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RESEARCH

Adherence to Suppression Therapy Guidelines After Thyroid Cancer Surgery

Petra Nemcikova[1,2] · Vojtech Kratochvil[2] · Samuel Srobar[2] · Vladimir Musil[3,4] · Richard Sotornik[1] · Tereza Grimmichova[1] · Ludmila Brunerova[1]

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Abstract

Objective Thyroid-stimulating hormone (TSH) suppression therapy with levothyroxine is essential for patients with differentiated thyroid cancer (DTC) after surgery. While it reduces recurrence risk in high-risk patients, its intensity should be tailored according to risk stratification. This study aimed to evaluate physicians' adherence to recommendations on TSH suppression therapy in patients with DTC after surgery and/or radioiodine therapy.

Design This prospective study included patients managed at two specialized centres following total thyroidectomy for DTC.

Methods Patients on a stable levothyroxine dose for at least 3 months were enrolled. Data collected at the last follow-up included serum TSH, free thyroxine (FT4), free triiodothyronine (FT3), thyroglobulin, and anti-thyroglobulin antibody levels. TSH values were categorized as within target range, below target (over-suppressed), or above target (under-suppressed) according to American Thyroid Association guidelines and recurrence risk (low, intermediate, high).

Results Of 365 patients (female/male ratio: 306/59; mean age: 54.7 years for females, 56.3 years for males), only 136 (37.3%) achieved target TSH levels. TSH was under-suppressed in 86 patients (23.6%) and over-suppressed in 129 patients (35.3%). Over-suppression was most prevalent (62%) in the low-risk group.

Conclusions Adherence to guideline-recommended TSH suppression therapy in DTC remains suboptimal, with frequent over-suppression, particularly in low-risk patients. These findings highlight the need for individualized suppression strategies balancing recurrence prevention and the avoidance of iatrogenic complications.

Keywords Differentiated thyroid cancer · Adherence to guidelines · Risk stratification · Suppression therapy · Over-suppression

Abbreviations

AE	Adverse event
AJCC	American Joint Committee on Cancer
ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
CI	Confidence interval
DTC	Differentiated thyroid cancer
FTC	Follicular thyroid cancer
PTC	Papillary thyroid cancer
RAI	Radioactive ^{131}iodine
TNM	Tumour/node/metastasis
TSH	Thyroid-stimulating hormone

✉ Vladimir Musil
vladimir.musil@lf3.cuni.cz

[1] Department of Internal Medicine, Third Faculty of Medicine and Faculty Hospital Kralovske Vinohrady, Charles University, Srobarova 50, 100 34 Prague, Czech Republic

[2] Department of Nuclear Medicine of Hospital Ceske Budejovice, B. Nemcove 585/54, 37001 Ceske Budejovice, Czech Republic

[3] Centre of Scientific Information, Third Faculty of Medicine, Charles University, Ruska 87, 100 00 Prague, Czech Republic

[4] Department of Anatomy, Second Faculty of Medicine, Charles University, Plzenska 311, 150 00 Prague, Czech Republic

1 Introduction

Differentiated thyroid carcinomas (DTC) comprise traditionally of papillary (PTC) and follicular (FTC) carcinomas. The recent WHO classification of thyroid neoplasms (2022) redefines follicular-derived tumours, based on but not limited to molecular genetic profiling, into benign, low-risk, and

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malignant categories, with non-invasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) as a low-risk subtype [1].

DTCs account for over 90% of thyroid malignant tumours and have a very good prognosis. In Czechia, 1079 new cases were diagnosed in 2022, with an incidence of 10.0 per 100,000 persons [2, 3].

Primary DTC treatment involves surgery, radioiodine therapy according to the risk stratification and thyroid hormone suppression therapy. The latter is a standard follow-up treatment, particularly in patients with high risk DTC to reduce the recurrence and cancer-related mortality [4]. Target TSH levels depend on risk: < 0.1 mIU/L for incomplete structural response, 0.5–2.5 mIU/L for low- and intermediate-risk patients, and 0.1–0.5 mIU/L for high-risk patients with excellent responses [4]. Nonetheless, excessive suppression may cause various adverse events including arrhythmias, osteoporosis, and mental health problems [5]. Despite the importance of this topic, only a few studies focused on the adherence to current guidelines in terms of suppression therapy, have been published so far, in general showing unsatisfactory results [6–14]. The aim of our study was to assess the adherence to current recommendations on suppression therapy in DTC among physicians from two centres.

