

Value of serum thyroglobulin in the follow-up of patients with differentiated thyroid carcinoma.

Makumkrong Poshyachinda*

Vacharee Buochum* Puangpayom Prichakas*

Poshyachinda M, Buochum V, Prichakas P. Value of serum thyroglobulin in the follow-up of patients with differentiated thyroid carcinoma. Chula Med J 1991 Oct; 35(10): 631-638

Determination of the serum thyroglobulin (Tg) level has been widely used as a tumor marker in the follow-up of patients with proven differentiated carcinoma of the thyroid. In this study, serial follow-up measurements of the serum Tg levels of 150 differentiated thyroid cancer patients were evaluated to determine the value of this method in patient management. The serum Tg levels determined at intervals of at least six months in each patient who was followed for a period of one to three years. Whole-body radioiodine scans were also carried out in all patients. The false-positive rate of serum Tg in patients in the remission group was 10.2% and the false-negative rate in the group with the disease was 13.1%. The sensitivity and specificity of serum Tg was 86.8% and 89.8%, respectively. The serum Tg level was more sensitive than whole-body radioiodine scan, the accuracy of measurement being much increased when these two modalities were combined. Increased discriminative value of serum Tg for the detection of residual cancer was noted in patients who were not on thyroid hormone therapy, but results also proved to be valuable during hormonal treatment. Hence, serum Tg determination is of value in the follow-up of patients and can reduce the frequency of whole-body radioiodine scan.

Key words: Thyroid cancer, Thyroglobulin, Tumour marker

Reprint request : Poshyachinda M, Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. July 16, 1991.

มาคุ้มครอง โปษยะจินดา, วัชร บัวพูน, พวงพยอม ปรีชาภาส. คุณค่าของซีรัม thyroglobulin ในการติดตามผู้ป่วยมะเร็งต่อมธัยรอยด์. จุฬาลงกรณ์เวชสาร 2534 ตุลาคม; 35(10): 631-638

ระดับซีรัม thyroglobulin (Tg) เป็น tumour marker ที่มีการใช้กันมากขึ้นเพื่อตรวจวินิจฉัยการเกิดโรคซ้ำ หรือการแพร่กระจายของมะเร็งในผู้ป่วยที่เป็น differentiated thyroid cancer ในรายงานนี้ ได้ทำการศึกษาผู้ป่วยมะเร็งต่อมธัยรอยด์ชนิด differentiated cell จำนวน 150 ราย เพื่อประเมินคุณค่าของการตรวจวัดระดับซีรัม Tg โดยเปรียบเทียบกับการทำสแกนผู้ป่วยทั้งตัวภายหลังการให้ไอโอดีน-131 ได้ทำการตรวจวัดระดับซีรัม Tg อย่างน้อยทุก 6 เดือน เป็นเวลา 1-3 ปี และทำสแกนทั้งตัวในผู้ป่วยทุกคน ผลการศึกษาพบว่า ความไวและความจำเพาะของซีรัม Tg เท่ากับ 86.8% และ 89.8% ตามลำดับ โดยมีอัตราผลบวเท็จและผลบวกเท็จเท่ากับ 13.1% และ 10.2% ตามลำดับ ระดับซีรัม Tg วินิจฉัยโรคได้ไวกว่าการสแกนทั้งตัว และเมื่อใช้การตรวจทั้ง 2 ชนิด ทำให้ความแม่นยำเพิ่มขึ้นมาก ความแม่นยำในการวินิจฉัยโรคด้วยวิธีตรวจวัดซีรัม Tg ไม่แตกต่างกันระหว่างที่ผู้ป่วยกำลังรับประทานยาธัยรอยด์ฮอร์โมนกับระหว่างที่หยุดยา แม้ว่าระหว่างที่หยุดยาระดับซีรัม Tg จะสูงกว่ามากก็ตาม ดังนั้นการตรวจวิธีนี้จึงเหมาะสมที่จะใช้ติดตามผู้ป่วยมะเร็งต่อมธัยรอยด์ภายหลังที่ได้รับการผ่าตัดแล้ว และยังช่วยลดการตรวจด้วยวิธีสแกนทั้งตัว โดยใช้สแกนในกรณีที่มีความจำเป็นเท่านั้น เพราะเป็นวิธีที่ยุ่ยยากและเสียเวลากว่ามาก

