Original Article

Role of Preablative Stimulated Thyroglobulin in Prediction of Nodal and Distant Metastasis on Iodine Whole-Body Scan

Meghana Prabhu, Sanju Samson[1], Avinash Reddy, Sunil Hejaji Venkataramanarao, Naveen Hedne Chandrasekhar[2], Vijay Pillai[2], Vivek Shetty[2], Moni Abraham Koriokose[2], Bushan Vaidhya[2], Subramanian Kannan[3]

Departments of Nuclear Medicine, [1]ENT, [2]Head and Neck Surgical Oncology and [3]Endocrinology, Diabetes and Metabolism, Narayana Health City, Bengaluru, Karnataka, India

Abstract

Background: Preablative stimulated thyroglobulin (ps-Tg) is an important investigation in the follow-up of patients with Differentiated thyroid cancer(DTC) after surgery. Levels of ps-Tg >2–10 ng/ml have been suggested to predict metastasis to cervical and extracervical sites. There is still debate on the need for routine iodine whole-body scan (^{131}I WBS) in the management of low-to-intermediate-risk DTC patients. **Objective:** We analyzed our data of patients with DTC who underwent total thyroidectomy to discuss the predictability of ps-Tg on metastatic disease on the ^{131}I WBS. **Materials and Methods:** Retrospective analysis of patient records. **Results:** One hundred and seventeen patients with DTC (95 papillary thyroid cancer [71 had classic histology, 8 had tall cell variant, 16 had follicular variant] and 22 follicular thyroid cancer [18 minimally invasive, 2 hurtle cell, and 2 widely invasive cancers]) had undergone total thyroidectomy. All these patients underwent ps-Tg assessment and an ^{131}I WBS. About 65% of them went on to have radioiodine ablation along with a posttherapy ^{131}I WBS. We divided the cohort into four groups based on their ps-Tg levels: Group 1 (ps-Tg <1), Group 2 (ps-Tg 1–1.9), Group 3 (ps-Tg 2–5), and Group 4 (ps-Tg >5). None of the patients in Group 1, 7% of those combined in Groups 2 and 3 (2 out of 28 patients), and 26% (12 out of 47) of those in Group 4 had either cervical or extracervical metastasis. Those with extracervical metastatic disease to lungs and bones had a mean (standard deviation) ps-Tg value of 436 (130) and median of 500 ng/ml and those with cervical metastatic disease had a mean Tg value of 31 (64) and median 6.6 ng/ml. **Conclusions:** A ps-Tg value in the absence of anti-Tg antibodies <1 ng/ml reliably excludes metastatic disease in DTC, while a value >5 ng/ml has a 26% risk of having either cervical or extracervical metastasis.

Keywords: *^{131}Iodine whole-body scan, differentiated thyroid carcinoma, thyroglobulin*

Introduction

Differentiated thyroid carcinoma (DTC), arising from the thyroid follicular epithelial cells, accounts for the vast majority of thyroid cancers. Of the DTCs, papillary thyroid cancer (PTC) comprises about 85% of cases compared to about 12% that have follicular histology. Overall treatment outcome regarding DTC is excellent, and the 10-year survival rate is about 90%; the rate of persistent or recurrent cases is 23–30%.[1] Surgery, selective postoperative radioactive iodine (RAI) therapy, and thyroid-stimulating hormone (TSH) suppressive therapy are the primary treatment modalities for DTC. Postoperative serum thyroglobulin (Tg) on thyroid hormone therapy or after TSH stimulation (preablative stimulated thyroglobulin [ps-Tg]) can help in predicting the presence of metastatic disease outside the thyroid bed on the iodine whole-body scan (^{131}I WBS), predicting potential future disease recurrence, guide need for radioiodine treatment.[1] However, the predictive value of the postoperative Tg value will be significantly influenced by a wide variety of factors including the presence of antithyroglobulin antibodies (anti-Tg Ab), the amount of residual thyroid cancer and/or normal thyroid tissue, the TSH level at the time of Tg measurement, the functional sensitivity of the Tg assay, the Tg cutoff used for analysis, the individual risk of having RAI-avid locoregional or distant metastasis, the time elapsed since total thyroidectomy, and/or the sensitivity of the posttherapy scanning technique (single-photon emission computed tomography [CT]/CT vs. planar imaging). No uptake outside the thyroid bed was identified in 132 low-risk patients with a ps-Tg of <1 ng/mL.[2-11] However, RAI-avid metastatic foci outside the thyroid bed were detected in 6.3% of intermediate-/

How to cite this article: Prabhu M, Samson S, Reddy A, Venkataramanarao SH, Chandrasekhar NH, Pillai V, *et al.* Role of preablative stimulated thyroglobulin in prediction of nodal and distant metastasis on iodine whole-body scan. Indian J Nucl Med 2018;33:93-8.

