Stimulated high serum thyroglobulin with negative whole body imaging do not warrant an aggressive diagnostic and therapeutic approach in differentiated thyroid cancer patients: A follow-up of 5 years or till recurrence

Manoj Gupta DRM, FEBNM,
Partha. S. Choudhury DNB,
Sudipta Nag MBBS,
Parul Gupta MBBS

Department of Nuclear Medicine, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

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Correspondence address:
Manoj Gupta MD,
Department of Nuclear Medicine,
Rajiv Gandhi Cancer Institute and
Research Centre, Sector 5, Rohini,
New Delhi, India, 110085.
Mb: +91-9540907949
Fax: +91-1127051037
docmanojgupta@yahoo.com

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Abstract

Objective: To study the clinical significance of stimulated high serum thyroglobulin (sTg) and of normal whole body imaging (WBI) in differentiated thyroid cancer (DTC) patients during their first follow-up and in a 5 years follow-up or till recurrence. **Subjects and Methods:** Sixty four DTC patients were retrospectively studied and were divided into two groups. Group 1, of 35 patients with disease free status on their first follow-up and group 2, of 29 patients with high sTg (>2μg/mL), but with normal WBI, iodine-131 (^{131}I) findings. Patients were categorized into low, intermediate and high risk patients based on the ^{131}I WBS findings. Histology, stage and risk-categories of both groups were statistically correlated. Best sTg cut-off for predicting recurrence was generated by receiver operating characteristic (ROC). Odd ratio for sTg trend was also analyzed for risk of recurrence in group 2. Independent t test was used for progression free survival (PFS) comparison of the two groups. **Results:** No statistical differences were seen in histology, stage and risk category distributions between the groups. Group 2 patients with high sTg (range 2.5-81μg/L, mean 20.5μg/L) on their first follow-up had higher risk of recurrence (odd ratio 4.304) but P value was insignificant (P:0.090). Eighty six per cent of group 2 patients showed decreasing trends and in 62% of group 2 patients, high serum sTg fell to normal. Indeed, decreasing trends of sTg reduced the risk of recurrence (odd ratio 1.3939, P: 0.79). Analysis by ROC showed that sTg>11μg/L was the best cut-off in predicting recurrence with sensitivity 100% and specificity 56%. High sTg was not associated with low PFS, (P:0.232), however patients with increasing sTg had significantly shorter PFS (P<0.005). **Conclusion:** High sTg with negative ^{131}I WBS did not warrant an aggressive DTC disease. These patients in their 5 years or till recurrence follow-up showed downward trends of serum sTg, no higher risk or recurrence and no shorter PFS.

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Introduction

Most differentiated thyroid cancer (DTC) patients with no detectable metastases are low risk patients and can be effectively treated with standard surgical resection and radioiodine-131 (^{131}I) treatment. These patients may never face the disease again after the above treatment. The risk of recurrence remains with intermediate and high risk categories of DTC for many years.

Locoregional recurrence in forms of a thyroid bed nodule or of several neck nodules is the most common sign of recurrence [1]. Recurrence rate in DTC patients as high as 15%-30% has been reported usually occurring within 10 years after initial diagnosis [2]. Therefore especially high risk patients should be regularly monitored.

The classical approach to follow-up these patients is regular ultrasound (US) of the neck, serum thyroglobulin (Tg) and a diagnostic ^{131}I whole body scan (^{131}I WBS). Generally, the low risk category patients skip this scan and can be monitored only by US and serum Tg measurements [3, 4]. Serum Tg is measured after stopping thyroxin (T4) for 3-4 weeks and is called stimulated Tg (sTg). Thyroglobulin measured after receiving T4 treatment is called unstimulated Tg (uT).

