The thyrotropin receptor in thyroid carcinoma

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Chapter 2

Associations of Serum Thyrotropin Concentrations with Recurrence and Death in Differentiated Thyroid Cancer

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ABSTRACT

Objective: The relation between serum TSH levels and risk for recurrence or thyroid carcinoma related death in patients with differentiated thyroid carcinoma (DTC) has only been studied to a limited extent.

Design: Single-centre observational study in 366 consecutive patients with DTC, who had all been treated according to the same protocol for initial therapy and follow-up. Median duration of follow-up was 8.85 years.

Methods: The relation between summarizing variables of unstimulated serum TSH concentrations (25th, 50th 75th percentiles, the percentage of suppressed and unsuppressed TSH values) and risk for recurrence or thyroid carcinoma related death was analyzed by Cox survival analyses in patients with at least 4 TSH measurements.

Results: In Cox-regression analysis, we found a positive association between serum TSH concentrations and risk for thyroid carcinoma related death and relapse, even in initially cured patients. The median of the individual TSH concentrations was the best indicator for thyroid carcinoma related death (hazard ratio (HR): 2.03 (confidence interval (CI): 1.22 – 3.37) and relapse 1.41 (CI 1.03 – 1.95). A threshold of 2 mU/l differentiated best between relapse free survival and thyroid carcinoma related death or relapse.

Conclusion: Our study supports current guidelines, which advise to aim at TSH levels in the low normal range in cured low risk patients, whereas TSH levels should be suppressed in non-cured or high-risk patients.

INTRODUCTION

Patients treated for differentiated thyroid carcinoma (DTC) receive thyroxin replacement therapy. The purpose of this therapy is not only to replace endogenous thyroid hormone, but also to suppress serum thyrotropin (TSH) levels in order to prevent relapse or progression of thyroid cancer. The rationale for TSH suppressive thyroxin replacement therapy is based on multiple clinical and experimental observations, reviewed in (82). It has been observed in case reports that high TSH levels may promote tumor growth, which is reversed by thyroxin therapy (202-204). Experimental studies have confirmed the expression and functional activity of TSH receptors in DTC (205-207) and the proliferative effects of TSH on thyroid carcinoma cells in vitro (208;209). TSH also stimulates protein synthesis and metabolism in DTC, which is the rationale for clinical diagnostic procedures, like TSH stimulated serum thyroglobulin (Tg) measurements (3;210) and TSH stimulated FDG-PET scintigraphy (79). Despite this notion, only four observational clinical studies have been published on the effects of thyroxin induced TSH suppression on the prevention of DTC recurrence or thyroid carcinoma related death (49;83-85). In the first study, Mazzaferri et al (49) found fewer recurrences and thyroid carcinoma related deaths in patients treated with TSH suppressive thyroxin dosages. In the second study, Cooper et al (84) showed that TSH suppression was an independent predictor in non-radioiodine treated high-risk papillary cancer patients. However, in these 2 studies initial therapy was not uniform with respect to the extend of surgery and radioiodine ablation therapy (49;84). In a recent publication, Jonklaas et al demonstrated in a multicenter study, that the degree of TSH suppression is a predictor of thyroid carcinoma specific survival in high risk patients, independently of radioiodine ablation therapy and the extent of thyroid surgery. As initial therapy in their cohort was not distributed uniformly, it was not studied whether TSH suppression after uniform initial therapy consisting of both near total thyroidectomy and radioiodine ablation has additional value. In addition, they did not study the value of TSH suppression in patients who were cured after initial therapy. In the fourth study, Pujol et al (83) studied 121 DTC patients who where all treated by total thyroidectomy and thyroid remnant ablation. They showed that a percentage of undetectable TSH values of less than 10% significantly predicted a lower relapse free survival. In this study, only the comparison of extreme TSH values showed a significant difference in relapse fee survival. The low number of thyroid carcinoma related deaths, did not allow to assess the prognostic value of TSH with respect to mortality. This lack of compelling evidence that prolonged suppression of serum TSH levels is associated with a better prognosis in low risk DTC together with the adverse effects of hyperthyroidism on bone mineral density (86) and cardiac function (87) was also reflected in recent guidelines to aim at normal TSH levels in low-risk DTC patients (211).