There is increasing evidence that the level of serum thyroglobulin (Tg) is a useful tumor marker in the follow-up of postoperative patients with differentiated thyroid cancer.⁽¹⁻⁴⁾ A high serum Tg level suggests the presence of disease, whereas a low or undetectable Tg level indicates that there is a high probability of the patient being free of disease. However, whether serum Tg can replace totalbody radioiodine scan remains controversial, since low serum Tg levels are occasionally found in patients with metastasis and high Tg levels are reported in some patients in whom there is an absence of disease.⁽⁵⁻⁸⁾

The objective of this study is to evaluate the merits of assessing serum Tg levels in the management of patients with differentiated thyroid cancer, employing serial Tg measurements and radioiodine scan.

Materials and methods

Patients

One hundred and fifty patients with differentiated thyroid cancer were studied. All patients had simultaneous Tg estimations and whole-body radioiodine scans at least once. Serial Tg measurements in these patients were followed for 1-3 years at intervals of at least six months. There were 126 female patients and 24 male patients, ranging in age from 11 to 80 years (Mean \pm SD = 37.9 ± 14.5). Sixty-four patients had papillary carcinoma, 56 had follicular carcinoma and 30 had mixed papillary/follicular carcinoma. All were treated by total or near total thyroidectomy with subsequent radioiodine treatment.

Comparison of serum Tg determination before and after withdrawal of thyroid hormone therapy was performed in 47 patients at intervals of 6-8 weeks.

The presence or absence of residual, recurrent or metastatic cancer was assessed clinically, by total body scans, by X-ray and bone scan. The analysis to determine the value of the Tg test in the presence or remission of the disease was based on the Tg measurement during withdrawal of thyroid hormone suppressive therapy.

Method

Serum thyroglobulin assay

Five millilitres of blood were taken from

each patient for serum Tg measurement after that patient had been withdrawn from thyroxine therapy for six weeks. In 47 patients, serum Tg levels were also determined prior to the discontinuation of thyroxine treatment. Serum thyroglobulin was measured by a double antibody radioimmunoassay kit (Diagnostic Product Corporation). The detection limit of the Tg assay was 2.6 ng/ml. The intra-assay and inter-assay coefficients of variation at 5 ng/ml. were 5% and 9%; at 100 ng/ml, 3% and 5%, respectively.

Total-body¹³¹I Scanning

Total-body scanning was performed 72 hours after administration of a 5 mCi (92 MBq) dose of ¹³¹I. Six weeks prior to scanning, thyroxine administration was stopped and replaced by triiodothyronine. Two weeks before scanning, triiodothyronine was discontinued.

Results

Cut-off limit of Tg level

The cut-off limit of the Tg level to distinguish pathological from nonpathological values was established in 24 patients having differentiated thyroid carcinoma. These patients, who showed no evidence of metastasis, had undergone thyroid surgery and successful radioiodine ablation of residual thyroid and were in remission of disease for a period of 5-8 years. The Tg levels in these patients ranged from undetectable to 10 ng/ml. The cut-off limit was then set at 10 ng/ml.

Of 150 patients, 98 were considered to be in remission of disease; 14 had only small thyroid remnants in the thyroid bed; 38 had recurrence or metastasis.

Serum Tg in patients with residual thyroid

Fourteen patients with faint uptake at the thyroid bed in the total-body scan were followed-up for 3-7 years. None had had clinical or laboratory evidence of persistent disease. The Tg levels in this group varied from an undetectable amount to 8 ng/ml. (Fig. 1). It was not possible to classify this group of patients as being in remission or having disease. Therefore, data in this group of patients were not included in the analysis to determine the value of the Tg test.