Address for correspondence:
Dr. Subramanian Kannan, 258/A Bommasandra Industrial Area, Hosur Road, Bengaluru - 560 099, Karnataka, India.
E-mail: subramanian.kannan@gmail.com

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.IJNM_130_17

Quick Response Code:

high-risk patients with a ps-Tg of <2 ng/mL.[12] The American Thyroid Association (ATA) guideline concludes stating that the likelihood of finding RAI-avid metastatic disease on the posttherapy scan is substantially lower (2.8%) if the postoperative Tg is undetectable in three different Tg assays than if it is undetectable only in a single assay (30%).[1] Conversely, the likelihood of identifying either locoregional or distant metastases on the posttherapy scan increases as ps-Tg values rise above 5–10 ng/mL.[5,13-15] While a ps-Tg of <1 ng/mL may not completely eliminate the possibility of identifying a metastatic foci outside the thyroid bed on a posttherapy RAI scan, ps-Tg values >5–10 ng/mL increase the likelihood of identifying RAI-avid metastatic disease on the posttherapy scan. ps-Tg values <1–2 ng/mL are strong predictors of remission, while ps-Tg values >10–30 ng/mL increase the likelihood of having persistent or recurrent disease, failing initial RAI ablation, having distant metastases, and dying of thyroid cancer.[1] Postoperative diagnostic RAI WBSs may be useful when the extent of the thyroid remnant or residual disease cannot be accurately ascertained from the surgical report or neck ultrasonography and when the results may alter the decision to treat or the activity of RAI that is to be administered. The ps-Tg value along with the ^{131}I WBS is likely to be helpful in identifying patients that may benefit from RAI ablation.

Aims

We analyzed our data of patients with DTC who underwent total thyroidectomy to discuss the predictability of ps-Tg and on metastatic disease on the ^{131}I WBS.

Settings and design

This was a retrospective study of health records.

Materials and Methods

We retrospectively studied 117 patients who underwent total thyroidectomy and had a ps-Tg assessment and a diagnostic ^{131}I WBS. The study was conducted from January 2015 to January 2016 at Narayana Health City, Bangalore, after approval by the Institutional Review Board. All 117 patients had undergone total thyroidectomy by a team of high-volume thyroid surgeons (authors NHC, VP, VS, MAK, and BV). Levels of Tg and anti-Tg Ab were determined using electrochemiluminescence immunoassay, and TSH level was determined using chemiluminescence immunoassay. The functional sensitivity of the Tg assay was <1 ng/ml, and values of anti-Tg Ab >100 IU/L were considered as positive anti-Tg Ab. Patient details were noted including age, sex, histology subtypes, lymph node metastasis, distant metastasis (bone/lung/others), findings on diagnostic ^{131}I WBS, serum TSH, ps-Tg, and anti-Tg Ab levels. These patients underwent ^{131}I WBS after levothyroxine (LT4) withdrawal and a low-iodine diet for 2–6 weeks when serum TSH >30 μIU/mL. Patients received ^{131}I at a dose that varied from 30 mCi (1.1 GBq) to 200 mCi (7.4 GBq) according to their ATA recurrence risk stratification. Posttherapy WBS was performed after 48 h and compared with the pretherapy WBS to assess if there was any alteration in the disease stage. We divided the cohort into four groups based on their ps-Tg levels – Group 1 (ps-Tg <1), Group 2 (ps-Tg 1–1.9), Group 3 (ps-Tg 2–5), and Group 4 (ps-Tg >5) – and analyzed the predictability of ps-Tg value on findings on the ^{131}I WBS.

Approval

The study was approved by our hospital's ethics committee.

Statistical analysis used

Results on continuous measurements are presented as mean (standard deviation [SD]) and median, and results on categorical measurements are presented as percentages (%). $P < 0.05$ was considered statistically significant. Mean (SD) and median Tg level were calculated for each of the four groups as described above.