To assess the relation between the degree of TSH suppression and prognosis in more detail, we studied the association between the degree of TSH suppression and long-term prognosis in a group of 366 consecutive DTC patients who were all treated by total thyroidectomy and radioiodine ablation therapy. Because the median duration of follow-up was 8.9 years, the number of thyroid carcinoma related deaths allowed us to study both relapse free survival and mortality, both in the total group and in a subgroup of patients

who were cured 1 year after initial therapy.

MATERIAL AND METHODS

PATIENTS AND METHODS

Three-hundred-and-sixty-six consecutive patients were included in the study. These patients had received initial therapy for DTC between January 1986 and January 2000. January 1986 was chosen as a starting date, because from that date forward, all relevant patient data were registered in a computerized database. Initial surgery and radioiodine ablation therapy were performed at the Leiden University Medical Centre or at one of the connected general hospitals. All hospitals are affiliated in the Regional Comprehensive Cancer Centre, using the same standardized protocol for the treatment and follow-up of DTC.

All patients were treated by near-total thyroidectomy, followed by routine radioiodine ablative therapy with 2800 MBq I-131. In case of incomplete tumor resection or when metastases were present, 6000 MBq was administered after thyroidectomy. Lymph node surgery was performed as follows: when lymph node metastases were the presenting symptom, a modified radical neck dissection (removal of lateral lymph nodes with preservation of sternocleidomastoid muscle, internal jugular vein and accessory nerve) was performed at the time of total thyroidectomy. When lymph node metastases were not the presenting symptom, neck inspection was performed during thyroidectomy and suspected lymph nodes removed. When lymph node metastases became apparent during follow up, a modified radical neck dissection was performed.

Follow-up was performed according to a standard protocol, consisting of unstimulated and at least one TSH stimulated serum Tg measurement, diagnostic 185 MBq I-131 scintigraphy and ultrasound. After initial therapy, levothyroxine therapy was started in a dose to suppress TSH levels (below 0.1 mU/l).

Cure, 1 year after therapy was defined as the absence of I-131 accumulation at diagnostic 185 MBq scintigraphy, Tg serum concentrations below 2 ug/l after TSH stimulation and no other indication for disease (212). When Tg antibodies were present at the time of evaluation of initial therapy, only those patients were considered cured in whom after prolonged follow-up no tumor became discernable.

Tumor presence during follow-up was defined as histologically or radiologically (X-ray, CT-scan, MRI-scan, FDG-PET scan or I-131 scintigraphy proven DTC and stimulated Tg levels above 2 ug/l (213). In case of recurrent disease or metastases, surgery was attempted if the lesion was solitary and accessible, followed by additional radioiodine therapy (6000 MBq). If the tumor could not be removed surgically, radioiodine therapy was given and repeated if necessary. All radioiodine therapies were followed after 7 days by whole body scintigraphy.

The following data were registered: age at diagnosis, sex, date of diagnosis, histology, TNM stage, serum Tg, Tg antibodies and TSH levels at regular intervals, date of cure, disease state one year after initial therapy, date of recurrence after cure, date of death, cause of

death and date of last follow up. TNM stage was registered according to the 5th edition (11). This was done because most patients were analyzed before the latest edition of the TNM classification. We used the following end-points of follow-up: date of death (82 patients), date of emigration (12 patients) and date of most recent contact (272 patients). Death causes were analyzed in all 82 patients who had died during follow-up. Death cause was investigated using medical records, death certificates, enquiries with other physicians involved in the treatment of each patient, enquiries in other hospitals, enquiries with general practitioners and autopsy findings. Death causes were divided into thyroid cancer related death and other causes.