High serum Tg is a surrogate marker of residual DTC tissue [5]. Therefore, an elevated Tg is always alarming. Elevated serum Tg in treated patients with distant metastases is expected to be due to functional metastases which are not visualized by a low dose of 74MBq. Indeed, these patients need aggressive approach using magnetic resonance imaging (MRI) or fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to localize the disease and may be treated empirical-

ly with high dose ^{131}I [6]. However, patients with unknown metastases but with elevated serum Tg and negative ^{131}I WBS and US pose a diagnostic dilemma. There are dif-different diagnostic and therapeutic approaches in medical literatures mainly due to the lack of understanding the etiologies and to having no proper guidelines suggesting their use [7, 8]. These patients undergo multiple cross-sectional ima-ging tests which may not be necessary and often receive an empirical high dose ^{131}I treatment with no further benefits [9]. The whole approach gives an unnecessary financial and psychological burden.

In the present paper we studied the clinical significance of elevated sTg with normal ^{131}I WBS.

Subjects and Methods

We retrospectively analyzed the data of 186 thyroid cancer patients, who were treated in our hospital from January 2006 till March 2009. Forty two of them with distant metastases were excluded from the study. The following inclusion and exclusion criteria were then applied for further patients' selection.

Inclusion criteria were: a) Patients with histologically proven DTC (papillary, follicular or Hürthle cell variant). b) Patients undergone total thyroidectomy or near total thyroidectomy or completion thyroidectomy with or without central compartment clearance and with or without lateral neck dissection as appropriated by the clinical stage [10]. c) Al. high risk criteria of histology were considered lympho-vascular invasion (LVI), minimal extra-thyroid extension, tumour size>4cm, pT3 in TNM staging, adjacent organ like esophagus, trachea, larynx or carotid vessels involvement (pT4 in TNM staging)/Lymph-node status if neck dissection was performed. d) Patients who had undergone a pre-treatment ^{131}I WBS. e) Stimulated Tg at the first follow-up in all patients. f) Patients with high sTg at the first follow-up should have at least 3 more serial sTg follow-up values in approximately 6 months intervals. g) Patients with at least one ^{131}I WBS during approximately the first 6 months of their follow-up. h) Patients with a neck US at the first follow-up and at least two more during approximately 6 months intervals or till recurrence. i) Patients with at least 5 years of follow-up with no recurrence. j) Cytologicaly proven recurrence.

Exclusion criteria: a) patients with distant metastases at presentation. b) Incomplete ablation shown on the ^{131}I WBS with high or normal serum sTg on the first follow-up. c) Abnormal US with high serum sTg on the first follow-up. d) Presence of anti-Tg antibodies. e) New lesions or progression on the first follow-up.

In summarizing inclusion and exclusion criteria, only patients with total ablation on the ^{131}I WBS, with normal sTg ($\leqslant$2μg/L) and US (group 1, complete response) and patients with total ablation on ^{131}I WBS with normal US and elevated serum sTg (>2μg/L) (group 2, biochemical incomplete response) were included for further study.

Out of the remaining 144 patients, 64 were included in the final study based on inclusion and exclusion criteria. Patients were categorized into: low, intermediate and high risk categories based on pathological features of final histopathology after thyroidectomy and on the^{131}I WBS findings (Table 1). Further high dose ^{131}I treatment was tailored for these patients [11].

We have added size>4cm in the intermediate risk category. Percentage distribution of risk categories are written in results e.g. Group 1 patients were 31.4% of the low, 60.0% of the intermediate and 8.6% of the high risk category, while group 2 patients were 13.8%, 82.8% and 3.4% respectively. Patients

Table 1. *Risk categories and ^{131}I dose range*

	Low (category 1)	Intermediate (category 2)	High (category 3)
Features	^{131}I dose range (1.11-1.85GBq)	^{131}I dose range (1.85-7.4GBq)	^{131}I dose range (5.55-7.4GBq)
Tumor size	>1cm	>4cm	Any
LVI	»	Yes	»
*High risk hirtology	»	»	»
Extrathyroid extension	»	»	»
Lymphonode involvements	»	»	»
^{131}I WBS (lesion outside thyroid beb)	»	No	»

**LVI: Lymphovascular invasion. High risk histology: Tall cell variant of papillary thyroid carcinoma, insular carcinoma. Hurthle cell carcinoma. DxWBS: diagnostic whole body scan.*

with intermediate risk had a DxWBS with residual thyroid bed tissue and were treated only with adjuvant dose of ^{131}I while high risk patients who had neck nodes positive on Dx WBS were treated with higher treatment doses. Hence the range of high risk category ^{131}I dose was higher.

