

High Negative Predictive Value (NPV) of Undetectable TSH Stimulated Tg for Disease Recurrence in both Low and High Risk Differentiated Thyroid Cancer

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Abstract

The extent, intensity and timing of the follow-up of differentiated thyroid cancer (DTC) patients remains unclear.

Recent studies identified an undetectable TSH stimulated Tg measurement after one year as a prognostic factor for the risk of recurrence during further follow-up, thereby further dividing patients based on risk for recurrence. Because patients experience their disease on an emotional basis rather than related to actual disease severity, follow-up should be targeted to detect recurrence without 'over-investigating' patients. The aim of our study was to investigate the recurrence rate in high and low risk patients with DTC and the need for repeated (TSH stimulated) Tg measurement.

Methods: We retrospectively reviewed the medical records of 264 DTC patients with absent Tg-Ab and identified the patients with persistent/ recurrent disease. We compared recurrence rates between patients with and without detectable TSH-stimulated Thyroglobulin levels.

Results: Recurrence rate was significantly higher in patients with positive stimulated Tg measurement within one year after treatment ($p < 0.001$) While the negative predictive value (NPV) of an undetectable Tg was 0.97 for both high and low risk patients. The percentage of high risk patients with undetectable Tg after one year however is significantly lower compared to low risk patients.

Conclusion: Recurrence rates for patients with undetectable TSH stimulated Tg one year after initial diagnosis is very low and identical for low and high risk patients. Therefore it seems sensible to discharge patients from a strict specialist follow-up regime.

Keywords: DTC; Follow-up; Recurrence; Tg measurement

Introduction

The main focus in the post surgical follow-up of patients with differentiated thyroid cancer (DTC) is the detection of persistent or recurrent disease. Because traditional treatment of DTC larger than 1 cm in our center consists of total thyroidectomy followed by I-131 ablation of the remaining thyroid tissue, this follow-up can be performed using (rh) TSH stimulated thyroglobulin (Tg) measurements. Tg is only produced by normal thyrocytes or well differentiated thyroid cancer cells. The presence of Tg therefore is indicative of persistent or recurrent disease. When compared to other diagnostic modalities like I-131 Whole body scintigraphy (WBS) and ultrasound (US), serum Tg level (rhTSH stimulated or after LT-4 withdrawal) is the most sensitive method to detect disease recurrence [1]. The majority of patients with DTC are initially classified as low risk patients. This could be explained by the increased use and sensitivity of ultrasound. However, restaging after initial therapy adds additional information for the risk stratification of patients. Low risk patients with excellent response to therapy could be classified as real low risk patients with minimal chance of recurrent disease during further follow-up. The intensity and form of the follow-up of these patients should be tailored based upon these revised risk stratification after initial therapy and the need for an intensive follow-up of the real low risk patients could be questioned. Baudin et al. [2] for example showed that the recurrence rate in low risk patients with undetectable Tg levels at the time of performing the control WBS was only 0.6%. Several other recent studies also show very high negative predictive value of TSH stimulated Tg measurement one year after initial therapy for the risk of recurrence [3-5].

For patients initially staged as high risk patients the same strategy could be followed based on their response to therapy after one year as shown by Tuttle et al. [5]. Excellent response to therapy might be the best predictor for the risk of recurrence. While it is important to detect recurrences in an early stage it should be taken into account that the quality of life of patients with DTC could be diminished by the type and number of investigations during follow-up. It has been shown that patients perceive their illness on an emotional basis unrelated to its actual severity and cancer stage [6]. An important factor in the follow-up of DTC patients, therefore, is to detect recurrent disease without 'over-investigating' these patients. The timing and intensity of the follow-up, however, remains largely unclear and guidelines are not explicit. The main problem in determining a proper management protocol is the absence of prospective trials and the inability to perform

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a randomized study, which would take more than 35 years before results would be available. Advice about the follow-up protocol is based on retrospective series and expert opinion. Aim of our study was to investigate the recurrence rate in patients with DTC and the need for repeated (TSH stimulated) Tg measurement during further follow-up based upon the stimulated Tg level one year after initial therapy.

