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Does an undetectable rhTSH-stimulated Tg level 12 months after initial treatment of thyroid cancer indicate remission?

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Summary

Objectives—Routine monitoring after the initial treatment of differentiated thyroid cancer (DTC) includes periodic cervical ultrasonography (US) and measurement of serum thyroglobulin (Tg) during thyrotrophin (TSH) suppression and after recombinant human TSH (rhTSH) stimulation. The aim of our study was to evaluate the utility of repeated rhTSH-stimulated Tg measurements in patients with DTC who have had no evidence of disease at their initial rhTSH stimulation test performed 1 year after the treatment.

Material and methods—A retrospective chart review of 278 patients with DTC who had repeated rhTSH stimulation testing after an initial undetectable rhTSH-stimulated serum Tg level.

Results—The number of rhTSH stimulation tests performed on individual patients during the follow-up period (3–12 years, mean 6·3) varied from two to seven. Biochemical and/or cytological evidence of potential persistent/recurrent disease based on detectable second or third rhTSH-stimulated Tg values and US findings was observed in 11 (4%) patients. Subsequent follow-up data revealed that in five cases, the results of the second stimulation were false positive, in one case – false negative. Combined with the negative neck US, the negative predictive value for disease-free survival was 98% after the first undetectable rhTSH-stimulated Tg and 100% after the second one.

Conclusions—In patients with DTC, the intensity of follow-up should be adjusted to new risk estimates evolving with time. The first rhTSH-stimulated Tg is an excellent predictor for remission, independent of clinical stage at presentation. Second negative rhTSH-Tg stimulation is additionally reassuring and can guide less aggressive follow-up by the measurement of nonstimulated Tg and neck US every few years.

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Disclosure

Nothing to declare.

Introduction

The goal of monitoring patients with differentiated thyroid cancer (DTC), following total/near total thyroidectomy and radioiodine treatment, is the early detection and treatment of persistent or recurrent disease. Although each of the staging systems extant may reliably predict disease-specific survival, they are less accurate at predicting disease recurrence, which can be observed in up to 30% of patients.[1] Clinically evident disease recurrence has been described as many as 30–40 years after initial therapy, but large, retrospective studies consistently demonstrate that the vast majority of recurrences are detected in the first 10–15 years of follow-up.[2] Recent data from the National Thyroid Cancer Registry indicate that more than half of the recurrences occurred within 3 years in patients with micro-papillary thyroid cancer (PTC).[3]

Earlier monitoring techniques were relatively insensitive and used neck palpation and baseline serum thyroglobulin levels that had relatively poor sensitivity. Although not yet proven, it is likely that the increased sensitivity of the follow-up testing paradigm that is now recommended will identify recurrent or persistent disease earlier than when prior techniques were employed, resulting in higher rates of detection of recurrence within the first 5 years of follow-up with earlier potentially successful therapeutic intervention.

Current guidelines and consensus statements recommend measurement of TSH-stimulated Tg combined with ultrasound of the neck 6–12 months after the initial therapy.[4–7] At this time, most patients (approximately 80%) will appear free of disease based on negative neck US and undetectable basal and stimulated serum Tg levels [with negative serum antithyroglobulin antibody (Tg Ab)]. Uncertainty persists regarding whether the subsequent follow-up should be based on the periodic measurement of basal serum Tg with neck US or whether rhTSH-stimulated Tg should be performed and at what frequency.[4,8–12] Recently modified ATA guidelines recommend that low-risk patients who have had remnant ablation, negative US and undetectable rhTSH-stimulated Tg levels can be followed with yearly clinical examination and Tg measurements on levothyroxine replacement.[4] This is a grade B recommendation based on studies that were limited by their number or consistency. There are no clear recommendations regarding the follow-up strategy in patients with moderate- to high-risk thyroid cancer who have no evidence of disease 1 year after the initial treatment.[4]

The goal of our study was to evaluate the utility of repeated rhTSH-stimulated Tg measurements in patients with DTC who have had no evidence of disease at an initial rhTSH stimulation test performed approximately 1 year after thyroidectomy and 131-I therapy.