Statistical analysis

Histology, stage and risk categories of both groups were correlated and P values were calculated. A receiver operating characteristic (ROC) curve was generated for the first follow-up sTg values in group 2 patients, to find out the best cut-off for predicting recurrence. Group 2 patients' sTg trend was also studied and odd ratios were calculated for the risk of disease recurrence in patients with decreasing sTg and progressing sTg. Independent t test was used for progression free survival (PFS) comparison in both groups.

Results

Group 1 had 35 patients, 10 males and 25 females, average age 41.4 years. The ratio between those younger than 45 years to those equal or more than 45 years was 1.7:1.0. Group 2 had 29 patients, 14 males and 15 females with average age 44.1 years. The ratio of those younger than 45 to those 45 years or older was 1.1:1.0. Overall, 58% (37/64) of patients belonged to age <45 years. Group 1 patients were 31.4% of the low, 60.0% of the intermediate and 8.6% of the high risk category, while group 2 patients were 13.8%, 82.8% and 3.4% respectively. Group 2 patients who were in the intermediate risk category, were more than those in group 1, however this difference was not significant (P: 0.1395). Histological characteristics of groups 1 and 2 patients are shown in Table 2.

Table 2. *Histological characteristics of group 1 and 2 patients*

Pathology	Group 1 (n-35)	Group 2 (n-29)
PTC	29 (82.8%)	26 (89.6%)
FTC	3 (8.6%)	1 (3.5%)
*High risk histology	3 (8.6%)	2 (6.9%)

*PTC: Papillary thyroid carcinoma. FTC: Follicular thyroid carcinoma. *High risk histology: Tall cell variant of papillary thyroid carcinoma, insular carcinoma. Hórthle cell carcinoma.*

Most patients of both groups had papillary thyroid carcinoma (PTC). There was no significant difference in the histology (P:0.6676) of both groups. Latest TNM stages were different for patients aged <45 and ⩾45 years [12]. In group 1 patients average age was less (41.4 years) as compared to group 2 (44.1 years) which may partly explain the reason of higher stage 1 percentage in group 1. There was no significant difference in stage distribution (P: 0.6035) of both groups.

The sTg trends after follow-up in groups 1 and 2 patients are given in Table 3. Group 2 patients were examined after high dose ^{131}I treatment (range 1.85-7.4GBq, mean 4.65GBq, median 5.55GBq). Thyroid hormone treatment was withdrawn for 4 weeks. On the first follow-up, these patients had complete ablation of the thyroid remnant as shown by ^{131}I WBS and by the normal neck US and also high sTg values (2.5-81μg/L, mean 20.5μg/L, median 12μg/L). All patients were then treated with a suppressive dose of T4 and followed-up for 6 months (2nd follow-up). In this 2nd follow-up, 25/29 (86.2%) of the patients showed decreasing trends of sTg and in 10/29 of them sTg fell to ≤2 μg/L. Fourteen patients showed further regression of sTg and in 18/29 (62.1%) of patients sTg became normal. In the 3rd follow-up 6/24 patients although their sTg was high >2ng/mL showed decreasing trends (Table 3) of sTg but still >2μg/L. These 6 patients were put on suppressive T4 and showed undetectable sTg serum values in their last follow-up. Five patients showed rising trends of sTg and developed disease recurrence. Only one patient with decreasing trends of sTg in the three follow-ups showed disease recurrence 55 months after surgery.

