had a good prognosis and serum TSH levels during the first year did not seem to influence the rate of disease recurrence in this group of patients.

Several authors [7, 13–16] have proposed appropriate reduction in the intensity of therapy in PTC patients with low or undetectable postoperative Tg. In a prospective study by Orlov et al. [13], 124 thyroid cancer patients with low- and intermediate-risk and postoperative s-Tg < 5 ng/mL and negative neck US were not referred for ^{131}I therapy. There has been no evidence of recurrent disease over the 6-year follow-up period. Rosario et al. [16] have prospectively studied the long-term efficacy of low activity ^{131}I therapy in intermediate-risk PTC patients with higher-risk features and postoperative non-stimulated Tg < 0.3 ng/mL. On the basis of a recurrence rate of 4%, the authors concluded that low postoperative non-stimulated Tg could be used as a criterion for the indication of low ^{131}I activity in intermediate-risk PTC patients even harboring higher-risk features. Our study highlighted the possibility of reducing the degree of TSH suppression in intermediate- and high-risk PTC patients with pre-ablation s-Tg < 1 ng/mL. Taken together, these results in combination with ours suggested that thyroid cancer patients with low or undetectable postoperative pre-ablation s-Tg levels generally had a good prognosis irrespectively of initial staging with appropriate reduction in the intensity of therapy and follow-up.

As is well known, the intensity of initial therapy including the extent of surgery and ^{131}I ablation therapy also significantly affects the prognosis of PTC patients [21, 22]. In the present study, the efficacy of TSH-suppression therapy was evaluated in intermediate- and high-risk PTC patients with pre-ablation s-Tg < 1 ng/mL using a cohort that was treated with a defined protocol for initial therapy. The median follow-up time was sufficiently long to appreciate long-term remission or disease recurrence. The tumor recurrence rate observed in our study (approximately 2.4%) was thus unlikely to be underestimated [23–27]. Nevertheless, the study has its limitations such as the retrospective nature of the inclusion. However, the management of our patients was harmonious with the national and international guidelines. In addition, the adverse effects of TSH-suppression therapy on cardiovascular disease and bone metabolism were not assessed. Moreover, since the study sampled and enrolled PTC patients from a single center, the number of patients with recurrent disease was small. Further multicenter or larger cohort-based studies are required to overcome this limitation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The study was approved by the Institutional Review Board of West China Hospital, Sichuan University and the requirement of written informed consent was waived.

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