2 Methods

Participants were recruited from the Tertiary Centre for the treatment of differentiated thyroid cancer (DTC) at the Department of Nuclear Medicine, Hospital České Budějovice (Southern Bohemia), and the Secondary Centre for the treatment of DTC at the Faculty Hospital Královské Vinohrady in Prague. The inclusion criteria were as follows: patients with DTC who were at least 1 year post-total thyroidectomy, regardless of whether they had undergone radioiodine therapy, and were on stable levothyroxine substitution–suppression therapy for at least the last 3 months, with target TSH levels documented at inclusion. The exclusion criteria involved any acute or decompensated chronic illness or non-compliance by the patient. The project and protocols were approved by the Ethics Committee of the Faculty Hospital Královské Vinohrady (EK-VP/13/0/2022) and conducted in accordance with the latest version of the Declaration of Helsinki. All participants provided written informed consent.

The initial levothyroxine dose was prescribed individually by the attending endocrinologist, taking into account patient body weight (approximately 1.6–2.2 µg/kg/day as a starting range), age, comorbidities, and ATA recurrence risk category. TSH values were routinely reassessed approximately 3 months after initiation or any dose adjustment, and therapy was modified when necessary to reach the target TSH level.

Target TSH levels were defined as:

- 0.5–2.0 mU/L in low-risk patients,
- 0.1–0.5 mU/L in intermediate-risk patients, and
- < 0.1 mU/L in high-risk patients,

according to the American Thyroid Association recommendations [4]. Higher TSH levels were categorized as insufficient substitution/suppression, while lower TSH levels than the target were categorized as over-suppression.

A total of 365 patients (306 females [83.8%]/59 males [16.2%], mean age: females 54.7 ± 15.3 years, males 56.3 ± 15.8 years) were included in the study. Basic characteristics of the participants are summarized in Table 1. Patients were stratified into three groups according to recurrence risk: low, intermediate, and high.

3 Statistical Methods

The statistical analysis was conducted with a structured and rigorous approach:

- Descriptive Statistics: Measures of central tendency (mean, median) and variability (standard deviation, percentiles) were calculated for continuous variables.
- Comparative Analysis: Risk-stratified adherence rates were calculated as proportions, highlighting differences across risk categories.
- Software Tools: Validated statistical software MATLAB a JASP 0.17.2.1 were used for data analysis and visualization, ensuring reproducibility and precision.
- Clinical Relevance: The results were interpreted within the framework of established guidelines, emphasizing their implications for patient care rather than focusing solely on numerical significance.

Table 1 Demographic composition of studied set of patients

Sex	Number of patients	Age ± st.dev [years]
Men	59	56.3 ± 15.8
Women	306	54.7 ± 15.3

4 Results

4.1 Demographic Composition

The analysed cohort consisted of 365 patients, with a significant predominance of females (306; 83.8%) compared to males (59; 16.2%). The mean age of male patients was 56.3 years (± 15.8 years), while the mean age of female patients was 54.7 years (± 15.3 years).

4.2 Adherence to Recommended TSH Levels (Fig. 1)

This stacked bar chart illustrates the proportion of patients with TSH levels within the recommended range (Target Levels), below the range (Under-suppressed), and above the range (Over-suppressed) for low-, medium-, and high-risk groups.

In addition, we evaluated whether the prescribed L-thyroxine doses were adequate in relation to patient body weight and ATA risk category; these data were incorporated into the analysis of achieved TSH suppression.

Overall, only 136 patients (37.3%) achieved serum TSH levels within the recommended target range according to their recurrence risk. The remaining participants had TSH levels either below (129 patients, 35.3%) or above (100 patients, 27.4%) the recommended treatment range.

The results according the risk stratification are summarized in Table 2.