The best sTg cut-off point at the first follow-up, by using the ROC curve was >11μg/L (Figure 1) predicting recurrence with sensitivity 100% and specificity 56.52%. Indeed it was found a zero recurrence rate in all patients with sTg ≤10μg/L after the first follow-up.

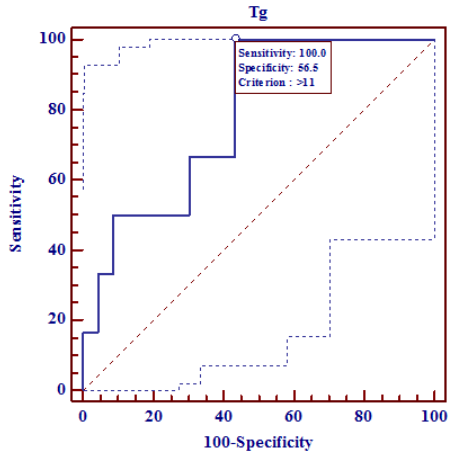


Figure 1. ROC curve of Group 2 patients' first follow up of sTg in predicting recurrence. A value of sTg>11ng/mL was found to be the best cut-off point.

	Area under the ROC curve (AUC)	95% Confidence interval	Significance level P (Area=0.5)	Associated criterion
sTg	0.782609	0.591008 to 0.913197	0.0043	>11

Group 1 patients (Table 3) received a high dose of ^{131}I treat-

Table 3. *A: Group 1 patients with their Tg trends and PFS*

S.No	Initial three follow up Tg			Last Tg(uTg)	PFS (months)
	1st (sTg)	2nd (uTg)	3rd (uTg)		
1	2	UD	UD	UD	106
2	<1	«	«	«	63
3	<1	<1	<1	<1	82
4	1.2	4	UD	UD	64
5	<1	UD	«	«	81
6	<2	«	«	1.98	84
7	<2	«	«	0.01	77
8	<1	«	«	UD	78
9	<1	«	«	«	80
10	<1	«	«	**13**	71
11	<1	«	«	UD	64
12	<1	«	«	«	70
13	<1	«	«	«	79
14	<1	«	«	«	67
15	<1	«	«	**20**	48
16	0.25	«	«	0.25	65
17	1	«	«	0.12	64

B: Group 2 patients with their sTg trends and PFS

S.No	Initial three follow up Tg			Last Tg(uTg)	PFS (months)
	1st (sTg)	2nd (sTg)	3rd (sTg)		
1	31	9	2	0.01	101
2	35	5	1.9	0.2	96
3	31	15	1	1.88	78
4	11	6	3	0.1	67
5	5	0.1	0.1	0.01	92
6	9	2	0.1	0.04	74
7	4	1.2	1	1.24	77
8	12	5	1.7	**97**	57
9	14	2	0.2	0.01	71
10	8	6	1.2	0.01	80
11	18	3	0.1	1.39	76
12	7	0.1	0.1	0.01	68
13	81	72	**125**	-	22
14	8	2.9	0.1	2.1	59
15	21	0.1	0.1	0.01	69
16	75	59.6	29.1	0.68	69
17	10	4	2	2	64

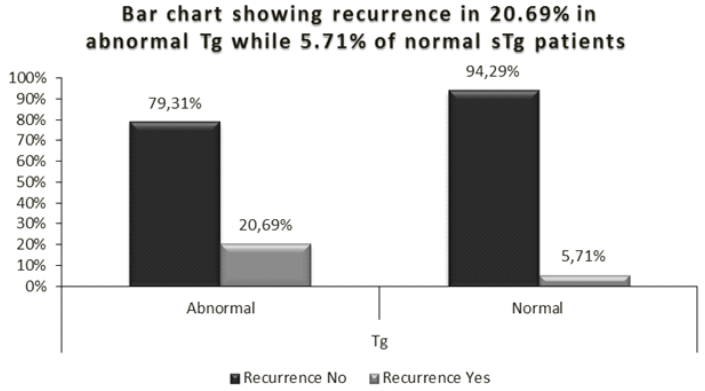
(continued)