TSH ANALYSES

Data from 6245 TSH measurements in 366 patients were retrieved from the Department of Clinical Chemistry. Of these, stimulated TSH levels (verifying all TSH levels > 10 mU/l) were discarded, which left 5680 measurements. Only patients were analyzed in whom at least 4 TSH measurements were available, leaving 4805 measurements in 310 patients.
After verifying that there was no time-dependency of TSH in our patient group (the average slope of TSH in all patients during the observation period being –0.001 mU/l*year (CI –0.002 – 0.000 mU/l*year), and because from a biological point of view there is no indication that the relation between TSH and thyroid carcinoma cells does change over time, we chose express TSH exposure using the following TSH summary parameters: for each patient: the 25th , 50th and 75th percentiles of all TSH measurements, the percentage of all TSH levels below 0.1 mU/l, 0.4 mU/l and 4.5 mU/l which is in line with the methods used in earlier papers (49;83-85).
The prognostic significance of TSH for thyroid carcinoma related death was analyzed in all patients as well as in patients who were cured 1 year after initial therapy. The prognostic significance of TSH for tumor relapse was analyzed in patients who were cured 1 year after initial therapy.

LABORATORY MEASUREMENTS

Serum TSH was determined throughout the study period with Elecsys E-170 on a Modular Analytics E-170 system (Roche Diagnostic Systems, Basel, Switzerland), reference range 0.4 – 4.5 mU/l, detection limit: 0.005 mU/l, intra-assay variability: 0.88-10.66%, inter-assay variability: 0.91-12.05%). Serum Tg was determined with IRMA (Tg kit, Brahms, Berlin Germany) on a Wallac (Wallac, Turku, Finland), intra-assay variability: 0.14-13.9%, inter-assay variability: 12.3-17.4 %). Serum Tg antibodies were determined with IRMA (Sorin Biomedica, Amsterdam, The Netherlands) on a Wallac (Wallac, Turku, Finland) intra-assay variability: 3.6-4.1%, inter-assay variability: 11.6%).
Until January 1997 serum Tg was measured using an immunoradiometric assay (IRMA), the Dynotest TG (Brahms Diagnostica GmbH, Germany) with a sensitivity of 0.3 µg/l. From January 1997, the Dynotest TG-s (Brahms Diagnostica GmbH, Germany) was used, with a sensitivity of 0.05 µg/l and an inter-assay variability of 0.3 µg/l. The comparability of the 2 methods is excellent: R2: 0.99, slope 0.99, intercept 0.09 (214). Serum Tg-antibodies were

also measured at these specific time points by the Ab-HTGK-3 IRMA (DiaSorin Biomedics, Italy).

STATISTICAL ANALYSES

Normally distributed data are presented as mean ± SD. Data that are not distributed normally are expressed as median and 25 and 75th percentiles. Categorical data are expressed as percentages. All statistical analyses were performed using SPSS for windows version 12.0 (SPSS Inc., Chicago, IL). Prognostic indicators for recurrence or thyroid carcinoma related death were identified using Cox-regression analyses. Indicators that were identified as significant for survival in were entered into a stepwise model. A p-value of < 0.05 was considered significant.

RESULTS

Characteristics of the patients are shown in Table 1. Mean age at time of surgery was 48 ± 18 years. Median duration of follow-up was 8.85 years (0.75 – 16.98) years. Three-hundred-and-ten patients (75 males, 235 females) were available, in whom at least 4 unstimulated TSH measurements were available. Thirty-nine (13%) of these patients died of thyroid carcinoma. Two-hundred-and-fifty patients (81%) were cured 1 year after initial therapy. Of the patients who were cured 1 year after initial therapy, 39 (16%) developed a relapse, whereas 10 (4%) died because of thyroid carcinoma.