- Low Risk Group (208 patients):
  - The recommended TSH range for this group was 0.5–2 mIU/l.
  - Target TSH levels were achieved in 86 patients (41.3%), while 37 patients (17.8%) exhibited under-suppression, and 85 patients (40.9%) experienced over-suppression.
- Intermediate Risk Group (131 patients):
  - The recommended TSH range was 0.1–0.5 mIU/l.
  - Adherence to these guidelines was observed in 38 patients (29.0%), while 49 patients (37.4%) were

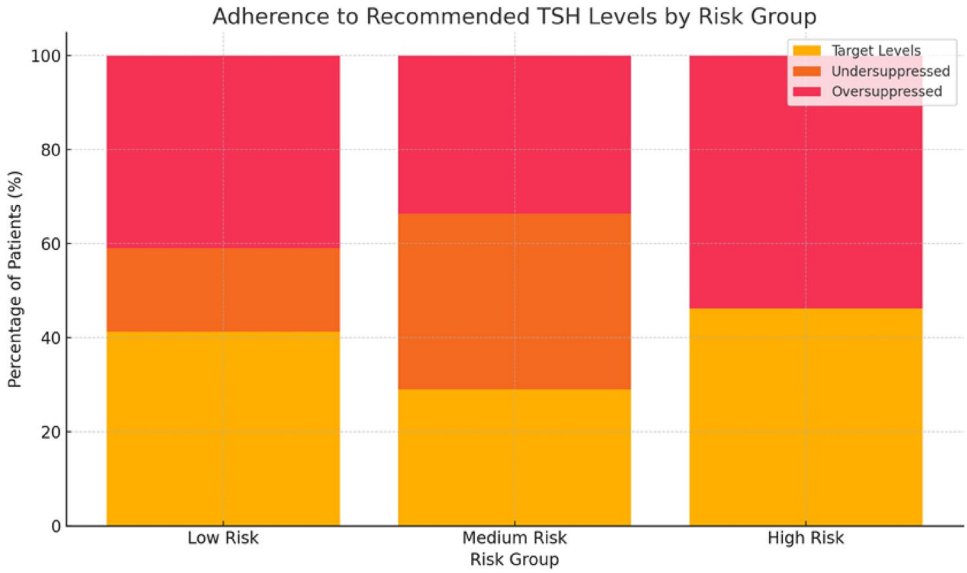

Fig. 1 Adherence to recommended TSH levels by risk group

Table 2 Rate of proper adherence of TSH level to recommended values for low, medium and high risk of reoccurrence thyroid carcinoma

Risk of recurrence	Recommended TSH level [mIU/l]	Target TSH levels (according to risk category)	TSH out of recommended range (according to risk category)		Total number of patients
			Under-suppressed	Over-suppressed	
Low	0.5–2	86 (41.3%)	37 (17.8%)	85 (40.9%)	208
Medium	0.5–2 up until 1 year after surgery or 0.1–0.5 later than 1 year after surgery	38 (29.0%)	49 (37.4%)	44 (33.6%)	131
High	< 0.1	12 (46.2%)	14 (53.8%)	–	26

Marginal values of TSH were considered as meeting the recommended levels

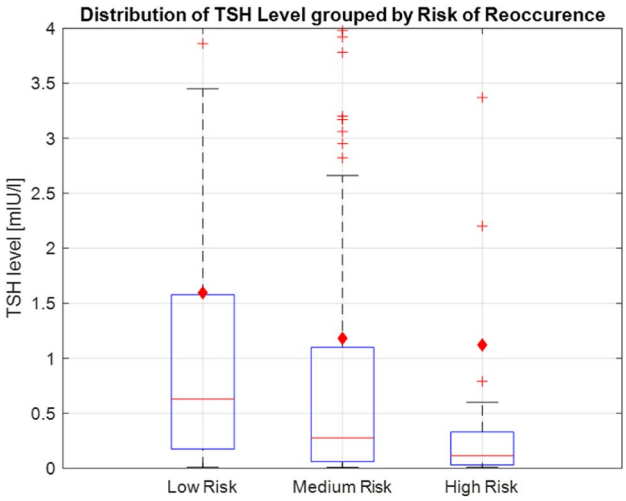

Fig. 2 Distribution of TSH levels by risk group

Table 3 Mean levels of TSH in studied population with low, medium and high ROR thyroid carcinoma

Risk of recurrence	TSH [mIU/l]		
	Mean ± st.dev	Value range	Percentile (25th, 50th, 75th, 90th)
Low	1.59 ± 6.88	0.01–98.28	0.17, 0.63, 1.59, 2.60
Medium	1.21 ± 2.49	0.01–18.00	0.06, 0.28, 1.10, 3.05,
High	1.10 ± 2.97	0.01–14.60	0.03, 0.12, 0.40, 4.01

under-suppressed, and 44 patients (33.6%) were over-suppressed.

- High Risk Group (26 patients):
  - For this group, the target TSH level was < 0.1 mIU/l, which aligns with aggressive management goals for high-risk thyroid carcinoma.
  - Adherence to this stringent target was achieved in 12 patients (46.2%), while 14 patients (53.8%) exhibited over-suppression.