Material and methods

The study was a retrospective analysis of medical records of patients with DTC treated and/or monitored at Washington Hospital Center, Washington, DC between years 1996 and 2009.

Inclusion criteria: (i) DTC diagnosed after total or near total thyroidectomy; (ii) postsurgical treatment with one dose of 131-I; (iii) undetectable basal and rhTSH-stimulated serum Tg levels approximately 12 months after initial treatment; (iv) standard monitoring procedures

for at least 3 years. Patients with detectable anti-Tg antibodies at any time were excluded. The protocol was approved by the Institutional Review Board. Patient's charts with ICD-9 disease code 193 (thyroid cancer) followed at Washington Hospital Center between years 1996 and 2009 were carefully reviewed to assess eligibility, and 278 individuals fulfilled the inclusion criteria and were analysed in the present study.

All patients underwent standard rhTSH stimulation testing.[7] After drawing a baseline blood sample for Tg measurement, 0·9 mg rhTSH (Thyrogen®; Genzyme Corporation, Cambridge, MA, USA) was administered intramuscularly with a second injection repeated 24 h later. Blood specimens were obtained approximately 72 h after the second rhTSH dose. During the subsequent years of the follow-up period, Tg measurements were performed with four immunometric assays with functional sensitivities of 0·1, 0·2, 0·5 and 0·9 ng/ml and were analysed by Quest Diagnostics (Madison, NJ, USA), LabCorp (Burlington, NC, USA) and the Washington Hospital Center Laboratory (Washington, DC, USA). All patients were screened for anti-Tg antibody using the chemiluminescence immunoassay by the above-mentioned laboratories. The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of stimulated Tg levels were assessed.

Results

The mean age at diagnosis, range of ages, gender breakdown, histologic type of cancer, clinical stage of disease, average activity of administered 131-I, range of 131-I dosages used in the treatment and the duration of follow-up are presented in Table 1.

All patients (278/278) had at least two rhTSH stimulation tests. The first test was performed approximately 1 year after initial treatment, serving as a parameter for the selection of patients eligible for the study (only patients with undetectable stimulated Tg levels were included), and the second test was performed 1–3 years after the first. In a large proportion of patients, additional rhTSH stimulation tests were performed. The total number of rhTSH stimulation tests performed during the follow-up period (3–12 years, mean 6·3) varied from two to seven (Fig. 1). During the interval of follow-up, cytological or biochemical evidence of potential persistent/recurrent disease was observed in 11/278 (4%) of patients (Table 2). There were no significant differences regarding stimulated TSH levels on day 5 after rhTSH in patients with biochemical or cytological evidence of potential persistent/recurrent disease, compared to the patients with no evidence of disease (mean TSH 9·1 uIU/ml *vs* TSH 11·2 uIU/ml, respectively).

After having a negative initial Tg response to rhTSH, 10/278 patients (3·6%) had detectable rhTSH-stimulated Tg values: 9/10 after a second rhTSH stimulation and 1/10 after a third test (Table 2). Of these 10 patients, five had a stimulated Tg between 0·5 and less then 1 ng/ml with no other direct evidence of disease. The remaining five patients had a rhTSH-stimulated Tg level between 1 and 3·9 ng/ml. These five patients presented with suspicious cervical lymph nodes documented by neck US in four cases and cervical and mediastinal node enlargement documented by MRI in one case, and the latter patient subsequently presented with liver metastases (Table 2). Two of the five patients had had fine needle aspiration cytology (FNAC) confirmed disease. In one patient, the FNA was read as benign

but did not include assessment of Tg washouts. FNA was not performed in 2/5 – in one case because of the clinical decision of the attending physician and in one case because of the patient's noncompliance.

Subsequent follow-up data enabled interpretation of the results of the second rhTSH stimulation test. In five cases (#6,7,8,9,10, Table 1), there was no evidence of disease during the whole follow-up period; in three cases, there was biochemical and/or cytological evidence of stable disease (patient #1,3,4, Table 1); in one case, there was an evidence of disease progression (patient #5, Table 1) and in one case, the results were inconclusive (patient #2, Table 1).