ALL PATIENTS

TSH related parameters of all 310 patients are given in Table 2. The median of the individual percentages of TSH values below the lower limit of normal (0.4 mU/l) was 73% and the median of the percentages below 0.1 mU/l was 50%. No differences in these percentages were observed between the different TNM stages. By univariate Cox regression analysis, significant indicators for thyroid carcinoma related death were: extrathyroidal tumor extension (T4), the presence of distant metastases and older age (Table 1). Significant TSH related predictors for thyroid carcinoma related death were the 25th and the 50th percentiles (median) of the serum TSH concentrations for each patient: the hazard ratio (HR) for the 25th percentile was 1.35 (a HR > 1 meaning a higher risk for the endpoint), the HR for the median TSH was 1.22.
The 25th percentile for a patient indicates that 25% of the measurements are below (or equal) to this value and 75% of the measurements are above (or equal) to this value. A higher 25th percentile value in a patient indicates that up to 75% of the TSH values are higher in this patient than in a patient with a lower 25th percentile.
When the significant variables assessed by univariate Cox regression analysis were introduced into a stepwise multivariate model, only T4, M1 and older age remained significant predictors (Tables 1,3).

TABLE 1. Patient characteristics

	N	N with 4 or more TSH Measurements	Thyroid Carcinoma Related Deaths N (%)	Cured Patients after 1 Year N (%)	Patients with Relapse after Cure N (%)	Thyroid Carcinoma Related Deaths after N (%)
Total	366	310	39 (13)	250 (81)	38 (16)	10 (4)
Gender	91 / 275	75 (24) /	13 (14) /	57 (76) /	11 (19) /	1 (2) /
(Male/ Female)		235 (76)	26 (14)	193 (82)	28 (15)	9 (5)
Stages						
T1	22	19	0 (0)	19 (100)	1 (5)	0 (0)
T2	188	164	8 (5)	153 (93)	17 (11)	4 (3)
T3	56	52	8 (15)	45 (87)	9 (20)	4 (9)
T4	96	75	23 (31) * #	33 (44) * #	12 (36)* #	2 (6) * #
N1	107	85	15 (18)	55 (65)	12 (22)	2 (4)
M1	52	42	19 (45) * #	10 (24) * #	10 (100)* #	2 (20) *
Histology						
Papillary	203	171	18 (11)	141 (82)	25 (20)	4 (3)
Follicular	72	63	13 (21) *	50 (79)	10 (7)	5 (10)
Follicular variant papillary carcinoma	68	56	5 (9)	45 (80)	3 (7)	1 (2)
Hürthle Cell	23	20	3 (15)	14 (70)	1 (7)	0 (0)
Age (continuous)			* #	* #	* #	* #
< 55 yr	210	204	4 (2)	188 (92)	18 (10)	1 (1)
> 55 yr	156	106	35 (33)	62 (58)	21 (34)	9 (15)

* Significant at univariate analysis
# Significant at multivariate analysis

TABLE 2.. Summarizing data of serum tsh concentrations in 310 patients after initial therapy for differentiated thyroid carcinoma . Data are expressed as median (25^{th}- 75^{th} percentiles). TSH values are expressed with 1 digit.

	All patients	**Patients Cured After 1 Year**
Individual TSH related parameters:	Median (25^{th} - 75^{th} percentiles)	Median (25^{th} - 75^{th} percentiles)
Percentiles of TSH values per patient:	(n=310)	(n=250)
25^{th} Percentile (mU/L)	0.0 (0.0 – 0.1)	0.0 (0.0 – 0.1)
50^{th} Percentile (mU/L)	0.1 (0.0 – 0.4)	0.1 (0.0 – 0.4)
75^{th} Percentile (mU/L)	0.4 (0.1 – 1.4)	0.4 (0.1 – 1.4)
Percentage of TSH values below the indicated values per patient:		
<0.1 mU/L	50 (30 – 73)	50 (29 – 73)
< 0.4 mU/L	73 (50 – 89)	72 (50 – 89)
< 4.5 mU/L	100 (90 – 100)	100 (90 – 100)

TABLE 3. Hazard ratios of serum tsh levels for thyroid carcinoma related death (a) and relapse (b) as calculated with cox-survival analysis. Only patients with a tsh value equal to or exceeding 4 were included.