Patients and Methods

We retrospectively reviewed the clinical (electronical) records of all consecutive patients with differentiated thyroid cancer evaluated at the University Medical Center Utrecht who had undergone total thyroidectomy and I-131 remnant ablation from January 1994 until January 2009. Patients were further subdivided in low and high risk patients after initial TNM staging. We used the AJCC TNM version 7 criteria in determining T stage of the various tumors [7]. Risk staging was done according to the European guidelines [8]. Low risk patients were defined as patients with small tumors (T1,T2), negative cervical lymph nodes (N0) and no evidence of distant metastasis at time of diagnosis. High risk patients had large tumors (T3,T4), positive lymph nodes or distant metastasis at time of diagnosis. Patient characteristics and follow-up parameters, e.g. laboratory measurements (thyroglobulin (Tg), thyroglobuline antibodies (Tg-Ab), total T4 and TSH), results of the diagnostic WBS after treatment (RxWBS) and during further follow-up (DxWBS), were recorded. In addition, tumor characteristics, preoperative and postoperative staging and results of surgery were registered. Patients were excluded from the study for the following reasons i) inadequate follow-up information ii) inadequate information for staging iii) age < 18 years at time of diagnosis iiiii) positive Tg-Ab iiiiii) medullary and anaplastic thyroid cancer. All patients received TSH suppressive therapy and had at least two or more serum Tg and Tg-Ab determinations during levothyroxine therapy. All patients also had at least two or more Tg and Tg-Ab determinations after levothyroxine withdrawal (until 2004) or after rhTSH injection (0.9 mg im, Thyrogen: Genzyme Therapeutics, Cambridge, MA). In all patients a Rx WBS and at least one DxWBS (9-12 months after initial diagnosis) were performed.

Laboratory analysis

Between 1994 and 1998 different Tg assays were used with functional sensitivities varying from 1 ng/ml to 3 ng/ml. From 1998 on all Tg and Tg-Ab levels were measured using the Brahms DYN0 test Tg-pluS (Brahms Diagnostica GmbH, Berlin, Germany). The functional sensitivity for this assay is 0.2 ng/mL, and therefore used as cut-off value.

TSH levels were measured simultaneously and exceeded 20 mU/l in all patients. Tg level was judged positive whenever the value of the functional sensitivity of the Tg test was exceeded. All Tg and Tg-Ab levels indicated in the text or tables are TSH stimulated measurements, either by LT4 withdrawal or rhTSH injection unless indicated otherwise.

Follow-up

During the first year of follow-up controls were performed at least once every 6 months. Thereafter controls were performed with 6-12 month intervals. Standard follow-up of low risk patients existed of clinical examination with or without ultrasound, TSH stimulated Tg measurement 1, 4 and 9 years after initial treatment, combined with a diagnostic whole body scan. After 2008 low risk patients with negative stimulated Tg level and a previously negative DxWBS were

no longer referred for another diagnostic whole body scan. For high risk patients follow-up consisted of yearly controls including clinical examination, neck ultrasound, TSH stimulated Tg measurement and Tg measurement every 6 months. A DxWBS was performed after 1,4 and 9 years.

Persistent/recurrent disease

Suspicion of persistent/recurrent disease was based on results of physical examination, laboratory analysis (Tg raised above functional sensitivity) and results of the DxWBS (uptake outside regions of physiological uptake) In some patients there were discrepancy between different tests. In these cases, additional imaging like CT or MRI was performed. For other patients a blind therapeutic dose was administered followed by a RxWBS and some were treated conservatively with repeated diagnostics after 6-12 months. A positive RxWBS, anatomic substrate on additional imaging or results of FNAC/histology had to be present to confirm disease persistence/recurrence; otherwise the patients were classified as No Evidence of Disease (NED).

Statistical analysis

Statistical analysis was performed using SPSS 15.0 (Chicago, Illinois). All demographic data are shown in mean values with standard deviation (\pm SD) unless indicated otherwise. Percentages are rounded to the nearest integer. For statistical analysis we used Chi-square and t-tests where appropriate. P-values < 0.05 were considered statistically significant.

Results

A total of 402 patients were referred to the department of Nuclear Medicine for ablation therapy after total thyroidectomy for differentiated thyroid cancer and were included in our database.