18	<1	UD	UD	0.01	61
19	<1	«	«	UD	74
20	<1	«	«	«	66
21	<1	«	«	«	76
22	<1	«	«	«	62
23	<1	«	«	«	61
24	<1	«	«	«	68
25	<1	«	«	«	63
26	0.9	«	«	0.01	73
27	<1	«	«	0.02	55
28	<1	«	«	0.27	67
29	0.2	«	«	0.01	70
30	0.7	«	«	0.01	62
31	0.12	«	«	0.01	85
32	1.7	«	«	UD	56
33	<1	«	«	0.05	60
34	0.78	0.59	0.01	0.01	59
18	7	4	2.4	0.22	66
19	8.2	0.1	0.1	0.01	70
20	11.2	15	23.3	47	30
21	14	0.43	2	0.01	60
22	60	103	**150**	-	21
23	25.2	12	4	1.09	66
24	20.7	27	70	105	33
25	2.9	2	1.8	0.01	63
26	33.9	42	59.9	68.02	55
27	25.5	16.9	5.3	0.01	66
28	2.5	1.6	0.1	0.01	59
29	3.3	3.1	2.8	0.19	62

sTg: stimulated thyroglobulin, uTg: un-stimulated thyroglobulin, UD: undetectable (<0.01μg/L), PFS: progression free survival (from the month of thyroid surgery to last follow up or recurrence), sTg values in bold are the level at which recurrence diagnosed.

Table 4. *Comparing recurrence rate in group 1 and group 2*

		Recurrence				
		No	Yes	Total	P value	Odd Ratio
Tg	Abnormal	23 (79.31%)	6 (20.69%)	29 (100.00%)		
	Normal	33 (94.29%)	2 (5.71%)	35 (100.00%)	0.09	4.304
Total		56 (87.50%)	8 (12.50%)	64 (100.00%)		



ment (range 1.33-7.4GBq, mean 4.04GBq, median 5.1GBq) and then received a T4 treatment for 6 months. They all had complete remnant ablation on the ^{131}I WBS, normal neck US values and normal sTg values (⩽ 2μg/L). After the first follow-up, all these patients were re-categorized to low risk (delayed risk stratification) and were followed-up with US examination of the neck and uTg. Second and third follow-ups were normal in all these patients. Only 2/35 (5.7%) of patients had recurrence. The overall combined recurrence rate in both groups was 12.5% (8/64).

Comparing the risk of disease recurrence (Table 4), it was noticed that group 2 patients had higher risk of recurrence as compared to group 1 with odd ratio of 4.304 but this was not statistically significant (P: 0.090). This may be due to studying a small number of patients. If we exclude the 5 patients with progression of sTg and include the remaining 24 patients with decreasing trends of sTg of group 2 and then compare the recurrence rate of these patients with the recurrence of group 1 patients, the odd ratio will become 1.3939 and P:0.7912. So, high sTg (>11μg/L) at the first follow-up was associated with high risk of recurrence; however a decreasing trend in sTg values in subsequent follow-up studies nullified this effect.

None of our patients died till the end of the study, during which PFS was examined (Table 5). Duration of follow up of these patients was high. In group 2, patients sTg was not associated with shorter PFS (P:0.232). Comparing only the 24 patients of group 2 having decreasing trends of serum sTg with those of group 1 (n35) we found P value for PFS further increased:0.477. This was after exclusion of the 5 patients who showed progression of sTg and had significantly low PFS (Table 3). We noticed that all patients in the low risk category (23.4%) did not develop recurrence. Hence, these patients even with high sTg required only to be followed-up.