Results

One hundred and seventeen patients with DTC (95 PTC [71 had classic histology, 8 had tall cell variant, and 16 had follicular variant] and 22 follicular thyroid cancer [18 minimally invasive, 2 hurtle cell, and 2 widely invasive cancers]) had undergone total thyroidectomy, and they underwent ps-Tg assessment before their ^{131}I WBS. About 74% were females and mean (SD) age was 41 (15) years. About 65% of them went on to have radioiodine ablation (RIA) at our institution along with a posttherapy ^{131}I WBS. Among those who did not undergo RAI, 32% had no uptake on ^{131}I WBS. None of the patients had an upstaging of their disease on the posttherapy scan. There were 34 patients (29%) in Group 1; of them, six patients were excluded as their anti-Tg antibody titers were >100 IU/L and five patients did not have any demonstrable uptake on their WBS and did not undergo RIA. Group 2 had 12 patients (10%); among them, three of them had anti-Tg >100 IU/L (excluded from analysis), none had extracervical metastatic disease, and only one patient had ipsilateral cervical metastasis picked up on the WBS. Group 3 had 19 patients (16%); among them, none had positive anti-Tg antibodies, two patients had no uptake on WBS, none had extracervical metastatic disease, and only one patient had ipsilateral cervical metastasis picked up on the WBS. Group 4 had 52 patients (45%); among them, five patients had anti-Tg >100 IU/L (excluded from analysis), two patients had no uptake on WBS, five patients had extracervical metastasis (four had bone and lung metastasis, two had concurrent lymph node metastasis, and one had isolated lung metastasis), and seven patients had cervical lymph node metastasis as diagnosed by the ^{131}I WBS. Among those in Group 4, 32 patients (62%) underwent RIA and no additional sites of metastatic disease were noted in them. Fourteen patients (12%) had anti-Tg

antibody titers >100 IU/L (median titers 219 IU/L); among them, three had cervical nodal metastasis, one had lung metastasis, and one had bone metastasis. While those with extracervical metastatic disease to lungs and bones had a mean (SD) ps-Tg value of 436 (130) ng/ml and median of 500 ng/ml, those with cervical metastatic disease had a mean Tg value of 31 (64) ng/ml and median 6.6 ng/ml. These results of the Tg and the WBS results are shown in Tables 1a-d. A ps-Tg value in the absence of anti-Tg antibodies <1 ng/ml reliably excludes metastatic disease in DTC, while a value >5 ng/ml has a 26% risk of having either cervical or extracervical metastasis [Figure 1].

Discussions

Our study reaffirms the value of ps-Tg in terms of predicting the staging of the disease on the ^{131}I WBS.

Table 1a: Details of patients with preablative stimulated thyroglobulin <1 µg/L

Age	Sex	DTC type	Subtype	Tumor	Node	Mets	ps-TSH	ps-Tg	Anti-Tg	Remnant on I WBS	Nodal metastasis	Distant metastasis	Therapeutic iodine dose
27	Female	PTC	Classical	T2	N0	M0	150	0.03	20	N	-	-	
38	Female	PTC	FVPTC				150	0.04	38.8	N	-	-	
44	Male	PTC	Classical	T3	N1b	M0		0.1	16.9	N	-	-	100
45	Female	PTC	Classical					0.22	2.83	N	-	-	
30	Female	PTC	FVPTC	T3	N1b	M0	43	0.4	47	N	-	-	
42	Male	PTC	Classical	T2	N1a	M0	83	0.04	12.8	Y	-	-	50
34	Female	FTC	MI	T2	Nx	M0	16	0.04	19	Y	-	-	
21	Female	FTC	MI	T3	N0	M0	118	0.04	19	Y	-	-	
26	Female	FTC	MI				150	0.04	16	Y	-	-	50
28	Female	PTC	Classical	T2	N1a	M0	150	0.1	64.9	Y	-	-	100
32	Female	FTC	MI	T3	Nx	M0	150	0.1	25.2	Y	-	-	50
39	Female	PTC	FVPTC	T2	N1a	M0	82	0.1	17.5	Y	-	-	100
54	Female	PTC	Classical				78	0.1	14.8	Y	-	-	50
42	Male	PTC	Classical	T2	N1a	M0	82	0.2	12.2	Y	-	-	50
38	Female	PTC	FVPTC	T2	N0		100	0.3	15.5	Y	-	-	50
35	Female	PTC	Classical	T3	N1	M0	85	0.4	10	Y	-	-	100
24	Female	PTC	FVPTC			M0	104	0.4	10	Y	-	-	50
25	Female	PTC	FVPTC	T3	N1a	M0	75	0.4	30.3	Y	-	-	100
27	Female	PTC	Classical	T3	Nx	M0	150	0.6	20	Y	-	-	
71	Female	PTC	Classical	T3	N1a	M0	70	0.69	11.38	Y	-	-	116
59	Male	PTC	Classical	T2	N1b	M0	47	0.7	22	Y	-	-	100
30	Female	PTC	Classical	T1	N0	M0	134	0.99	9	Y	-	-	

