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Follow-up of patients with thyroglobulin-antibodies: Rising Tg-Ab trend is a risk factor for recurrence of differentiated thyroid cancer

Siegrid G. A. de Meer^a, Wessel M. C. M. Vorselaars^a, Jakob W. Kist^{a,b}, Marcel P. M. Stokkel^b, Bart de Keizer^c, Gerlof D. Valk^d, Inne H. M. Borel Rinkes^a, and Menno R. Vriens^a

^aDepartment of Surgical Oncology and Endocrine Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; ^bDepartment of Nuclear Medicine, Netherlands Cancer Institute, Amsterdam, The Netherlands; ^cDepartment of Nuclear Medicine and Radiology, University Medical Center, Utrecht, Utrecht, The Netherlands; ^dDepartment of Endocrinology, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Purpose: Differentiated thyroid cancer is the most common endocrine malignancy. Recurrences (5–20%) are the main reason for follow-up. Thyroglobulin (Tg) has proven to be an excellent disease marker, but thyroglobulin-antibodies (Tg-Ab) may interfere with Tg measurement, leading to over or underestimation. It is proposed that the Tg-Ab trend can be used as a marker for disease recurrence, yet few studies define trend and have a long-term follow-up. The objective of our study was to investigate the value of a well-defined Tg-Ab trend as a surrogate marker for disease recurrence during long-term follow-up. **Methods:** We retrospectively studied patients treated at the Nuclear Department of the University Medical Center Utrecht from 1998 to 2010 and the Netherlands Cancer Institute from 2000 to 2009. All patients with Tg-Ab 12 months after treatment were included. The definition of a rise was >50% increase of the Tg-Ab value in a 2 year time period. A decline as >50% decrease of the Tg-Ab value. **Results:** Twenty-five patients were included. None of the patients with declining or stable Tg-Ab without a concomitant rise in Tg developed a recurrence. Four patients did suffer a recurrence. Three of these patients had a rising Tg-Ab trend, in two of these patients Tg was undetectable. **Conclusions:** Tg-Ab trend can be used as a crude surrogate marker for long-term follow-up of Tg-Ab patients. A rising trend in Tg-Ab warrants further investigation to detect recurrent disease. Stable or declining Tg-Ab levels do not seem to reflect a risk for recurrence.

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Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy. Survival rates are excellent, however, recurrences occur in 5–20% of the patients (1). Recurrences are the main reason for follow-up. The thyroid specific thyroglobulin (Tg) is the primary tumor marker for detecting recurrences and, combined with ultrasound of the neck, the current gold standard for DTC follow-up. However, 20–25% of DTC patients also have thyroglobulin-antibodies (Tg-Ab) present (2,3). These antibodies interfere with Tg measurements by over or underestimating Tg values, depending on the test used (4). Immunoradiometric assays (IRMA) are considered to be consistently more sensitive than radioimmunoassays (RIA) and usually give an underestimation of the Tg level,

whereas RIAs can also overestimate the Tg level (5). So any sample with a positive Tg-Ab result is unreliable for measuring serum Tg concentrations and the value of the otherwise excellent tumor marker is of limited use (6). Consequently, Tg-Ab positivity poses a dilemma in follow-up of a significant proportion of DTC patients. Some authors have suggested that Tg-Ab can be used as a surrogate marker, especially in the case of de novo appearance more than one year after diagnosis (6–10), while others found contradictory results (11).

A major limitation of these studies is the absence of a clear definition of ‘trend’. The study of Kim et al. (12) is one of the few studies that does define trend, and it has been incorporated in a consensus meeting regarding this subject. This

CONTACT Menno R. Vriens, MD, PhD  mvriens@umcutrecht.nl  University Medical Center Utrecht, Department of Surgical Oncology and Endocrine Surgery, Room G04.228, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.

Siegrid G. A. de Meer and Wessel M.C.M. Vorselaars contributed equally to the manuscript.

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definition of trend is as follows: a $\geq 50\%$ rise in concentration of measured Tg-Ab 6–12 months after remnant ablation compared to measurements during remnant ablation. A decline was defined as a $\geq 50\%$ decline in Tg-Ab levels. However, the clinical application of this definition in patients at 12 months after primary treatment has not yet been studied.

The aim of the current study was, therefore, to determine whether Tg-Ab trends can serve as a surrogate marker for disease recurrence in patients with well differentiated thyroid cancer during long-term follow-up using the definitions mentioned above.