Table 5: *Independent T test for progression free survival*

	Sample size	Mean±SD	Median	Min-Max	P value
Group 1	35	69.11±11.03	67	48-106	0.232
Group 2	29	64.52±19.03	66	21-101	

SD: standard deviation

Discussion

Detection of DTC recurrence has become more sensitive due to high-resolution US and highly sensitive sTgvalues. Thyroglobulin is a tissue specific 660kDa protein, that serves as a precursor in thyroid hormone biosynthesis [13]. It is synthesized by both thyroid follicular cells and differentiated cancer cells. High serum Tg in the follow-up of DTC patients after adequate surgery and ^{131}I treatment with negative imaging results is suspicious of recurrence. Several studies suggested that a baseline Tg of 2μg/L is predictive of pe-rsistent disease and future metastases. In our study all pati-ents in group 1 had sTg ⩽2μg/L while in group 2 had >2μg/L. Gaille-

ux et al (2000) [14] reported the data of 256 DTC patients previously treated with thyroidectomy and with 3700MBq of ^{131}I 46/256 of which had high sTg and 9/46 (20%) had recurrence. The authors thus reported a high recurrence rate. Indeed, their patients group included patients with high sTg and positive ^{131}I WBS. A clear difference between risk categories, stage distribution and ^{131}I administration was lacking. We have selected a very specific group of patients with a specific diagnostic dilemma. Baudine et al (2003) [15] published a similar study with a different perspective. They included 37 patients with high sTg and negative ^{131}I WBS and reported a positive predictive value (PPV) of 42% for recurrence, for patients with sTg 5-10μg/L and 53% for patients with sTg more than 10mg/L. In our study both figures were 20%. The above authors also noticed that a single value of sTg was less predictive of disease recurrence while a rising slope of sTg had PPV of 83%. In our study we also noticed similar results and reported that all patients with increasing sTg had recurrence (PPV 100%). Moreover, we also studied the PFS of the risk category. In our study, a low risk patient with high sTg had no additional risk of recurrence. We noticed that all cases with recurrence occurred in intermediated and high risk group patients in both groups. A high sTg with negative imaging as an individual factor was associated with a higher risk of recurrence (odd ratio 4.304) but this was not statistically significant (P: 0.090). A recent study published by Pelttariet al (2010) [16] showed that disease recurrence rate was significantly higher in patients with detectable sTg after initial ^{131}I treatment, compared to that of patients with undetectable sTg.Risk categories and stage distribution were not clearly defined.

Many causes of high sTg with negative ^{131}I WBS have been reported in the medical literature [17]. Some of the most common causes for false negative (FN)^{131}I WBS and false positive (FP) sTg are given below: a) Inadequate withdrawal of T4. b) High iodine pool (iodinated contrast, betadine or amiodarone). c) Very small residual thyroid tissue. d) Low dose 74MBq ^{131}I WBS. e)Trapping or organification defect in the tumor cells. f) Dedifferentiated tumor. g) False positive sTg due to circulating anti-Tg antibodies or to benign disease (possible thyroiditis) or to persistent residual thyroid tissue to erroneous Tg result, or to ectopic thyroid tissue.

All our all patients were followed-up after 4 weeks of T4 withdrawal with low iodine diet in the last week. Organification or trapping defects were unlikely because all patients had positive post therapy ^{131}I WBS. One of the reasons that can explain this scenario is small residual thyroid tissue which is below the detectable limit of low dose for performing a^{131}I WBS (74MBq). The small residual thyroid tissue which was producing Tg becomes atrophic over time. All patients from both groups were anti-Tg antibodies (TgAb) negative. Ectopic thyroid tissue was unlikely to be present in patients showing either decreasing or increasing trends of sTg, moreover ^{131}I WBS was also negative in all cases.

Heemstra et al (2007) [18] reported highest diagnostic accuracy for recurrence of Tg at 6 months after initial therapy (sTg cut-off value was 10μg/L sensitivity 100%, specificity 93%). However, in our study sTg was>11μg/L at the first follow-up with a sensitivity of 100% and specificity of 56.5%. Low specificity was due to decreasing trends of sTg in many patients (86.2%). However patients with rising trends of sTg showed 100% specificity. Three of our patients had sTg values >50μg/L and 2/3 showed disease recurrence. These numbers are insufficient for conclusion.