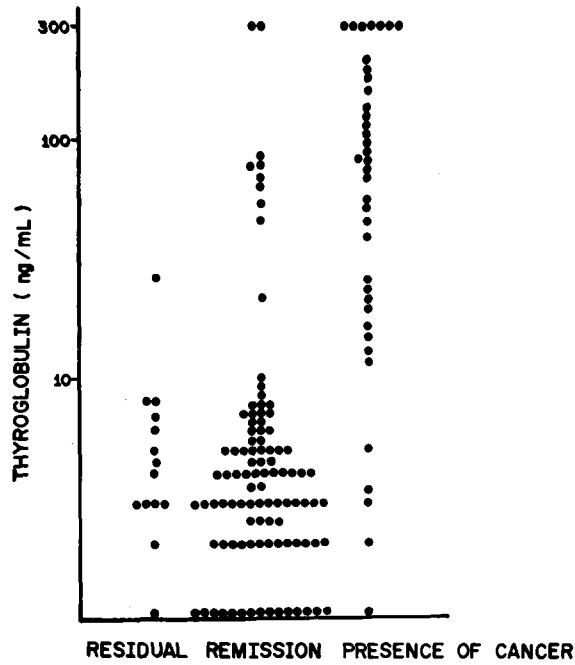


Figure 1. Serum Tg levels in patients with differentiated thyroid cancer.

Serum Tg in patients with or without residual cancer

Eighty-eight of 98 patients without evidence of residual cancer had Tg levels lower than 10 ng/ml, whereas 33 of 38 patients with cancer had Tg levels greater than 10 ng/ml, (Fig. 1). The sensitivity and specificity of the serum Tg test in the diagnosis of disease in these patients was 86.8% and 89.8%, respectively, and overall accuracy was 88.9%. Thus, the false-positive rate in the remission group was 10.2% and the false-negative rate in the group with

disease was 13.1%.

Comparison of serum Tg and total-body scan

Comparison of simultaneous serum Tg measurements and total-body scans in patients with disease or in remission is shown in Table 1. The sensitivity of the total-body scan in detection of disease was 78.9%. The detection rate was increased to 100% by combining the serum Tg test and total-body scan.

Table 1. Comparison of serum Tg level and total-body scan.

	Cancer	
	Present (cases)	In remission (cases)
Tg + ve / scan + ve	25	—
Tg + ve / scan - ve	8	10
Tg - ve / scan + ve	5	—
Tg - ve / scan - ve	—	88
Total	38	98

Serum Tg level in euthyroid and hypothyroid status

Serum Tg values in 47 patients (nine with residual thyroid, 24 from the group in remission and 14 from the group with disease) were studied while they were on thyroid hormone and when they were hypothyroid. The results are shown in Figure 2. In the patients with residual thyroid, four of them with elevated serum Tg levels when hypothyroid were

suppressed to less than 10 ng/ml when euthyroid; the majority of patients without residual cancer exhibited Tg levels less than 10 ng/ml in both euthyroid and hypothyroid status (Table 2). Ten of 14 patients with cancer had high Tg levels in the hypothyroid state; these levels were much reduced when they were in euthyroid status when compared with hypothyroid status, but were still above the cut-off value (Fig. 2).