Materials and methods

Patients

We retrospectively reviewed all patients treated for DTC at the department of Nuclear Medicine of the UMC Utrecht (Utrecht, the Netherlands) between January 1998 and August 2010, and all patients treated at the Department of Nuclear Medicine of the Netherlands Cancer Institute (Amsterdam, the Netherlands) between 2000 and 2009. All patients with detectable Tg-Ab 12 months after primary treatment were included in this study.

Patients were treated with total thyroidectomy, additional lymph node dissection if indicated, and postoperative RAI (3700–7400 MBq). Patient characteristics and follow-up parameters, e.g. laboratory measurements (Tg and Tg-Ab levels) and the results of all imaging modalities were recorded. In addition, tumor characteristics, preoperative and postoperative staging, and results of surgery were registered. Furthermore, data regarding disease status during follow-up and duration of follow-up were recorded.

Exclusion criteria were age under 18 years, missing data regarding the stage of disease, missing follow-up information within the year after treatment, missing laboratory measurements, and/or distant metastases at the time of presentation. Patients with distant metastases were excluded because these patients are not suitable for follow-up with Tg and/or Tg-Ab only and therefore a different follow-up protocol applies.

Laboratory measurement

In the UMC Utrecht, Tg and Tg-Ab levels were measured using the Brahms DYNOfest Tg-pluS and the BRAHMS anti-Tg RIA-kit (Brahms Diagnostica GmbH, Berlin, Germany). The Tg method is a high-sensitivity IRMA. After 2002 the functional sensitivity (FS), defined as the lowest Tg-level that can be measured with a variation less than 20%, for this assay is 0.2 $\mu\text{g/L}$, and 20 U/mL for the Tg-Ab assay. Up until 2002, the FS was 1.0 $\mu\text{g/L}$ for Tg and 20 U/ml for Tg-Ab, respectively. In the Netherlands Cancer Institute, Tg-Ab levels were assessed by a competitive electrochemiluminescence immunoassay whereby serum TgAb competes for biotinylated human Tg with ruthenium-labeled TgAb. The Tg-TgAb complexes form and bind streptavidin-coated microparticles and are magnetically captured onto the surface of an electrode. Tg levels were measured by a sandwich immunoassay (Cobas6000, Roche Diagnostic GmbH, D-68298 Mannheim).

The FS of this assay for Tg was 0.1 $\mu\text{g/L}$ and 22 U/mL for Tg-Ab. In both centers Tg and Tg-Ab levels were judged positive when patients had a value above the functional sensitivity. TSH levels were measured simultaneously and exceeded 20 mU/L in all patients. All Tg and Tg-Ab levels indicated in the text or tables are TSH stimulated measurements, either by LT4 withdrawal or after rhTSH stimulation.

Tg-Ab trend

For Tg-Ab trend analysis we divided the follow up in periods of 24 months starting from 12 months after primary treatment. Within each period patients were divided in to four groups according to changes in Tg-Ab concentration. The Tg-Ab trend was recorded as increasing when, in one of these periods of 24 months, Tg-Ab levels increased with $>50\%$. When Tg-Ab levels declined $>50\%$ or normalized to an undetectable value the trend was recorded as decreasing, and as undetectable, when Tg-Ab levels were below the detection limit. Tg-Ab trend was recorded as persistent stable when Tg-Ab levels were elevated, but fluctuations were $<50\%$ (15,16).

Recurrent and suspicion of recurrent disease

Recurrences can occur in patients that have been judged as free of disease, frequently described as ‘no evidence of disease’ (NED). A recurrence had to be proven by cytology, histology or positive post- ^{131}I therapy scan. Suspicion of recurrent disease was defined as either ^{131}I therapy was given because of rising biochemical markers (Tg and/or Tg-Ab) or suspicious lesions found at physical examination for which further investigation was initiated.

Imaging modalities

Neck ultrasound was performed at least yearly. In order to provide an anatomic substrate for patients with detectable Tg and/or Tg-Ab additional imaging modalities were used, such as DxWBS, MRI, CT, Iodine-124 (^{124}I), and ^{18}F -FDG PET/CT scanning.

Risk classification

In this study the 2015 ATA risk classification was used (13). Patients with distant metastases (M1) were excluded from analysis. For TNM-classification and stage grouping we used the 7th edition of the TNM-classification (13).

Statistical analysis

Statistical analysis was performed using SPSS 23.0 (Chicago, Illinois, USA). All demographic data are shown in mean values with standard deviation (\pm SD) unless indicated otherwise.