4.3 Quantitative Analysis of TSH Levels (Fig. 2, Table 3)

The boxplot shows the distribution of TSH levels for low-, medium-, and high-risk groups, including the median, interquartile range, and outliers. Red diamonds show mean, red line shows median, blue box range corresponds to 25 and 75 percentiles, whiskers correspond to 1.5 interquartile range and red crosses correspond to outlier data. In total 15 datapoints are outside of shown range. For low-risk group 7 points with maximum value 98.27 mUI/l, for medium-risk 6 points with maximum value 18mIU/l, for high-risk 2 points with values 5.5 and 14.6 mIU/l.

TSH levels exhibited significant variability across risk categories

- Low Risk Group:
  - The mean TSH level, including outliers, was 1.59 mIU/l (± 6.88), with a range from 0.01 to 98.28 mIU/l.
  - Exclusion of outliers refined the mean to 0.88 mIU/l (± 0.85). Percentile analysis revealed a median TSH level of 0.63 mIU/l, with the 75th percentile reaching 1.59 mIU/l.
- Medium Risk Group:
  - The mean TSH level, including outliers, was 1.21 mIU/l (± 2.49), spanning 0.01–18.00 mIU/l, while outlier exclusion refined the mean to 0.50 mIU/l (± 0.61).
  - The median TSH level was 0.28 mIU/l, with the 75th percentile at 1.10 mIU/l.
- High Risk Group:
  - The mean TSH level, including outliers, was 1.10 mIU/l (± 2.97), with a range of 0.01–14.60 mIU/l.
  - Excluding outliers refined the mean to 0.15 mIU/l (± 0.16).
  - The median TSH level was 0.12 mIU/l, with the 75th percentile at 0.40 mIU/l.

4.4 Analysis by Treatment Centre

The majority of patients (341) were treated at the Department of Nuclear Medicine in Ceske Budejovice, while a smaller cohort (24 patients) received care at the Division of Endocrinology of the Department of Internal Medicine at the Faculty Hospital Kralovske Vinohrady. The significantly larger patient population at the Department of Nuclear Medicine reflects its role as a referral centre for radioiodine therapy in thyroid cancer management, contributing to the substantial discrepancy in patient distribution between the two centres. To ensure robust statistical validity, data from both centres were analysed as a combined dataset.

5 Discussion

In our study, we identified unsatisfactory adherence to current guidelines on TSH suppression therapy, particularly in low- and intermediate-risk groups, with a high prevalence of over-suppression observed in 40.9% of low-risk and 33.6% of intermediate-risk patients.

Recent research has shown that suppressive therapy in low-risk patients is unwarranted and does not improve overall survival or reduce recurrence risk; on the contrary, it may lead to considerable side effects such as atrial fibrillation, osteoporosis, and impaired quality of life [6, 7]. The benefit of suppression therapy in intermediate- and even high-risk patients remains controversial, calling for a more individualized approach based on dynamic risk assessment and long-term response to therapy [8].

A pivotal recent study by Shi et al. [9] evaluated over 1000 patients with DTC across multiple centres in China and demonstrated that strict adherence to ATA-guided suppression targets was associated with improved disease-free survival in high-risk patients but conferred no measurable benefit in the low-risk group. Furthermore, the study reported increased incidence of osteoporosis and anxiety symptoms in over-suppressed low-risk patients, emphasizing the need to balance guideline-driven therapy with patient safety and quality of life considerations [9]. These findings reinforce our own observation of high rates of unnecessary suppression in low-risk patients and support the adoption of a more conservative therapeutic approach in this population.

The reasons for excessive suppression observed in our cohort are likely multifactorial. A key factor may be physician concerns about disease recurrence, leading to a more aggressive therapeutic approach even in low-risk patients where current evidence does not support such intensity. This "better safe than sorry" strategy is deeply rooted in clinical practice, particularly among physicians who prioritize minimizing the risk of recurrence over potential long-term side effects. In addition, variability in physician practice patterns and interpretation of ATA guidance may contribute, as well as patient-related factors such as limited adherence to follow-up schedules. Taken together, these factors illustrate the challenges of translating evidence-based recommendations into routine clinical practice.