PTC: Papillary thyroid cancer, I WBS: Iodine whole-body scan, TSH: Thyroid-stimulating hormone, DTC: Differentiated thyroid cancer, FVPTC: Follicular variant papillary thyroid carcinoma, ps-Tg: Preablative stimulated thyroglobulin, FTC: Follicular thyroid carcinoma, MI: Minimally invasive, Anti-Tg: Anti-thyroglobulin, Y: Presence, N: Absence as N is already used for Nodal status, -: absence of metastasis

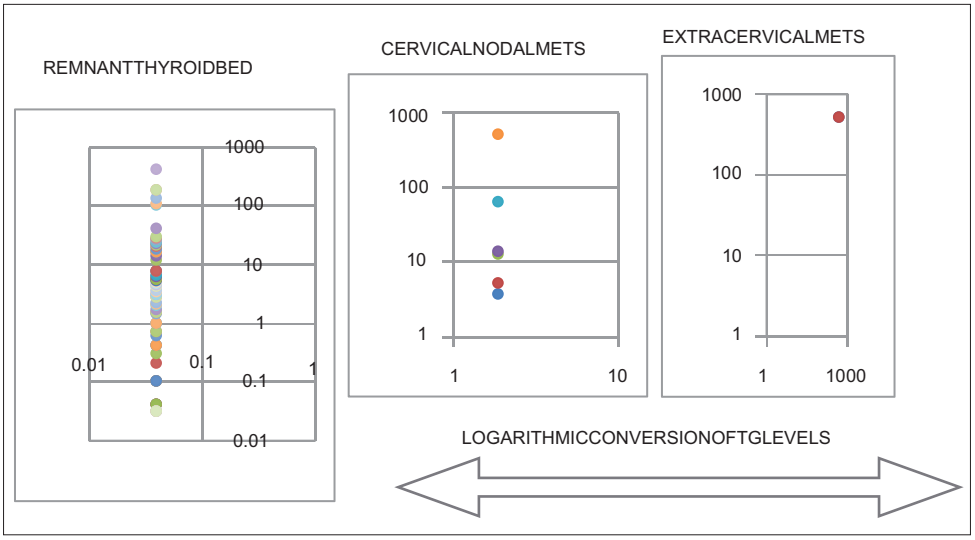

Figure 1: Scatter plot between Tg levels and findings as per I^{131} whole-body scan. The Tg data have been reproduced in logarithmic scale

Table 1b: Details of patients with preablative stimulated thyroglobulin 1-1.9 µg/L

Age	Sex	DTC type	Subtype	Tumor	Node	Mets	ps-TSH	ps-Tg	Anti-Tg	Remnant on I WBS	Nodal metastasis	Distant metastasis	Therapeutic iodine dose
32	Female	PTC	Classical	T2	N1b	M0	150	1	21.6	Y	-	-	25
37	Male	PTC	Classical	T3	N1a	M0	39	1	9	Y	-	-	39
59	Female	PTC	Classical	T2	N0	M0	72	1.13	245.2	N	-	-	100
31	Female	PTC	FVPTC	T3	Nx	M0	34	1.2	9	Y	-	-	100
31	Female	PTC	Classical	T2	N1b	M0	150	1.4	30.7	N	-	-	
66	Female	PTC	TCV	T4	N1	M0	54	1.4	18.9	Y	-	-	100
40	Female	PTC	Classical	T3	N1a	M0	125	1.4	115	Y	-	-	50
19	Female	PTC	FVPTC	T3	N1a	M0	150	1.5	83.9	Y	-	-	50
12	Female	PTC	Classical	T1	N1a	M0	150	1.5	22.8	Y	-	-	
60	Female	PTC	Classical	T2	N0	M0	100	1.7	14	Y	-	-	50
30	Female	PTC	Classical	T2	N0	M0	90	1.9	10.4	Y	Y	-	100
28	Female	PTC	Classical	T1b	N1a	M0	100	1.9	504	N	-	-	