Results

Patients

In total 443 patients were treated for differentiated thyroid cancer in both hospitals (Figure 1). A total of 64 (14%) patients had positive Tg-Ab levels at time of diagnosis. One patient died within the year after primary treatment as a result of metastatic thyroid cancer. Twenty-nine patients (7%) had positive Tg-Ab 12 months after primary treatment. Four patients were excluded, two due to pulmonary metastasis, one due to persistent disease

diagnosed within one year after primary treatment and one due to non-radical tumor resection without subsequent RAI.

As a result, 25 patients were included. Baseline characteristics are shown in Table 1. Most patients were female (76%). The majority of tumors were of papillary origin (88%). The mean follow-up period was 96 months (SD 77.5, range 25–296). Nine-teen patients (76%) had no evidence of disease during the entire follow-up period, four patients (16%) had a recurrence, and two patients (8%) had the suspicion of recurrent disease.

Tg-Ab trend during follow up are shown in Table 2. Descriptive case presentations of all patients ($n = 6$) with recurrent or suspicion of recurrent disease are presented in Table 3. A plot of the Tg-Ab trend for these six cases is shown in Figure 2.

Tg-Ab trend

12–36 months follow-up ($n = 25$)

Eleven patients had a declining trend of Tg-Ab levels. One of these patients (case no. 1) was diagnosed with suspicion of recurrence based on a palpable lesion in the neck detected 31 months after primary treatment. The year before Tg-Ab trend was declining to zero, Tg levels were undetectable and DxWBS was normal. Additional CT showed no lesions indicating metastasis and fine needle aspiration of the palpable lesion showed no malignant cells.

Nonetheless, based on the high clinical suspicion, lymph node extirpation was performed, revealing a follicular proliferation; recurrent disease was therefore not confirmed. During further follow-up (248 months) of this patient Tg-Ab and Tg levels remained undetectable and no recurrences were diagnosed.

Seven patients had an increasing trend of Tg-Ab levels. Two of these patients were diagnosed with recurrent disease (cases no. 2 and 3) and one with suspicion of recurrent disease (case no. 4). In all three cases, Tg levels were undetectable. In case no. 2 ^{18}F -FDG PET/CT was performed due to increasing Tg-Ab levels, showing a pathologic lymph node in the neck; histology after resection confirmed metastasis of PTC. During follow-up

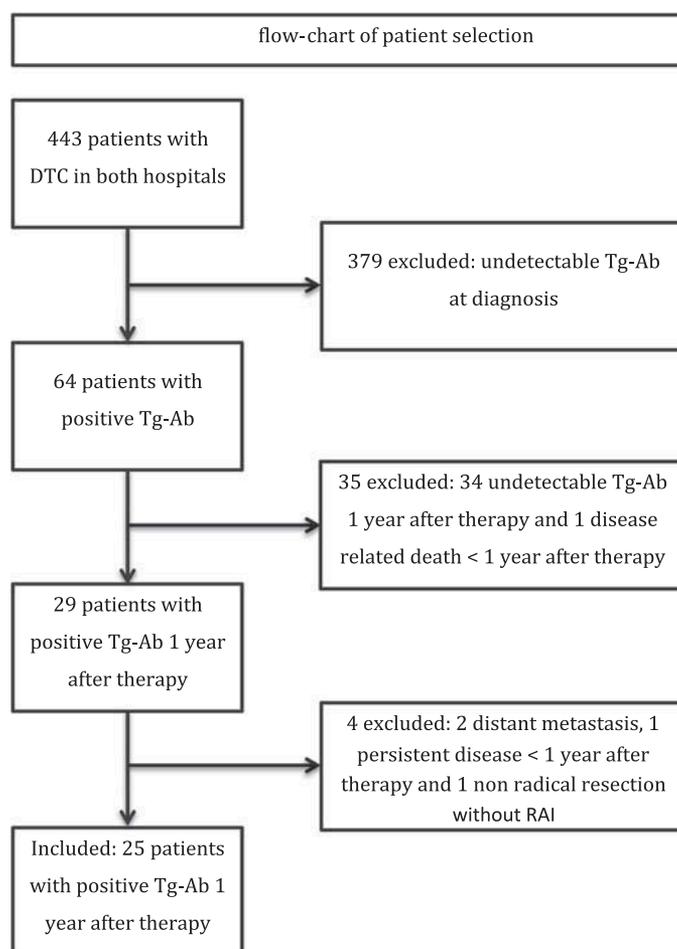


Figure 1. Flowchart of patient selection. *Note.* DTC = differentiated thyroid cancer; Tg-Ab = thyroglobulin-antibodies.