Only in two patients did unstimulated Tg rise to detectable values as measured by the assay with functional sensitivity of 0·2 ng/ ml – in patient #3, 7 years after the first biochemical evidence of disease provided by the rhTSH stimulation test and in patient #5 –4 years after the first evidence of disease recurrence based on detectable second stim-Tg level. There was no patient with undetectable rhTSH-stim Tg values, who presented with detectable baseline Tg levels. The disease course in patients with a positive second or third rhTSH stimulation test and the interpretation of biochemical and structural findings are summarized in Figs 2 and 3.

Based on clinical decisions made by the attending endocrinologist, 9/11 patients were followed without further treatment. One patient (#4) underwent right neck dissection, documenting PTC in two cervical lymph nodes. Patient #5 who presented with the evidence of disease progression with biopsy proven metastases of PTC to the liver underwent cryoablation of the lesions.

In addition to the ten above-mentioned patients, one additional patient with undetectable first and second rhTSH-stimulated Tg values (<0·5 ng/ml) had FNAC proven residual disease in a cervical lymph node, detected 13 months after the initial treatment, and we consider this to reflect a false-negative rhTSH-Tg value (Patient 11, Table 2). The diagnostic accuracy of subsequent rhTSH-stimulated Tg tests performed after an initial negative one had been assessed in two contexts:

1. Does it change the therapeutic approach?
2. Does it change the management strategy?

In regard to the first question, only one patient presented with progressive disease warranting additional treatment. When a true-positive value is defined as associated with evidence of disease progression, the NPV of the first rhTSH-stimulated Tg is 99·6% and increases to 100% with a second rhTSH-Tg stimulation with sensitivity 100%, specificity of 97·1%, but PPV of only 11·1%. In regard to the second question, a second rhTSH stimulation was of value for the one above-mentioned patient with evidence of progressive disease, but also for the patients with stable disease or inconclusive results of stimulated Tg. The NPV of the first rhTSH stimulation test in such circumstances is 97·8%, and when combined with neck US, it increases to 98%. Sensitivity, specificity, NPV and PPV of subsequent stimulations are summarized in Table 3. The combination of a second rhTSH-Tg stimulation test and a negative neck US results in NPV of 100% with sensitivity of 100%.

Discussion

The results of the present study confirm the utility of a single rhTSH-Tg stimulation test performed 1 year after initial thyroidectomy and 131-I therapy. Subsequent rhTSH-Tg stimulation testing is of limited value as a tool indicating necessity for altered management or therapeutic intervention. A NPV of 99·6% for the first rhTSH-Tg stimulation test is a very good predictor of progression-free survival. Nevertheless, the second rhTSH stimulation test can be helpful in guiding the aggressiveness of the follow-up strategy. The NPV for disease-free survival of the first rhTSH-Tg stimulation combined with a negative neck US is 98% and increases with a second stimulation test to 100% with sensitivity of 100%.

In a study of 68 patients, Castagna *et al*.[9] suggested that repeated rhTSH stimulation testing was of limited value in patients with an initial negative test performed approximately 12 months after initial therapy. In comparison with the latter report, the present study is based on larger number of patients (n = 278), inclusion of patients with more aggressive subtypes of thyroid cancer (columnar and tall cell variant of PTC, follicular thyroid cancer with poorly differentiated areas, Hurthle cell thyroid cancer), representation of all clinical stages of disease (clinical stage I–IV compared to I–III), longer duration of follow-up (mean 6·3 years compared to 4·7 years) and a larger number of rhTSH stimulation tests (up to 7 compared to 2).

Kloos and Mazzaferri reported a NPV of 98% for an undetectable first rhTSH-stimulated Tg, but the mean time for the first rhTSH stimulation test after initial therapy in their study was 5·5 years, which likely increased the NPV for being free of disease. Moreover, in their study, only 47% (32/68) of patients with an initial undetectable rhTSH-stimulated Tg level had undergone a second rhTSH stimulation over a mean 3·2-year follow-up period, which could have limited the identification of patients with persistent/recurrent disease.[13]

A lesson from our study is that although the majority of patients with detectable second or third stimulated Tg levels had negative or nonspecific imaging findings (neck US, WBS, CT, MRI or PET) and did not require further treatment, continued close monitoring of this group of patients was warranted. In patients with a history of DTC, the significance of detectable but small lymph nodes and persistent low levels of Tg without evidence of structural disease remains unknown,[4] and the proper management of these patients can be a challenge. Some studies have suggested employing a cutoff value for a rhTSH-stimulated Tg level of >2 ng/ml as indicating the need to consider additional evaluation and treatment during follow-up.[14] However, in a higher risk group of patients, Tg levels even below 2 ng/ml may suggest significant metastatic disease, as documented by Robbins *et al*.[6] This was confirmed in our series, in which one patient with documented progressive disease had a relatively low rhTSH-stimulated Tg level of 1·5 ng/ml.