Several other studies have addressed adherence to guidelines on TSH suppression therapy in DTC patients. Yavuz et al. [10] conducted a multicentric cross-sectional study in Turkey, involving patients with low risk of recurrence. Severe TSH suppression (TSH < 0.01 mU/L) was identified in 8.8% of patients, moderate suppression (0.01–0.1 mU/L) in 24.6%, and mild suppression (0.1–0.5 mU/L) in 28%. Only 29.2% of patients achieved target TSH levels, while 50.4% experienced excessive suppression—findings closely mirroring our results.

Papaleontiou et al. [11] highlighted disparities in recommendations between endocrinologists and surgeons in a survey conducted in Georgia and Los Angeles. They found that 80.4% of physicians recommended TSH suppression for intermediate-risk patients, 48.8% for low-risk patients, and 29.7% for very low-risk patients. Surgeons were less likely than endocrinologists to recommend suppression therapy for intermediate-risk patients (OR 0.36; 95% CI 0.19–0.69).

In our study, patients from the tertiary centre in České Budějovice were followed by specialists in nuclear medicine, while patients from the secondary centre in Prague were managed by endocrinologists. However, due to the marked disparity in sample size, a valid comparison between specialties could not be performed.

Ming et al. [12] reported that only 61.4% of intermediate- and high-risk patients in a multicenter prospective study in China achieved target TSH levels. Similarly, Zhou et al. [13] found that more than 70% of intermediate- to high-risk patients did not meet their TSH targets. Díaz-Soto et al. [14] noted that nearly 20% of low-risk patients with excellent therapeutic responses still had inadequately suppressed TSH levels.

The American Thyroid Association (ATA) guidelines, published in 2016 [15], remain the cornerstone for the management of DTC. However, as shown in our study and others, real-world adherence to these recommendations remains suboptimal. Incorporating recent evidence—including that of Shi et al. [9]—into clinical practice highlights the growing need for personalized suppression strategies that take into account not only risk stratification, but also patient comorbidities, treatment response, and quality of life. Notably, the ATA is currently preparing updated recommendations, which are expected to reflect this shift toward individualized care and greater attention to quality-of-life outcomes.

6 Study Limitations

This study has several limitations. The majority of participants were recruited from the Tertiary Centre for Nuclear Medicine, one of the main facilities for the treatment of differentiated thyroid cancer (DTC) in Czechia, specializing in radioiodine therapy and managing approximately 600 patients annually. The Secondary Centre at Kralovske Vinohrady University Hospital primarily functions as a general endocrinology outpatient clinic and cares for a limited number of DTC patients. Consequently, a meaningful comparison between the secondary and tertiary centres was not feasible.

Furthermore, the study design did not allow us to directly verify the adequacy of initial L-thyroxine dosing relative to body weight or to fully capture dose adjustments during follow-up. Data on patient adherence were based on indirect indicators and may not fully reflect real-life compliance. Finally, our cross-sectional design offers only a snapshot of practice patterns and cannot establish causal relationships between physician decision-making, patient adherence, and achieved TSH levels.

7 Conclusion

In summary, only 37.3% of patients with differentiated thyroid cancer (DTC) in our cohort achieved serum thyroid-stimulating hormone (TSH) levels within the recommended target range. Despite the availability of established guidelines, a substantial proportion of low- and intermediate-risk patients were treated with levothyroxine doses resulting in excessive suppression. This may expose patients to avoidable risks, including cardiovascular and skeletal complications.

Our findings, consistent with recent studies including Shi et al. [9], emphasize the importance of tailoring TSH suppression therapy to the individual patient's risk profile, comorbidities, and long-term treatment response. The observed tendency toward overtreatment in low-risk patients likely reflects physician concerns about recurrence as well as variability in practice patterns.

Clinicians should carefully balance the potential benefits of aggressive suppression against its adverse effects, especially in low-risk patients, and strive to align clinical practice more closely with contemporary evidence and forthcoming guideline updates.

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Author Contributions P.N performed the study concept and design, collected data and drafted the manuscript. V.K, R.S and T.G collected data and revised the manuscript. S.S made statistical analysis. V.M collected data, assessed the risk of bias and revised the manuscript. L.B performed the study concept and design and revised the manuscript. All authors read and approved the manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical Approval The project and protocols were approved by the Ethics Committee of the Faculty Hospital Kralovske Vinohrady (EK-VP/13/0/2022) and was carried out in accordance with the latest version of the Declaration of Helsinki. All participants signed the informed consent.

Informed Consent All participants signed the informed consent.

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