Flow chart

One-hundred and sixty-eight adult patients could be classified as low risk patients. Of these 168 adult low risk patients, 9 patients had positive Tg-Ab and for 27 patients no results of laboratory analysis after one year were available and were subsequently excluded. Two-hundred-one patients were classified as high risk patients. Forty-nine of these patients had missing data about Tg level within 12 months of follow-up. Another nineteen had positive Tg-Ab and were subsequently excluded. One patient was excluded based on a definite histological diagnosis of an anaplastic carcinoma. A total of 132 patients in both groups remained for final analysis.

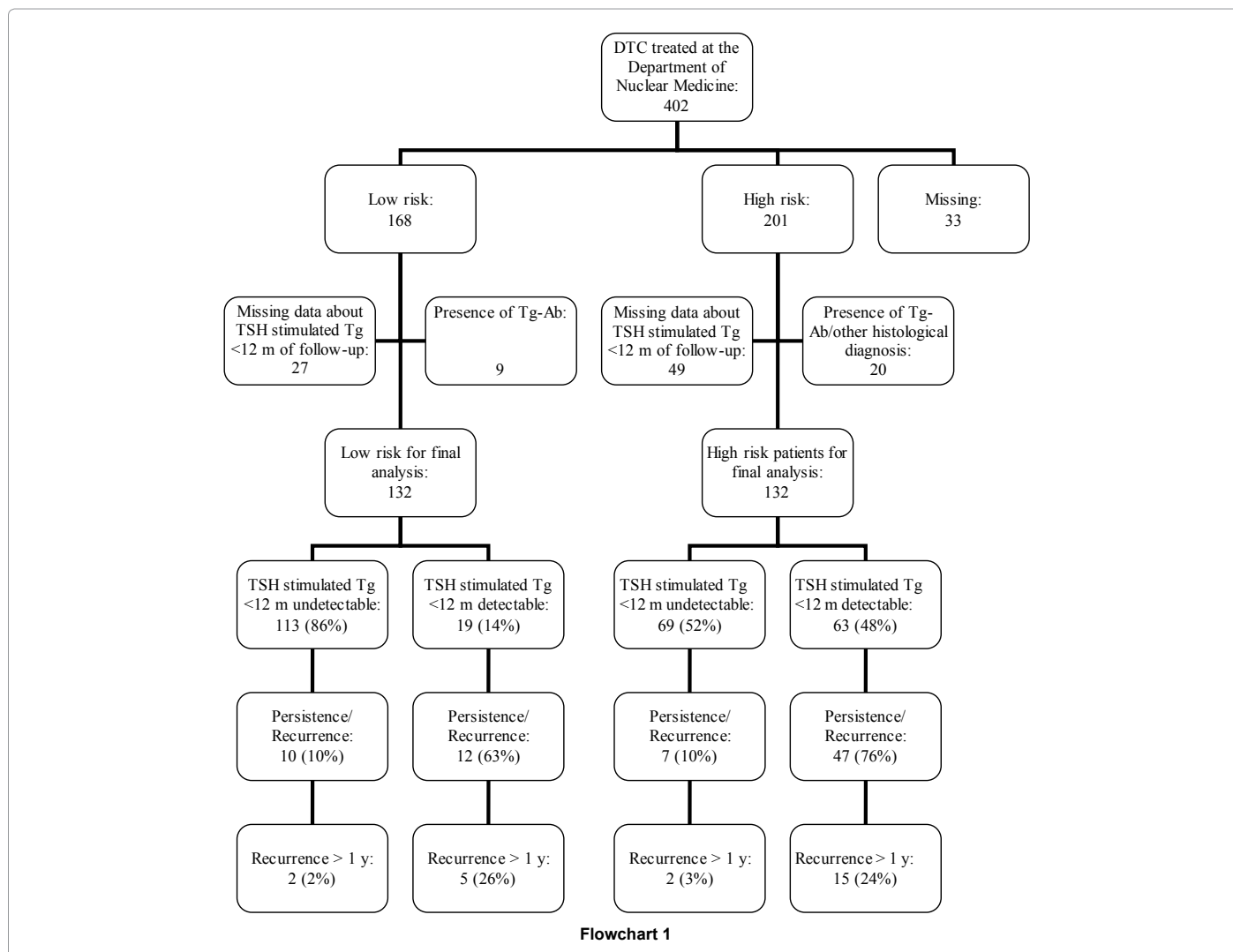
Demographic data, clinical features and final outcomes of the 264 low and high risk patients are presented in Table 1. As expected, the majority of patients were female in both groups (76% and 68%). Mean age was 47 years old for low risk patients and 50 years for high risk patients, this differences was not statistically significant ($p=0.505$) Statistically significant differences between groups were observed for mean tumor size (22 mm for low risk patients and 33 mm for high risk patients, $p<0.001$), recurrence rate (17% for low risk patients and 41% for high risk patients, $p<0.001$) and disease related mortality (0.8% vs. 5%, $p=0.031$). Median follow-up varied from a median of 48 months for high risk patients compared to 56 months for low risk patients. Most patients (81%) had at least three TSH stimulated Tg measurement during follow-up.