In conclusion, this study showed that patients with high sTg and negative ^{131}I WBS do not always warrant aggressive approach. Eighty six point two percent of these patients showed downward trends of sTg serum value and did not have a significant high risk of disease recurrence and also low PFS. Only those patients with rising trends of sTg had a high disease recurrence rate and low PFS and thus required an aggressive diagnostic and therapeutic follow-up. Of group 2, 5/29 patients showed a rising trend and all developed recurrence. While 24/29 patients of group 2 showed decreasing trend and only one patient developed recurrence.

Bibliography

1. Durante C, Montesano T, Torlontano M et al. Papillary thyroid cancer: Time course of recurrence during post surgery surveillance. *J Cl in Endocrinol Meta*b, 2013; 98(2): 636-42.
2. Mazzaferri EL, Jhaing SM. Long term impact of surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994; 97: 418-28.
3. American Thyroid Association (ATA) Guidelines. Task force on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009; 19: 1167-214.
4. Johnson AN, Tublin ME. Postoperative Surveillance of Differentiatted Thyroid Carcinoma: Rational, Techniques, and Controversies. *Radiology* 2008; 2: 429-44.
5. Gupta M, Chia SY. Circulating thyroid cancer markers. *Curr Opin Endocrinol Diabetes Obes* 2007; 14: 383-8.
6. Pryma DA, Mandel SJ. Radioiodine Therapy for Thyroid Cancer in the Era of risk stratification and alternative targeted therapies. *J Nucl Med* 2014; 55: 1485-91.
7. Silberstein EB. The problem of the patients with thyroglobulin elevated but negative iodine scintigraphy: the TENIS syndrome. *Semin Nucl Med*. 2011: 41(2): 113-20.
8. Basu S, Dandelar M, Joshi A, D'Cruz A. Defining a rational step care algorithm for managing thyroid carcinoma patients with elevated thyroglobulin and negative on radioiodine scinitigra-phy (TENIS): consideration and challenges towards developing an appropriate roadmap. *Eur J Nucl Med Mol Imaging* 2015; 42: 1167-71
9. Mazzaferri EL. Empirically treating high serum thyroglobulin. *J Nucl Med* 2005; 46: 79-88.
10. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. *CA: A Cancer J for Clinicians* 2013; 63: 374-94.
11. Pacini F, Castagna MG, Brilli L, Pentheroudakis G. Thyroid Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals Oncology* 2012; 23(supplement 7): 110-19.
12. Edge S, Byrd DR, Compton CC et al. AJCC cancer staging manual 7th edn, *Springer* 2010; 87-96.
13. Ringel MD, Ladenson PW. Controversies in the follow-up and management of well differentiated thyroid cancer. *Endocrine-Related Cancer* 2004; 11: 97-116.
14. Cailleux AF, Baudin E, Travagli JP et al. Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid

cancer? *J Clin Endocr Metab* 2000; 85: 175-8.
15. Baudin E, Do Cao C, Cailleux AF et al. Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. *J Clin Endocrinol Metab* 2003; 88: 07-11.
16. Pelttari H, Valimaki MJ, Loyttyniemi E et al. Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study. *Europ J Endocrinol* 2010; 163: 757-63.
17. Ma C, Kuang, A, Xie J, Ma T. Possible explanations for patients with discordant findings of serum thyroglobulin and ^{131}I whole body scanning. *J Nucl Med* 2005; 46: 1473-80.
18. Heemstra KA, Liu YY, Stokkel M et al. Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma. *Clin Endocrinol* 2007; 66: 58-64.

A view of the traditional upper city of Thessaloniki. Oil on canvas. K. Gounaris, 2009.