Recommendation 77 of the recently modified guidelines for thyroid cancer by the American Thyroid Association (ATA) indicates that in the absence of structurally evident disease, patients with rhTSH-stimulated Tg levels <5 ng/ml can be followed on treatment with levothyroxine only, reserving additional therapy for those patients with rising serum Tg levels or other evidence of disease progression during the follow-up period.[4] Management

questions facing the clinician include the frequency of repeat neck US, usefulness and frequency of performing subsequent rhTSH stimulations test, selection of patients likely to develop disease progression, the significance of metastatic disease in small lymph nodes and the risks of metastasis to distant sites during follow-up observation.

Taking into consideration that the optimal follow-up strategy should be based on tests with a high sensitivity for early detection of recurrent disease and a high NPV for disease recurrence, we suggest that a first rhTSH stimulation test combined with the neck US with NPV of 98% fulfils these requirements, but the second negative rhTSH-stimulated Tg test together with the negative neck US characterized by NPV of 100% and sensitivity of 100% can be further reassuring.

We propose that after having a negative second stimulation test, patients can be followed less aggressively. An optimal management strategy in this group of patients may be the measurement of baseline serum Tg measurements during levothyroxine treatment and neck US every few years. This is based on our observation that none of the patients with undetectable second rhTSH stimulation had any evidence of disease during the subsequent follow-up period. Our study also indicates that assessment of risk stratification should be dynamic and the intensity and methods of follow-up should be adjusted to new risk estimates that may evolve with time. Notably in our series, the proportion of patients categorized initially as high risk based on clinical staging was 11·9% for stage III, 1·8% for stage IVa and 0·4% for stage IVc. Moreover, patients with worrisome histology like columnar or tall cell variant PTC, Hurthle cell or follicular thyroid cancer with poorly differentiated areas, which formed 11·8% of the study population, had no evidence of disease during the follow-up period. Although the proportion of high-risk patients in our series was relatively small, it reflects what is commonly seen in clinical practice among patients who obtained complete remission after the initial treatment. The single patient with stage IVc disease in our series, who obtained transient remission after the initial treatment, but subsequently developed disease progression, was at continued high risk of mortality and morbidity of thyroid cancer. A limitation of the present study is its retrospective design which predicated use of Tg results from different clinical laboratories. On the other hand, our study reflects common clinical practice where Tg measurements occur in various laboratories over time. The functional sensitivity of the Tg assays used in our study varied from 0·1 to 0·9 ng/ml. Nevertheless, Schlumberger *et al.* have documented that disease detection by stimulated Tg measurements was similar for the Tg assays with functional sensitivity of 0·9 ng/ml compared to tests with functional sensitivity of 0·2–0·3 ng/ml. An advantage of the more sensitive assay, improved disease detection, was seen only with measurements during treatment with levothyroxine. A further decrease of functional sensitivity to 0·11 and 0·02 ng/ml increased the test sensitivity at the expense of decreased specificity.[15] The strengths of our study include the analysis of a large number of patients, during a mean follow-up period exceeding 6 years (range up to 12 years), and inclusion of high-risk patients characterized by clinical stage III and IV disease or worrisome histology, with conclusions based on a large number of repeated rhTSH stimulation tests.

We conclude and recommend that in patients with differentiated thyroid cancer (i) the frequency and intensity of follow-up should be adjusted to new risk estimates evolving with

time; (ii) a first rhTSH-stimulated Tg at 1 year after initial treatment is an excellent predictor for remission and long-term disease-free survival independent of clinical stage at presentation and (iii) one additional negative rhTSH-Tg stimulation test at 3 years together with a negative neck ultrasonography will provide a negative predictive value of 100% and sensitivity of 100% and may be used as a tool selecting the patients who might be followed with baseline Tg measurement and neck ultrasonography every few years.