Recurrent/persistent disease

The overall persistence/recurrence rate for low risk patients was 17%. For high risk patients this rate was statistically significant higher with 54% ($p < 0.001$). In both groups 78% of the patients diagnosed with recurrent/persistent disease were diagnosed within the first year of follow-up.

Persistence/recurrence rate related to the value of the TSH stimulated Tg level within one year

Of the low risk patients a total of 113 patients (86%) had undetectable Tg levels. The percentage of high risk patients with undetectable Tg level was significantly lower with 52% ($p < 0.001$). The recurrence rate



Flowchart 1

	Low risk	High risk	p-value
Gender	Male: 32 (24%) Female: 100 (76 %)	40 (30%) 92 (68%)	0.269
Age	Median: 47 (± 15)	50 (±17)	0.505
Tumor size	Median: 22 mm (± 9.6 mm)	Mean: 33 (±22)	<0.001
Tumor histology	Papillary: n=95 (72%) Follicular: n=23 (18%) Hurthlecell n=14 (10%)	N =101 (77%) N=21 (24%)N= 10 (8%)	0.327
Initial presentation	Solitary nodule: 88 (67%) MNG: 20 (14%) Non-specified diffuse swelling neck: 8 (6%) Other (e.g cysts, other malignancy): 16 (12%)	49 (37%) 25 (19%) 9 (7%) 47 (29%)	
Follow-up duration (m)	Mean: 56	Mean: 48	0.323
Persistence/Recurrence	N= 23 (17%)	N= 54 (41%)	<0.001
Mortality rate	N= 3 (2%)	N=8 (6%)	0.159
Disease related mortality	N= 1 (0.8%)	N= 7 (5%)	0.031

Table 1: Demographic and tumor data low and high risk patients 1998-2010.

for high and low risk patients was significantly lower for patients with undetectable Tg level compared to patients with detectable Tg level (10% vs. 63% for low risk patients ($p < 0.001$) and 10% vs. 73% ($p < 0.001$) for high risk patients. Recurrence rate for patients with undetectable Tg measurement within the year was therefore identical between high and low risk patients ($p = 0.928$). The recurrence rate for patients with detectable Tg level within the year of follow-up was also not statistically different between low and high risk patients ($p = 0.408$).

Recurrences during further follow up in patients with undetectable Tg within the first year of follow-up

When analyzing the recurrences that occurred during further follow-up (longer than 12 months after initial treatment) of the patients with undetectable Tg levels within 12 months, the recurrence rate for low and high risk patients was 2%. The NPV of an undetectable Tg level for recurrence after one year was 0.97 in both low and high risk patients (Table 2). Two high risk patients developed a recurrence during further follow up, while initial stimulated Tg level was undetectable. Both patients were suspected to have recurrent disease based on a rising rhTSH-Tg level. One patient was successfully treated with a therapeutic activity of 7400 Mbq. The other patient was repeatedly treated, received external radiotherapy and is not considered disease free up to date. Two low risk patients also developed a recurrence during further follow-up. One patient had rising stimulated Tg levels with palpable lymph nodes in the neck, the other patient had noticed a gradual increase in neck circumference. Low risk patients were treated successfully with radioactive iodine, one patient was treated with an extra dose of 7400 MBq, the other patient was treated twice before considered disease free (Table 3).