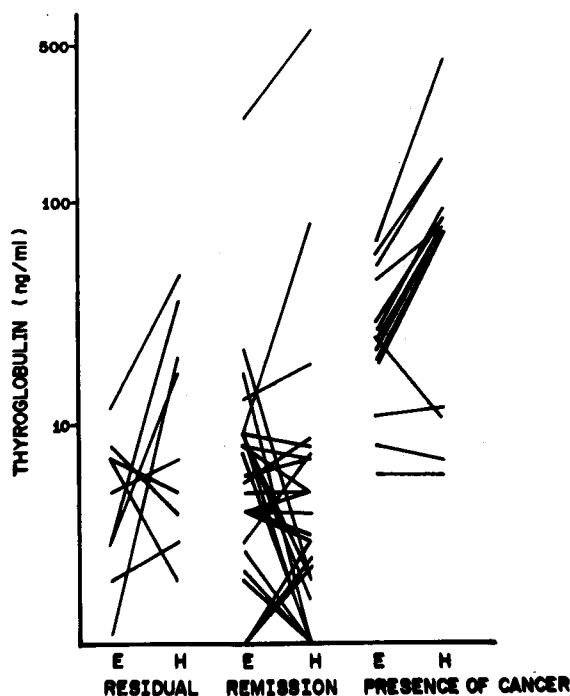


Figure 2. Paired serum Tg levels in the euthyroid (E) and hypothyroid (H) state in the same patient.

Table 2. Serum Tg in euthyroid and hypothyroid patients.

	Total cases (M)	Serum Tg (ng/ml)			
		Euthyroid		Hypothyroid	
		<10	>10	<10	>10
Remission group	24	21	3	21	3
Cancer present	14	3	11	4	10
Residual thyroid	9	9	-	5	4

Discussion

Our critical level of serum Tg was established from the upper range of Tg values in thyroid cancer

patients who were in remission for a minimum period of three years. Thus, this cut-off Tg level is relatively high, which would tend to decrease the sensitivity of Tg measurement in the detection of residual or early

relapse of disease and metastasis, but would increase the specificity of the test.

It is not surprising that all nine patients with faint activity at the thyroid bed had normal Tg levels since these patients remained in apparent remission of disease for a minimum period of three years. Although it is not possible to judge whether this residual uptake was normal tissue or residual tumor, Tg measurement can replace total-body scan in the follow-up of these patients.

The results of the present study confirms the findings of other studies⁽⁹⁻¹¹⁾ that serum Tg is a specific and sensitive marker for detecting the presence or remission of well-differentiated thyroid cancer after thyroidectomy. In this study, the concordance between serum Tg values and the presence or absence of cancer was 88.9%. There were seven patients in whom the finding of a rising Tg level preceded scan evidence of recurrence and metastasis for about 6-12 months, one of these developing a palpable neck node three months after the elevation of serum Tg. The finding regarding the predictive value of serum Tg in the diagnosis of recurrence and metastasis has been observed by several authors.^(3,5,9)

The serum Tg false-negative rate in this study was relatively high compared with that of others.^(5,9,12) This may be due partly to our high cut-off value, the interference of antithyroglobulin antibody or perhaps the assay system. However, some thyroid cancer may have low Tg-synthesizing cells or a defect in thyroglobulin secretion.⁽¹³⁾

Ten patients with elevated serum Tg levels without clinical, scan and other evidence of the presence of cancer had persistently high serum Tg levels during the monitoring period of 2-3 years. Two of these patients had Tg levels over 300 ng/ml. All but two had node metastasis before surgery and radioiodine ablation. Thyroglobulin antibody was weakly positive in three cases, the remaining seven cases being negative. The high levels of serum Tg with negative thyroglobulin antibody may indicate the presence of cancer before it has become detectable by other means as evinced in this and others studies.^(5,6,9,14)

The effect of T4 replacement therapy on the serum Tg level has been reported with conflicting views. Some studies^(1,6) demonstrated improved specificity of high serum Tg measurement when patients were taking T4, but others^(5,12,15,16) had the

opposite view. Our study confirms that Tg levels were much higher in recurrence and metastasis in most patients not receiving T4. When these patients were on T4, serum Tg levels were greatly reduced but were still above the cut-off limit. Tg levels in a few patients in this group remained low when they were on and off T4. Tg levels were lower than the cut-off value in all but one patient in the residual thyroid group while they were on T4. Most patients without residual cancer had Tg levels lower than the critical value when they were on and off T4. Hence, monitoring of serum Tg levels in patients during T4 therapy still provides worthwhile results as has been reported by others.^(9,12,17)

In our study, the sensitivity of total-body scan in the detection of residual cancer was slightly lower than serum Tg estimation, i.e. 78.9% and 86.8%, respectively. In combining these two modalities, the detection rate was much improved (100%). Six of eight patients who had false-negative total-body scans had cervical nodes and/or lung metastasis, one had local recurrence with pulmonary metastasis. The false-negative scans may arise from several factors; for example, some cancer tissue, especially nodal metastasis, does not accumulate radioiodine or some may be visualized only with a therapeutic amount of radioiodine.^(7,10,16,18) One of our patients also illustrated the detection of metastasis when the patient was scanned after an ablative dose of ¹³¹I. Figure 3 demonstrates a case of recurrent cancer in whom the Tg level increased prior to the availability of clinical evidence.