		Univariate Analysis – single covariate			Stepwise analyses with significant co-variates	
A. Thyroid Carcinoma Related Death			**p**	**Hazard Ratio (CI)**	**p**	**Hazard Ratio (CI)**
Total Group	All stages combined	25^{th} percentile	0.007	1.35 (1.08 – 1.69)	n.s.	
		Median TSH	0.028	1.22 (1.02 – 1.46)		
	T1-3 M0	Median TSH	0.044	1.63 (1.01 – 2.64)	n.s.	
	T4 M1	n.s.				
Patients cured 1 year after initial therapy	All stages combined	n.s.				
	T1-3 M0	Median TSH	0.006	2.03 (1.22 – 3.37)	0.013	2.14 (1.18 – 3.89)
		Percentage TSH values > 4.5 mU/L	0.009	1.06 (1.01 – 1.11)	0.021	1.07 (1.01 – 1.13)
	T4 M1	n.s.				
B. Relapse			**p**	**Hazard Ratio (CI)**	**p**	**Hazard Ratio (CI)**
	All stages combined	n.s.				
	T1-3 M0	Median TSH	0.020	1.46 (1.06 – 2.01)	0.033	1.41 (1.03 – 1.95)
	T4 M1	n.s.				

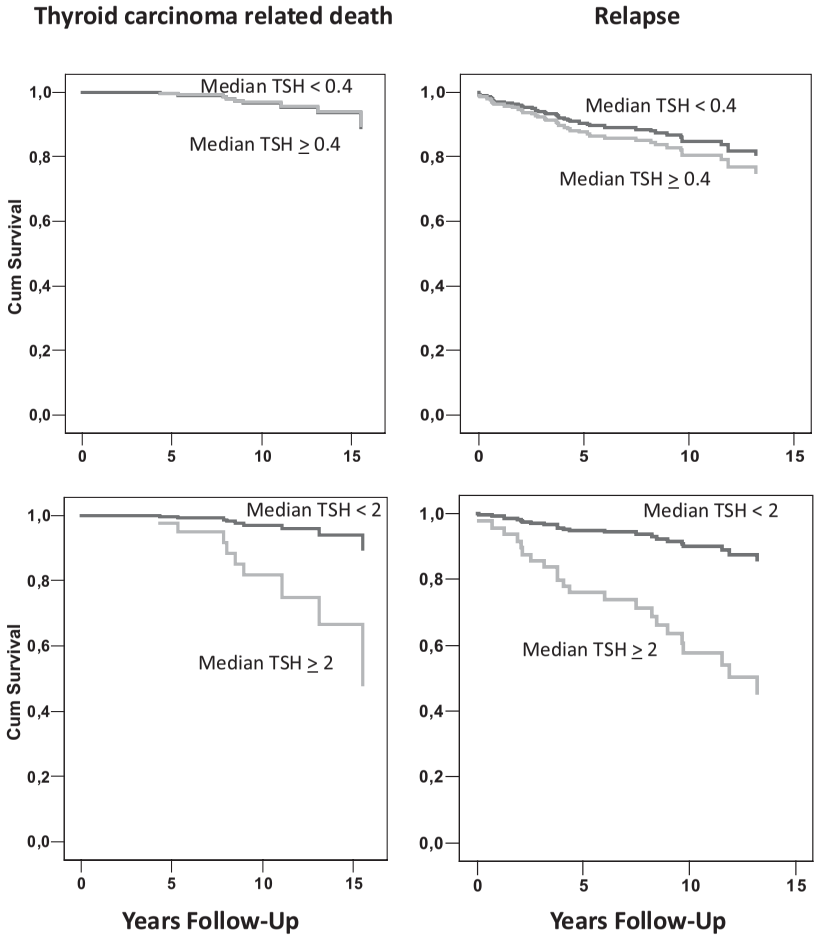

FIGURE 1. Relation between the median (50th percentile) of serum TSH concentrations and thyroid carcinoma related death and relapse in 250 patients who were cured 1 year after initial therapy for differentiated thyroid carcinoma.