Discussion

There are several other studies confirming a high NPV of TSH-stimulated Tg measurement [2,5,9-12]. Although our center uses a different Tg measurement method, our results are consistent with recent publications about this subject. When using the functional

sensitivity of our Tg method as a cut-off value, the negative predictive value of TSH-stimulated Tg was 99% in our study. The high NPV was also applicable to high risk patients. A recent report from Brassard et al. also reports this high NPV in a large prospective cohort of over 700 patients [11]. Main difference with our study, besides the prospective character of their study, is the Tg method used and the cut-off value, which they calculated using ROC-curves, while we used the functional sensitivity of our test as a cut-off value. With the results of our study as an addendum to the previous reports it seems that no matter which Tg measurement is used, as long as it is a sensitive method, in low and high risk patients with undetectable TSH-stimulated Tg levels 9 to 12 months after treatment, the risk of recurrence is very low (~2%). This is confirmed by the results of Tuttle et al. [5] who found response to therapy to be a better predictor for recurrence than initial risk staging based on tumor size and lymph node involvement. Therefore, as also proposed by Brassard et al. [12], TSH-stimulated Tg determination may be avoided, resulting in lower costs of follow-up and possibly enhanced quality of life for DTC patients. Although recurrences are infrequent in the group of patients with undetectable TSH-stimulated Tg, recurrences do occur in approximately 2% of these patients. In our study these patients were diagnosed with recurrent disease based on physical examination, ultrasound, TSH-stimulated Tg or other imaging studies. Suspicion of recurrence was never based upon rising Tg levels on Levo-thyroxine therapy. This could possibly be explained by the higher sensitivity of TSH-stimulated Tg measurement and therefore early detection of recurrence. It is questionable whether this early detection of recurrences with TSH-stimulated Tg has an influence on survival rate, because most recurrences were small foci of disease mostly located in the neck. Although there have been several studies investigating the predictive value of low Tg values during the follow-up of DTC patients, results have not yet been incorporated into a consensus statement or a new guideline for the follow-up. The last European consensus protocol for the follow-up of patients with DTC has been published in 2006 and its advice is comparable with the recommendations of the American guideline [10]. The American guideline, published in 2009 advises annual physical examination and Tg measurement on Levo-thyroxine therapy (Tg-on) for low risk patients with no evidence of disease after one year (based on TSH stimulated Tg measurement, physical examination and ultrasound) [12]. The obvious advantages of Tg0 on measurements are that they are easily performed, cheap and less invasive for the individual patient. After several years of additional research of the prognostic value of Tg measurements and the recurrence rate in DTC patients it seems sensible to incorporate the results of these studies into a new guideline specific for the follow-up of all DTC patients. Basically, we propose (in concordance with Tuttle et al.) a re-staging after 9-12 months based on response to therapy. Excellent responders, with a very low chance of recurrent disease could possibly be monitored less rigidly. Overall results of this less strict regime could result in lower costs for the health care system and advances in quality of life for the DTC patient. Possibly the general follow-up could be regulated by a general practitioner with specialist follow-up by referral.

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	Tg undetectable	Tg elevated	p-value
Persistence/Recurrence within the year			
Low risk:	7.1%	52.7%	$P < 0.001$
High risk:	6%	66%	$P < 0.001$
Persistence/Recurrence within year			
Low risk:	2.7%	10.5 %	$P = 0.027$
High risk:	3 %	20.6%	$P = 0.001$

Table 2: Persistence/recurrence rates related to initial (rh) TSH stimulated Tg level for low and high risk patients.

	Undetectable Tg	Detectable Tg
Recurrence > 1 year Low risk	2	2
High risk	2	15
No recurrence > year	111	17
Low risk		
High risk	67	48
Total Low risk	113	19
High risk	69	63

Low risk patients		High risk patients	
Sens : 2/2=0.5	PPV: 2/19=0.11	Sens: 15/17=0.88	PPV: 15/63=0.24
Spec: 111/127=0.87	NPV: 111/113=0.97	Spec: 67/115=0.58	NPV: 67/69=0.97
Sens = sensitivity	PPV= positive predictive value		
Spec= specificity	NPV = negative predictive value		

Table 3: Recurrent disease > 1 year related to (rh)TSH stimulated Tg after one year.

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