Tg-Ab and Tg levels remained undetectable and no further recurrence was diagnosed. Case no. 3 presented with a palpable lesion in the neck. Ultrasound and additional CT showed four suspicious lesions. Fine needle aspiration showed lymphogenic PTC metastasis. This was confirmed histologically after additional neck dissection, revealing four metastatic lymph nodes. During subsequent follow-up Tg-Ab levels remained detectable with a persistent stable trend while Tg levels remained undetectable. No further recurrence was found. Case no. 4 was suspected of having recurrence based on increasing Tg-Ab trend with undetectable Tg levels and suspicious uptake on DxWBS at 27 months after primary treatment. The patient was treated with high dose I-131 therapy. However, the post-therapy scan did not show any uptake. Further follow-up revealed no recurrences.

One additional patient with increasing Tg-Ab trend was dismissed from follow-up 27 months after primary treatment based on undetectable Tg levels and normal DxWBS.

Seven patients had a persistent stable Tg-Ab trend. None of these patients developed recurrent or suspicion of recurrent disease.

36–60 months follow-up (n = 21)

Eight patients had declining trends of Tg-Ab levels. Of these eight patients, four declined to zero, one was dismissed from further follow-up. Forty-four months after treatment one patient with declining Tg-Ab trend (case no. 5) was diagnosed with recurrent disease based on a rising Tg level and a palpable lesion in the neck. In this patient the Tg-Ab trend had been declining since primary treatment. The patient was treated with I-131 therapy. Post-therapy scintigraphy showed

Table 1. Baseline characteristics of patients with positive Tg-Ab ($n = 25$) at one year after primary treatment.

Variable	Number (%) or mean \pm SD (range)
Gender	
Male	6 (24.0%)
Female	19 (76.0%)
Mean age	43.3 \pm 13.4 (25–82)
Histological subtype	
PTC	22 (88.0%)
FTC*	3 (12.0%)
T Classification (7th)	
Tmissing	1 (4.0%)
T1a	3 (12.0%)
T1b	8 (32.0%)
T2	9 (36.0%)
T3	3 (12.0%)
T4a	1 (4.0%)
N Classification (7th)	
N0	11 (44.0%)
N1a	7 (28.0%)
N1b	5 (20.0%)
N1a/N1b	2 (8.0%)
TNM Stage (7th)	
I	16 (64.0%)
II	3 (12.0%)
III	3 (12.0%)
IV	3 (12.0%)
Risk classification	
Low risk	10 (40.0%)
Intermediate risk	10 (40.0%)
High risk	5 (20.0%)
Mean follow-up in months	95.9 \pm 77.5 (25–296)

*Two patients with Hurthle Cell differentiation and one patient with PTC with follicular growth pattern.

Tg-Ab = thyroglobulin-antibodies; PTC = papillary thyroid cancer; FTC = follicular thyroid cancer.

uptake in a suspicious lesion in the neck thereby confirming recurrent disease.

Two patients had an increasing trend and ten patients a persistent stable Tg-Ab trend. No events occurred in both groups and from the persistent stable group six patients were dismissed from follow-up. During this period Tg-Ab levels of one patient remained undetectable.

60–132 months follow-up ($n = 13$)

No events occurred during this period and seven patients were dismissed from follow-up, four due to persistent stable trend and three due to undetectable trend.

132–156 months follow-up ($n = 6$)

One patient (case no. 6) had an increasing Tg-Ab trend and was diagnosed with recurrence 133 months after primary treatment. Besides rising Tg-Ab levels,

Table 2. Trend analyses of Tg-Ab levels and corresponding disease status during different periods of follow-up.

Period of follow-up in months	Tg-Ab trend	n		Recurrent disease	Suspicion of recurrent disease
		=	NED		
12–36 ($n = 25$)	Declining	11	10	-	1
	Increasing	7	4	2	1
	Stable	7	7	-	-
	Undetectable	-	-	-	-
36–60 ($n = 21$)	Declining	8	7	1	-
	Increasing	2	2	-	-
	Stable	10	10	-	-
	Undetectable	1	1	-	-
60–84 ($n = 13$)	Declining	4	4	-	-
	Increasing	2	2	-	-
	Stable	4	4	-	-
	Undetectable	3	3	-	-
84–108 ($n = 10$)	Declining	-	-	-	-
	Increasing	2	2	-	-
	Stable	4	4	-	-
	Undetectable	4	4	-	-
108–132 ($n = 6$)	Declining	1	1	-	-
	Increasing	1	1	-	-
	Stable	1	1	-	-
	Undetectable	3	3	-	-
132–156 ($n = 6$)	Declining	1	1	-	-
	Increasing	1	-	1	-
	Stable	-	-	-	-
	Undetectable	4	4	-	-
> 156 ($n = 5$)	Declining	-	-	-	-
	Increasing	-	-	-	-
	Stable	1*	1	-	-
	Undetectable	4**	4	-	-

*Case with persistent stable between 156–180, declining between 180–204 and persistent stable between 204–296 with NED until follow-up was ended at 296 months after primary treatment.