PTC: Papillary thyroid cancer, WBS: Iodine Whole-body scan, ps TSH: Preablative stimulated thyroid-stimulating hormone, DTC: Differentiated thyroid cancer, FVPTC: Follicular variant papillary thyroid carcinoma, TCV: Tall cell variant, ps-Tg: Preablative stimulated thyroglobulin, Anti-Tg: Anti-thyroglobulin, Y: Presence, N: Absence as N is already used for Nodal status, -: absence of metastasis

Table 1c: Details of patients with preablative stimulated thyroglobulin 2-5 µg/L

Age	Sex	DTC type	Subtype	Tumor	Node	Mets	ps-TSH	ps-Tg	Anti-Tg	Remnant on I WBS	Nodal metastasis	Distant metastasis	Therapeutic iodine dose
60	Male	FTC	MI	T1	Nx	M0	47	2	10.5	Y	–	–	68
32	Female	PTC	TCV	T3	N1b	M0	129	2.1	9	Y			
30	Female	PTC	Classical	T3	N0	M0	150	2.2	22.5	N	–	–	
71	Male	PTC	TCV	T4	N1a	M0	54	2.2	21.1	Y			50
32	Male	PTC	FVPTC	T2	N0	M0	150	2.5	9	Y	—	—	51.6
37	Male	PTC	Classical	T1b	Nx	M0	105	2.6	19.2	N	–	–	
70	Female	PTC	Classical	T3	N1a	M0	79	2.69	15.07	Y	–	–	116
53	Male	PTC	Classical	T2	N0	M0	0	2.8	13.6	Y			50
16	Female	PTC	Classical			M0	150	3	30.7	Y	–	–	100
39	Female	PTC	Classical	T2	N1	M0	52	3	18.7	Y	—	—	50
37	Female	FTC	MI	T3	Nx	M0	105	3.4	22.7	Y	–	–	74
35	Female	PTC	Classical	T3	N1a	M0	142	3.5	9	Y			30
26	Female	PTC	FVPTC			M0	150	3.6	32.1	Y	Y	–	100
60	Female	PTC	Classical	T3	N1b	M0	100	4.2	50.1	Y			100
30	Female	FTC	MI	T3	Nx	M0	103	4.3	9	Y			
30	Female	PTC	Classical	T3	N1a	M0	113	4.4	39.1	N	—	—	
48	Male	PTC	Classical	T3	N1a	M0	122	4.4	19	Y			50
32	Male	PTC	Classical	T3	N1b	M0	127	4.6	22.7	Y	–	–	30
48	Male	PTC	Classical	T2	N2	M0	150	5	17.9	Y	–	–	100

FTC: Follicular thyroid carcinoma, PTC: Papillary thyroid cancer, I WBS: Iodine Whole-body scan, ps TSH: Preablative stimulated thyroid-stimulating hormone, DTC: Differentiated thyroid cancer, FVPTC: Follicular variant papillary thyroid carcinoma, TCV: Tall cell variant, ps-Tg: Preablative stimulated thyroglobulin, MI: Minimally invasive, Anti-Tg: Anti-thyroglobulin, Y: Presence, N: Absence as N is already used for Nodal status, -: absence of metastasis

This can help tailoring RIA, using it routinely for those with ps-Tg >5 ng/ml, individualizing for those with ps-Tg between 1 and 5 ng/ml, and avoiding in those with ps-Tg <1 ng/ml, provided there is no antibody interference to Tg measurement. In one of the prospective studies with a follow-up of 6 years, patients with ps-Tg <1 µg/L did not receive RAI, while those with ps-Tg >5 µg/L routinely did and those with ps-Tg 1–5 µg/L received RAI on the basis of several clinical risk factors.[16] In this study, 116 (90%) patients in this cohort have not received RAI therapy with no evidence of residual/recurrent disease, whereas among the 13 patients who received RAI, 1 (8%) had pathologic residual/recurrence disease.