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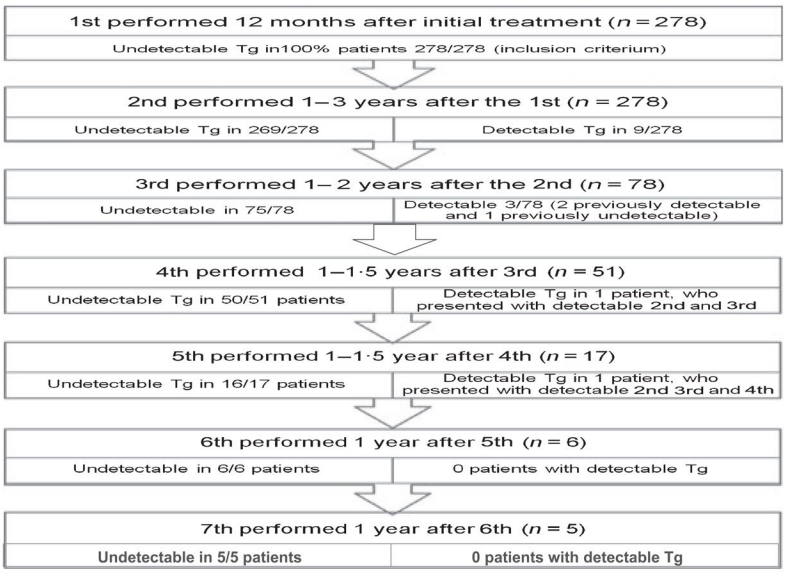

Fig. 1.

The number of repeated rhTSH stimulation tests during the follow-up period.