In conclusion, serial estimations of serum Tg provide a useful and highly specific marker in the follow-up of differentiated thyroid cancer after thyroid ablation. When the serum Tg level is low, there is a high probability that cancer is no longer present, thus making radioiodine scans unnecessary. An elevated Tg level during T4 suppression suggests the presence of residual cancer even if the radioiodine scan is negative. These patients should be followed-up closely because they are highly suspect of having occult disease. However, caution should be used when the Tg level alone is relied upon. Radioiodine scans are useful for the monitoring of patients with metastatic disease who are undergoing treatment and those with an elevated serum Tg level. It is obvious that these two tests are complementary and render a high degree of sensitivity and reliability when used in combination.

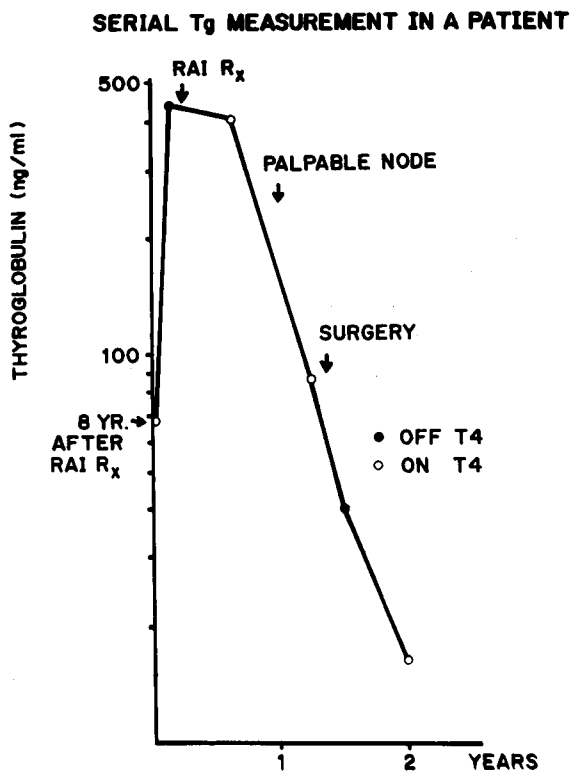


Figure 3. A patient with mixed papillary and follicular thyroid carcinoma: the first serum Tg level eight years after thyroidectomy and radioiodine treatment (RAI Rx) was high. ¹³¹I total-body scan showed functioning thyroid tissue at the thyroid bed only. RAI Rx was then give. A cervical node was palpated seven months later. Serum Tg fell to a normal level after sugical removal of the metastatic lymph node.

References

1. Black EG, Cassoni A, Gimlette TMD, Harmer CL, Maisey MN, Oates GD, Hoffenberg R. Serum thyroglobulin in thyroid cancer. *Lancet* 1981 Aug 29; 2(8244): 443-5
2. Charles MA, Dodson LE. Jr, Waldeck N, Hofeldt F, Ghaed N, Telepak R, Ownbey J, Burstein P. Serum thyroglobulin levels predict total body iodine scan findings in patients with treated well-differentiated thyroid carcinoma. *Am J Med* 1980 Sep; 69(3): 401-7
3. Barsano CP, Skosey C, DeGroot LJ, Refetoff S. Serum thyroglobulin in the management of patients with thyroid cancer. *Arch Intern Med* 1982 Apr; 142(4): 763-7
4. Harley EH, Daly RG, Hodge JW. Thyroglobulin assay in the postoperative management of differentiated thyroid cancer. *Arch Otolaryngol*