a. Relation between a median serum TSH concentration cut-off value of 0.4 mU/L and thyroid carcinoma related death.
b. Relation between a median serum TSH concentration cut-off value of 2 mU/L and thyroid carcinoma related death.
c. Relation between a median serum TSH concentration cut-off value of 0.4 mU/L and thyroid carcinoma relapse.
d. Relation between a median serum TSH concentration cut-off value of 2 mU/L and thyroid carcinoma related relapse.

PATIENTS WHO WERE CURED ONE YEAR AFTER INITIAL THERAPY

Two-hundred-and-fifty patients were cured one year after initial therapy. When all 250 patients were analyzed, the median of the proportion of TSH values below the lower limit of normal (0.4 mU/l) was 72% and the median of the proportion below 0.1 mU/l was 50% (Table 2). No differences in these percentages were observed between the different TNM stages.

Thyroid Cancer Related Death

By univariate Cox regression analysis, significant indicators for thyroid carcinoma related death were: extrathyroidal tumor extension (T4), the presence of distant metastases and older age (Table 1). Significant TSH related predictors for thyroid carcinoma related death were the 50th percentile (HR: 2.03) and the percentage of TSH values above 4.5 mU/l (HR: 1.06).

When the significant variables detected by univariate Cox regression analysis were introduced into a stepwise multivariate model, T4, M1 and older age remained significant predictors for thyroid carcinoma related death (Table 1). For all cured patients, the 50th percentiles (HR: 2.14) of TSH values and the percentage of TSH values above 4.5 mU/l (HR: 1.07) were significant independent predictors for thyroid carcinoma related death (Table 3).

The effect of median TSH on thyroid carcinoma related death became only discernible at a cut-off level of 2 mU/l (Figure 1). At cut-off levels of 0.1 and 0.4, no significant difference in thyroid carcinoma related death was observed (Figure 1).

To investigate the relation of TSH in patients with recurrent and/or metastatic whose tumor did- or did not accumulate radioiodine we studied the 38 patients with recurrence after initial cure. Of these patients, 8 had metastases with radioiodine uptake. None of these patients died, whereas the 12 of the 30 patients who had no uptake of radioiodine died. In an additional analysis in which we built an interaction term comprising TSH and radioiodine uptake, we found a hazard ratio for thyroid carcinoma related death of 2.24 (CI 1.53 – 3.29) in patients without radioiodine uptake vs. patients in whom radioiodine uptake was present.

Relapse Free Survival

At univariate Cox regression analysis, significant indicators for relapse in patients who were cured 1 year after initial therapy were: extrathyroidal tumor extension (T4), the presence of distant metastases and older age (Table 1). A significant TSH related predictor was the 50th percentile (HR: 1.46)

When the significant variables obtained by univariate Cox regression analysis, were introduced into a stepwise multivariate model, T4, M1 and older age remained significant predictors for relapse (Table 1). For all cured patients, the 50th percentile of TSH (HR: 1.41) was a significant independent predictor for thyroid carcinoma related death (Table 3). The effect of median TSH on relapse became only discernible at a cut-off level of 2 mU/l (Figure 1). At cut-off levels of 0.1 and 0.4 mU/l, no significant differences in relapse were observed (Figure 1)