Surgical remnant and laboratory techniques can significantly affect serum Tg and anti-Tg levels. The limitations include the absence of posttherapy WBS data in 35% of patients, staging of the disease was done at the time of initial assessment, and long-term follow-up data of this cohort are not available at the time of submission.

Table 1d: Details of patients with pre-ablative stimulated Tg >5

Age	Sex	Path	Variant	*t*	*n*	M	Pre-abl tsh	Pre-abl tg	Pre-ab anti-tg	Remnant	Nodal mets	Distant mets	Rai dose
47	F	PTC	Classical	T2	N1b	M0	89	5.1	55	Y	Y		
59	M	FTC	WI	T3	Nx	M0	60	5.23		Y			30
37	M	PTC	FVPTC	T2	N0	M0	41	5.44	2	Y			50
38	M	PTC	Classical	T1b	N1a	M0		5.6	26.8	Y			100 100
34	F	PTC	Classical	T2	N1a	M0	89	6.3	39.4	Y			
30	F	PTC	Classical	T3	N0	M0	75	6.5	16.5	Y			
70	F	PTC	Classical			M0	65	7.6	15.4	Y			30
70	F	PTC	Classical	T3	N1	M0	65	7.6	15.4	Y			
47	F	PTC	Classical				51	7.8		Y			
27	M	PTC	Classical	T3	N1b	M0	90	8.1	9	Y	Y		137 20
44	M	PTC	Classical	T3	N1b	M0	115	11.9	20.7	Y			
22	F	PTC	TCV	T3	N1b	M0	128	12.6	9	Y	Y		
63	M	PTC	Classical	T1a	Nx	M0	47	13.3	9	Y			
31	F	PTC	FVPTC	T3	Nx	M0	91	13.7	39.2	Y	Y		100
68	F	PTC	Classical	T1	N0	M0	150	13.9	12	Y			
60	F	PTC	TCV	T3	N0	M0	100	16.4	13.8	Y			70
60	F	PTC	Classical				150	16.4	23	Y			50
31	F	PTC	FVPTC			M0	100	17.8		Y			100
48	M	PTC	Classical	T3	N1b	M0	150	20.3	20.7	Y			30
49	F	PTC	Classical	T3	N1a	M0	150	21.6	9	Y			100
53	F	FTC	MI	T3	Nx	M0	150	22.1	15.5	Y			30
33	F	PTC	Classical	T3	N1b	Mx	178	22.1	1.04	N			
28	F	PTC	Classical			M0	100	24.2	14.8	Y			
65	F	PTC	Classical	T3	N1b	M0	119	26.5	19.1	Y			50
30	M	PTC	FVPTC			M0	134	26.6	12.8	Y			
66	F	PTC	Classical	T2	N1a	M0	150	28.5	12.3	Y			140 50
28	F	FTC	MI	T3	N0	M0	65	30.3		Y			
39	M	PTC	TCV			M0	150	40.1	16.4	Y			141
48	F	PTC	Classical	T3	Nx	M0	82	61.5	26.8	Y	Y		
28	M	PTC	Classical	T1	N0	M0	150	70.7	9	Y			150
20	F	PTC	Classical	T4a	N1b	M0	150	105.1	20.1	Y			
11	F	FTC	MI	T3	N0	M0	150	108	11.4	Y			
28	F	FTC	MI	T3	Nx	M0	48	131.2	10.2	Y			100
52	M	PTC	Classical	T3	N1b	MX	150	181.6	21.1	Y			100 50
25	F	PTC	Classical	T1	N1b	M0	150	189	30.3	Y			
33	F	PTC	Classical				49	196	39.3	N			
35	M	PTC	Classical	T3	N1b	M0	103	205.8	10	Y	Y		100
37	F	PTC	Classical	T1b	N0	M1	103	241	9	Y	Y	Y	200 70
38	M	PTC	Classical	T3	N1b	M0	150	420	10.6	Y			
57	F	FTC	MI	T4	N0	M1	73	501	20	Y		Y	217
70	M	FTC	WI	T3	N0	M1	46	501	52.9	Y	Y	Y	200
19	F	PTC	FVPTC	T3	Nx	M0	150	0.03	15.5	Y			50
24	F	PTC	FVPTC			M0	104	0.03	10	Y			50
56	F	FTC	HC				62	0.03	72.2	Y			100
56	f	FTC	MI				62	0.03	18.7	Y			
38	M	FTC	MI				76	0.03	41.1	Y			
36	M	FTC	MI	T3	N0	M1	121	501	40	Y		Y	180