**All 4 cases had undetectable Tg-Ab levels and NED until follow-up was ended at 161, 196, 248, and 258 months after primary treatment.

Tg-Ab = thyroglobulin-antibodies; NED = no evidence of disease.

Tg levels were rising and a palpable lesion in the neck was found during physical examination. Lymph node extirpation confirmed solitary PTC metastasis and the patient was treated additionally with I-131 which also showed uptake in pulmonary metastasis. Tg-Ab trend analysis for this patient showed a rise of less than 50% from 84 months onwards, with an increasing trend of over 50% from 120 months after primary treatment. No cases were dismissed follow-up during this follow-up period.

156 months follow-up ($n = 5$)

After more than 156 months of follow-up no events occurred.

Table 3. Descriptive case presentation of all patients ($n = 6$) with recurrent or suspicion of recurrent disease.

Case	Gender	Age	Histology	TNM	Risk classification	Event type	Months after initial treatment	Tg-Ab trend	Tg level ($\mu\text{g/L}$)	Detection	Treatment and results
1	Female	25	PTC	T1N1M0	Intermediate	Suspicion of recurrence	31	Declining	< 1	Palpable lesion, on CT not suspect for metastasis. FNAC showed no malignant cells	Lymph node extirpation showing follicular proliferation. Further FU (248 months) without recurrence.
2	Female	48	PTC	T2N1M0	Intermediate	Recurrence	31	Rising	< 1	Positive lymph node on FDG-PET	Lymph node extirpation showing PTC metastasis
3	Male	65	PTC	T2N0M0	Low	Recurrence	22	Rising	<0.2	Palpable lesion suspect on ultrasound and CT. FNAC showed PTC metastasis. No uptake on DxWBS and I-124 PET.	Additional lymph node dissection showing 4 with PTC metastasis
4	Male	82	PTC	TxN2M0	Intermediate	Suspicion of recurrence	27	Rising	0.2	Uptake on DxWBS	I-131 therapy with no uptake on post-therapy scan
5	Female	37	PTC	T4N0M0	High	Recurrence	44	Declining	20	Rising Tg level and palpable lesion. Negative DxWBS	I-131 therapy with uptake in a suspicious lesion on post-therapy scan
6	Female	60	PTC	T2N1M0	High	Recurrence	133	Rising	3.3	Palpable lesion with biopsy showing PTC metastasis. CT showing lymph node and pulmonary metastasis	Lymph node extirpation showing PTC metastasis

Tg-Ab = thyroglobulin-antibodies; Tg = Thyroglobulin; PTC = papillary thyroid cancer; FNAC = fine needle aspiration cytology; DxWBS = Diagnostic Radioiodine Whole-Body-Scintigraphy.

Total of Tg-Ab trends and corresponding events

Over the total follow-up period 25 declining trends were recorded in which one recurrence (with concurrent increasing Tg level) and one suspicion of recurrent disease occurred (which proved not to be a lymph node metastasis). Fifteen increasing trends were registered with 3 recurrences (one with concurrent increasing Tg level and two with undetectable Tg level) and 1 suspicion of recurrent disease (post-therapy ^{131}I scan showed no uptake). Furthermore, no

events occurred in 32 stable and 31 undetectable trends (Table 4).