DISCUSSION

In the present study we investigated the association between serum TSH concentrations in patients during follow-up for DTC, thyroid carcinoma specific mortality and risk for recurrence. The study differed from earlier studies in the homogeneity of the patient group with respect to initial therapy (49;84;85), the study size and the duration of follow-up (83).
We found positive associations between serum TSH concentrations and risk for thyroid carcinoma related death and relapse. In a multivariate Cox-regression analysis model, in which tumor stage and age were also included, this association remained significant in patients who have been cured 1 year after initial therapy. The median of the TSH concentrations in each patient appeared to be the best predictor for thyroid carcinoma related death and relapse. However, subsequent analyses revealed that this effect became apparent at higher median TSH values (cut-off level of 2 mU/l). No differences in risks for thyroid carcinoma related death and relapse were observed between suppressed TSH levels (both TSH < 0.4 mU/l and <0.1 mU/l) and unsuppressed TSH levels (TSH levels within the reference range). Interestingly, this association between TSH levels and risk for relapse or thyroid carcinoma related death was present both in patients with initial stages T1-3 and M0 and with stages T4 or M1. Even for initial tumor stage T1-3 and M0, median TSH was an independent predictor for thyroid carcinoma related death. These results differ from the studies of Mazzaferri et al (49) and Cooper et al (84), who did not find an independent relation between TSH and prognosis. Our patient group is comparable with the study of Pujol et al. (83). Pujol et al found a difference in relapse between the extremes of TSH suppression (continuously undetectable vs. continuously unsuppressed). Pujol et al, however, did not report the relation between TSH levels and thyroid carcinoma related death. Our study results are in line with the recent report of Jonklaas et al. (85) who demonstrated that the degree of TSH suppression is a predictor of thyroid carcinoma specific survival in high risk patients, independently of radioiodine ablation therapy and the extent of thyroid surgery. Our analysis extends their findings in the respect that in patients who received total thyroidectomy and radioiodine ablation, and who were cured 1 year after initial therapy, TSH remains an independent predictor for disease specific survival. Our study confirms the findings of Jonklaas et al. that this relation is only present at TSH levels in the higher normal range, so that sustained TSH suppression is not recommended in low risk patients.
Because our study is based on retrospective data, the analyses might have been susceptible to bias. However, we could not find differences in summarizing parameters of serum TSH levels between high-risk and low-risk patients. In addition, differences in follow-up intensity between patients with higher and lower TSH levels could result in bias. However, the amount of TSH measurement per year did not differ significantly between patients who died of thyroid carcinoma and who did not. Moreover, even if such a difference would have been present, lower, rather than higher, TSH levels would be expected in high risk patients. Therefore, we believe that the results of our study are valid.
The percentage of patients reaching the target TSH range was lower than favorable (~73% below < 0.4 mU/l). We found no differences in TSH levels between high- and low-risk patients so that physician-related differences in target TSH levels between high- and low risk patients is an unlikely explanation. Another explanation could be that over time, the

physicians would have been less focussed on keeping TSH at the target levels. However, we did not find any time dependency of TSH.

The results of our study, e.g. that the deleterious effects of TSH on thyroid carcinoma recurrence or thyroid carcinoma related death become apparent above a median TSH of 2 mU/l, provide a rationale for the advice in the recently published European and United States guidelines for the follow-up of thyroid carcinoma to aim at TSH levels in the lower normal range (0.4 – 1 mU/l) in low-risk DTC patients (215;216) as unnecessary TSH suppression is associated with lower bone mineral density (86) and cardiac dysfunction (87;217).

Although relation between TSH levels and risk for thyroid carcinoma related death or recurrence was also present in non-cured patients and patients with an initially high risk, subgroup analysis did not reveal a safe TSH threshold in these patients. Because we found indications that the hazard of elevated TSH levels for thyroid carcinoma related death is especially important in non-iodine accumulating metastases, and given the findings of Jonklaas et al (85) we advice to maintain suppressed TSH levels (<0.1 mU/l) in patient categories with initial high risk and/or recurrent tumor.