Conclusions

A ps-Tg value in the absence of anti-Tg antibodies <1 ng/ml reliably excludes metastatic disease in DTC, while a value >5 ng/ml has a 26% risk of having either cervical or extracervical metastasis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al.* 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1-33.
2. Pelttari H, Välimäki MJ, Löyttyniemi E, Schalin-Jäntti C. Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: A 16-year follow-up study. Eur J Endocrinol 2010;163:757-63.
3. Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J, *et al.* The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: A meta-analysis involving 3947 patients. J Clin Endocrinol Metab 2012;97:2754-63.
4. Giovanella L, Ceriani L, Suriano S, Ghelfo A, Maffioli M. Thyroglobulin measurement before rhTSH-aided 131I ablation in detecting metastases from differentiated thyroid carcinoma. Clin Endocrinol (Oxf) 2008;69:659-63.
5. Giovanella L, Ceriani L, Ghelfo A, Keller F. Thyroglobulin assay 4 weeks after thyroidectomy predicts outcome in low-risk papillary thyroid carcinoma. Clin Chem Lab Med 2005;43:843-7.
6. Phan HT, Jager PL, van der Wal JE, Sluiter WJ, Plukker JT, Dierckx RA, *et al.* The follow-up of patients with differentiated thyroid cancer and undetectable thyroglobulin (Tg) and Tg antibodies during ablation. Eur J Endocrinol 2008;158:77-83.
7. Vaisman A, Orlov S, Yip J, Hu C, Lim T, Dowar M, *et al.* Application of post-surgical stimulated thyroglobulin for radioiodine remnant ablation selection in low-risk papillary thyroid carcinoma. Head Neck 2010;32:689-98.
8. Kim TY, Kim WB, Kim ES, Ryu JS, Yeo JS, Kim SC, *et al.* Serum thyroglobulin levels at the time of 131I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2005;90:1440-5.
9. Toubeau M, Touzery C, Arveux P, Chaplain G, Vaillant G, Berriolo A, *et al.* Predictive value for disease progression of serum thyroglobulin levels measured in the postoperative period and after (131)I ablation therapy in patients with differentiated thyroid cancer. J Nucl Med 2004;45:988-94.
10. Piccardo A, Arecco F, Puntoni M, Foppiani L, Cabria M, Corvisieri S, *et al.* Focus on high-risk DTC patients: High postoperative serum thyroglobulin level is a strong predictor of disease persistence and is associated to progression-free survival and overall survival. Clin Nucl Med 2013;38:18-24.
11. Polachek A, Hirsch D, Tzvetov G, Grozinsky-Glasberg S, Slutski I, Singer J, *et al.* Prognostic value of post-thyroidectomy thyroglobulin levels in patients with differentiated thyroid cancer. J Endocrinol Invest 2011;34:855-60.
12. Park EK, Chung JK, Lim IH, Park DJ, Lee DS, Lee MC, *et al.* Recurrent/metastatic thyroid carcinomas false negative for serum thyroglobulin but positive by posttherapy I-131 whole body scans. Eur J Nucl Med Mol Imaging 2009;36:172-9.
13. Robenshtok E, Grewal RK, Fish S, Sabra M, Tuttle RM. A low postoperative nonstimulated serum thyroglobulin level does not exclude the presence of radioactive iodine avid metastatic foci in intermediate-risk differentiated thyroid cancer patients. Thyroid 2013;23:436-42.
14. de Rosário PW, Guimarães VC, Maia FF, Fagundes TA, Purisch S, Padrao EL, *et al.* Thyroglobulin before ablation and correlation with posttreatment scanning. Laryngoscope 2005;115:264-7.
15. Oyen WJ, Verhagen C, Saris E, van den Broek WJ, Pieters GF, Corsten FH, *et al.* Follow-up regimen of differentiated thyroid carcinoma in thyroidectomized patients after thyroid hormone withdrawal. J Nucl Med 2000;41:643-6.
16. Orlov S, Salari F, Kashat L, Freeman JL, Vescan A, Witterick IJ, *et al.* Post-operative stimulated thyroglobulin and neck ultrasound as personalized criteria for risk stratification and radioactive iodine selection in low- and intermediate-risk papillary thyroid cancer. Endocrine 2015;50:130-7.