Discussion

This study evaluates the use of the trend of Tg-Ab level as a marker for disease status during the follow-up of DTC patients with detectable Tg-Ab levels 12 months after primary treatment using predefined clear definitions for trends in Tg-Ab

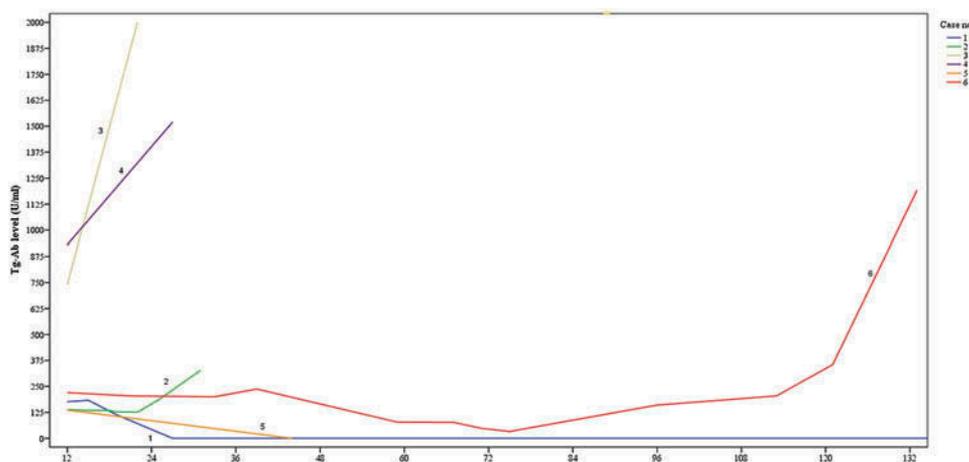


Figure 2. Overview of Tg-Ab levels (U/ml) all cases ($n = 6$) with recurrent or suspicion of recurrent disease.

Table 4. Cumulative trend analysis of Tg-Ab levels and corresponding disease status.

Tg-Ab trend	$n =$	NED	Recurrent disease	Suspicion of recurrent disease
Declining	25	23	1	1
Increasing	15	11	3	1
Stable	32	32	-	-
Undetectable	31	31	-	-

Tg-Ab = thyroglobulin-antibodies; NED = no evidence of disease.

levels. The current study shows that if Tg-Ab levels are declining or stable, the risk of recurrence is negligible. Thus, in these cases no further imaging is warranted. However, when Tg levels are rising concurrently with declining or undetectable Tg-Ab levels, this presents an indication for additional imaging to search for a possible recurrence. In case of rising Tg-ab levels, we recommend that the treating physician should actively try to diagnose recurrence, although one should be aware that no recurrence will be found in the majority of the patients.

Of the patients with detectable Tg-Ab 12 months after primary treatment, four (15%) were diagnosed with a recurrence during further follow-up. Three of the four recurrences occurred during the first three years after initial therapy. One patient had a recurrence after 133 months precipitated by rising Tg-Ab and Tg-levels. Three out of four patients showed a rise in Tg-Ab before recurrence was confirmed, while the other patient had a declining Tg-Ab level, with a concomitant rise in the Tg level. In our cohort

no patients were diagnosed with recurrent disease when Tg-Ab levels were stable or undetectable.

Our data are in concordance with the published clinical position statement by Verburg et al. on Tg-Ab positive patients that changes in serum TgAb levels can be used as an imprecise surrogate marker and that the trend is of greater value than the absolute level (14). Most studies report a low recurrence rate in patients with Tg-Ab levels that eventually become negative (3,6). By some authors it is proposed that Tg-Ab persistence alone for more than 3 years after initial treatment may suggest recurrence or persistent disease (15). Our study, however, does not support these results. The presence of Tg-Ab, in some patients for as long as 156 months after primary treatment, was not found to be a predictor for recurrent disease as long as Tg-Ab level remained stable.

If Tg-Ab levels are rising, additional diagnostic modalities such as US of the neck, DxWBS, ^{18}F -FDG and ^{124}I PET/CT are available to the clinician for further evaluation of this patient group (9,16–22). This applies, off course, to patients with a rising Tg level independently of the Tg-Ab trend.

A limitation of our study is the relatively small number of patients. However, it is similar to the number of patients presented in other studies investigating Tg-Ab positive patients (12,23,24). This underlines that the number of patients in clinical practice is also low. Statistical significance could not be assessed due to this limited number of events and therefore limits the strength of our conclusion.

The retrospective nature of our study could introduce detection bias. Where patients with a rising Tg-Ab level would have additional investigations, and patients with stable or declining levels would not.

Main strengths of our study are the long mean follow-up period and the use of a well-defined definition for trend, making the reliability and reproducibility of our data more robust.

Conclusion

The trend in Tg-Ab levels can be used as a crude surrogate marker for Tg. In patients with declining or stable Tg-Ab levels, without a concomitant rise in Tg, the risk of recurrence is negligible. In contrast, a rise in the Tg-Ab trend >50% in a 2 year time period in patients without detectable Tg warrants the need for additional diagnostic work-up to detect possible recurrent disease.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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