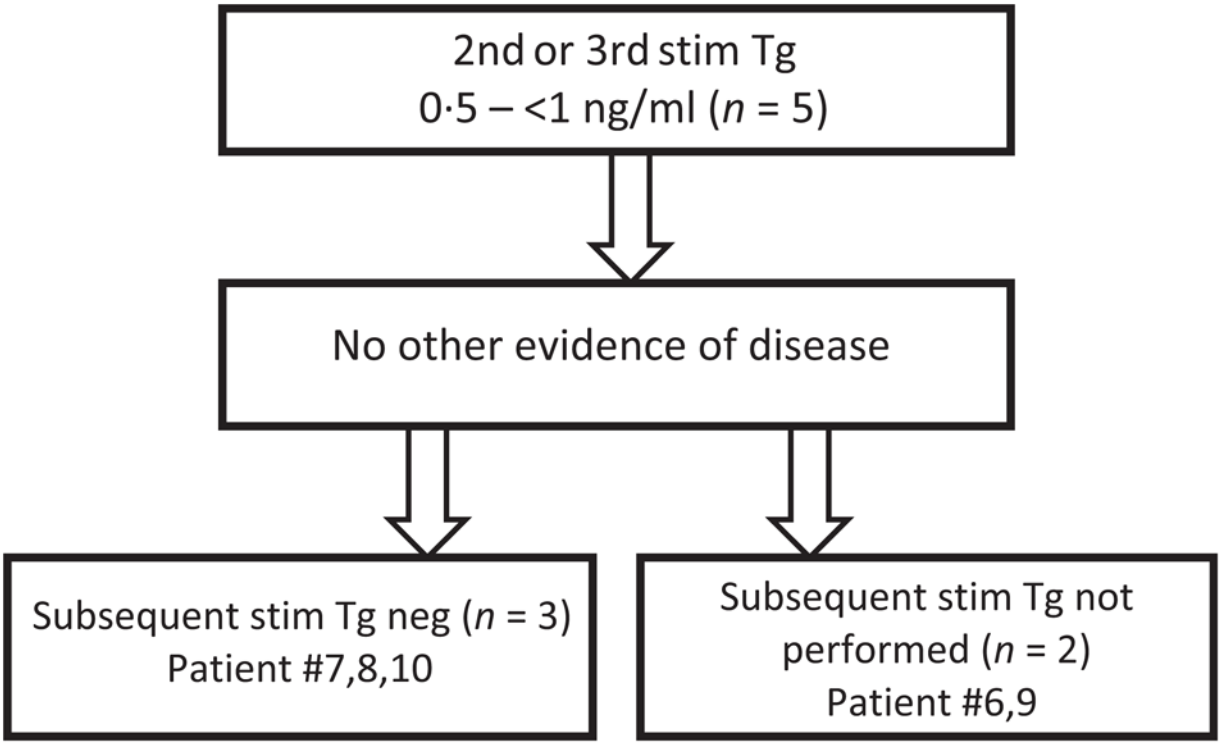

Fig. 2.
False-positive rhTSH stimulated Tg.

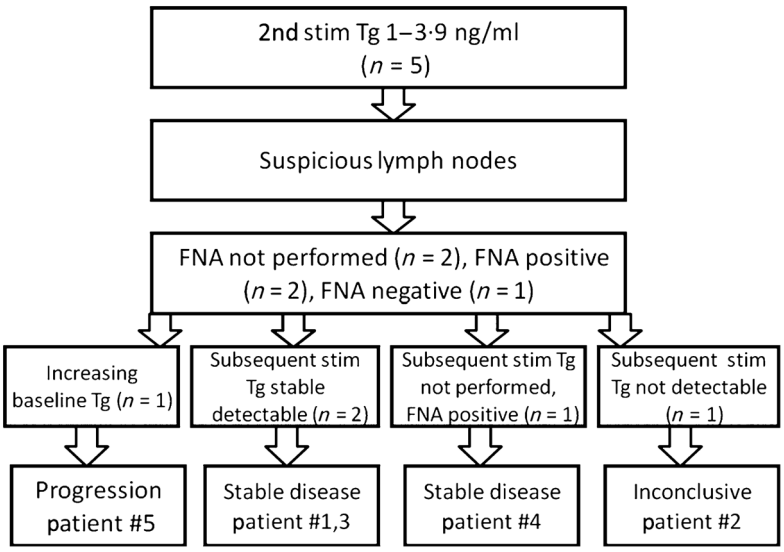

Fig. 3.

Follow-up data in patients with detectable stimulated Tg and abnormal imaging studies.

Table 1

Demographics of patient population

Total number of patients	278
Mean age at diagnosis (years)	45·5 (±12·4)
Range of ages (years)	14–71
Female	226 (81·3%)
Male	52 (18·7%)
Histology	
Papillary thyroid cancer (PTC)	156/278 (56·1%)
Follicular variant of PTC (PTCFV)	52/278 (18·7%)
PTC columnar or tall cell variant	10/278 (3·6%)
Follicular thyroid cancer (FTC)	24/278 (8·6%)
FTC with poorly differentiated areas	2/278 (0·7%)
Hurthle cell thyroid cancer	21/278 (7·5%)
WDTC no detailed histological data *	13/278 (4·8%)
Clinical stage at presentation	
I	181/278 (65·1%)
II	39/278 (14%)
III	33/278 (11·9%)
IVa	5/278 (1·8%)
IVb	0/278 (0%)
IVc	1/278 (0·4%)
Unknown	19/278 (6·8%)
131-I dosage (mCi) (Mean ± SD)	136·8 (±29·5)
Range of 131-I dosage (mCi)	29–218
Duration of follow-up (years) (Mean ± SD)	6·3 (±2·5)
Range of follow-up period (years)	3–12

* WDTC documented in medical records, but no pathology report available.

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Table 2

The clinical characteristics of 11 patients with either biochemical or cytological evidence of potential residual thyroid cancer (R, right, L, left)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Age at diagnosis	32	39	23	33	62	56	69	25	36	64	26
Sex	Female	Female	Female	Female	Female	Female	Female	Female	Female	Male	Female
Pathology	PTC	PTC	FTC	PTC	PTCFV	PTC tall cell variant	PTC	PTC	PTC columnar cell variant	PTC	PTC
Stage	I	I	I	I	IVc	IVa	I	I	I	I	I
Tumour size (cm)	2	1·5	3 × 2·5 × 2	No data	2 foci 1·5 and 0·2	3 × 1·8 × 1·8 extra-thyroid extension	Multifocal, all foci <1 cm	0·9 min extra-thyroid extension	2 foci 0·9 and 0·8	1·2	1·8 × 1·3 cm min. extra-thyroid extension
Lymph node mets at diagnosis	Not examined	Yes	Not examined	Not examined	Present, and distant met to the oesophagus	No	No	Yes	Yes	No	Yes
131-I activity (mCi)	150	130	150	No data	150	150	103·1	29·4	157·2	99·5	150
Stim Tg1 (ng/ml)	<0·5	<0·9	<0·2	<0·5	<0·9	<0·5	<0·5	<0·9	<0·5	<0·5	<0·5
Stim Tg2 (ng/ml)	1·0	3·9	1·0	2·5	1·5	0·6	<0·5	0·5	0·6	0·8	<0·5
Stim Tg3 (ng/ml)	0·6	<0·5	0·6		Suppressed 1·2		0·7	<0·2		<0·5	
Stim Tg 4 (ng/ml)			1·2		Suppressed 4		<0·2				
Stim Tg5 (ng/ml)			1·4		Suppressed 7·6 → 97·4		<0·2				
Duration of follow-up (years)	5	9	9 (6· 2010 suppressed Tg 0·6)	6	7	6	7	7	8	7	3
Clinical follow-up	Neck US: stable 1·9 ·× 0·9 × 0·4 cm R level III cervical lymph node with calcifications, FNA benign, stable over time until July 2010	Neck US: L level III lymph node 2·4 × 0·3 × 0·7, stable, FNA not performed, CT chest, abdomen, pelvis neg, PET-CT neg	123-I uptake: anterior lower cervical region, neck US R lymph node 1·3 × 0·3 × 0·8 increase in size 1·1 × 2·2 × 0·3 cm, FNA (i) nondiagnostic, (ii) not performed, chest CT negative	Neck US: R level III lymph nodes 1·5 × 0·3 × 0·7 cm and 0·6 × 0·2 × 0·6 cm., stable L two level II lymph nodes 0·7 × 0·3 × 0·8 cm and 0·9 × 0·4 × 0·7 cm, stable July 2010 R neck dissection 2	Level IV L lymph node 1·1 × 0·6 × 1·2 FNA – negative neck MRI stable slightly enlarged lymph node at the level of the thoracic inlet, PET-CT neg, PET-CT 3 months later: R hepatic lobe hypodensity,	Neck US neg	123-I uptake suprasternal notch, neck MRI small benign appearing cervical lymph nodes, chest CT neg	Neck US neg	Neck US neg	Neck US neg	Neck US residual tissue thyroid bed FNAC PTC

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
				LN positive PTC	conspicuous by CT, but with no metabolic activity by PET scan, MRI three hepatic lesions 2·1, 2·6 and 1·5cm biopsy – two lesions positive for PTC						

Table 3

Negative (NPV) and positive (PPV) predictive values, sensitivity and specificity of subsequent stimulated Tg levels

	TP	FP	TN	FN	NPV (%)	PPV (%)	Sensitivity (%)	Specificity (%)
Tg1	0	0	272	6	97·8	NA	NA	100
Tg2	5	4	268	1	99·6	55·5	83·3	98·5
Tg3	2	1	75	0	100	66·6	100	98·7
Tg4	1	0	50	0	100	100	100	100
Tg5	1	0	16	0	100	100	100	100
Tg6	0	0	6	0	100	NA	NA	100
Tg7	0	0	5	0	100	NA	NA	100

TP, true-positive result defined as evidence of disease progression (increasing Tg level and/or increasing size of metastatic foci), stable disease (stable detectable Tg and stable imaging studies) or inconclusive results of rhTSH-Tg stimulation tests during follow-up period.

FP, false-positive result defined as detectable rhTSH-Tg and no other evidence of disease during the follow-up period.

TN, true-negative result defined as undetectable Tg and no evidence of disease during follow-up period (biochemical and cytological and based on abnormal imaging studies).

FN, false negative defined as undetectable Tg and evidence of disease (biochemical and/or cytological and/or based on abnormal imaging studies).

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