Head Neck Surg 1988 Apr; 112(4): 333-5

5. Grant S, Luttrell B, Reeve T, Wiseman J, Wilmshurst E, Stiel J, Donohoe D, Cooper R, Bridgman M. Thyroglobulin may be undetectable in the serum of patients with metastatic disease secondary to differentiated thyroid carcinoma. Follow-up of differentiated thyroid carcinoma. *Cancer* 1984 Oct 15; 54(8): 1625-8
6. Ericsson UB, Tegler L, Lennquist S, Christensen SD, Stahl E, Thorell JI. Serum thyroglobulin in differentiated thyroid carcinoma. *Acta Chir Scand* 1984; 150(5): 367-75
7. Ramanna L, Waxman AD, Brachman MB, Sensel N, Tanasescu DE, Berman DS, Catz B, Braunstein GD. Correlation of thyroglobulin measurements and radioiodine scans in the follow-up of patients with differentiated thyroid cancer. *Cancer* 1985 Apr; 55(7): 1525-9
8. Ronga G, Fiorentiona A, Fragasso-G, Fringnelli FM and Todino V. Complementary role of whole body scan and serum thyroglobulin determination in the follow-up of differentiated thyroid carcinoma. *Italy J Surg Sci* 1986 Jan; 16(1): 11-5
9. Black EG, Sheppard MC, Hollenberg R. Serial serum thyroglobulin measurements in the management of differentiated thyroid carcinoma. *Clin Endocrinol* 1987; 27(1): 115-20
10. Girelli ME, Busnardo B, Amerio R, Scotton G, Casara D, Betterle C, Piccolo M, Pelizzo MR. Serum thyroglobulin levels in patients with well-differentiated thyroid cancer during suppression therapy: study on 429 patients. *Eur J Nucl Med* 1985; 10(5-6): 252-4
11. Szanto J, Vincze B, Sinkovics I, Karika Z, Daubner K, Peter I, Kazatsay I, Eckhardt S. Postoperative thyroglobulin level determination to follow up patients with highly differentiated thyroid cancer. *Oncology* 1989; 46(2): 99-104
12. Shah DH, Kumar A, Dandekar SR, Vijayan U, Krishna BA, Sharma SM. Serum thyroglobulin in management of thyroid cancer. *Proceedings of IAEA Symposium on Nuclear Medicine and Related Radionuclide Applications in Developing Countries.* 26-30 August 1985, p323-333, Vienna, Austria
13. Dralle H, Schwarzrock R, Lang W, Bocker W, Ziegler H, Schroder S, Geerlings H. Comparison of histology and immunohistochemistry

- with thyroglobulin serum levels and radioiodine uptake in recurrences and metastases of differentiated thyroid carcinomas. *Acta Endocrinol* 1985 Apr; 108(4): 540-10
14. Pacini F, Martino E, Bambini G, Aghini-Lombardi F, Taddei D, Lari R, Pinchera A, Baschieri L. Humoral markers for thyroid carcinoma. *Cancer Detect Prev* 1985; 8(1-2): 17-22
15. Pacini F, Lari R, Mazzeo S, Grasso L, Taddei D, Pinchera A. Diagnostic value of a single serum thyroglobulin determination on and off thyroid suppressive therapy in the follow-up of patients with differentiated thyroid cancer. *Clin Endocrinol (Oxford)* 1985 Oct; 23(4): 405-411
16. Girelli ME, Busnardo B, Amerio R, Casara D, Betterle C and Piccolo M. Critical evaluation of serum thyroglobulin (Tg) levels during thyroid hormone suppression therapy versus Tg levels after hormone withdrawal and total body scan results in 291 patients with thyroid cancer. *Eur J Nucl Med* 1986 Sep; 11(9): 333-5
17. Valimaki M and Lamberg BA. How to deal with undetectable and low measurable serum thyroglobulin levels in the follow-up of patients with differentiated thyroid carcinoma. *Acta Endocrinol* 1985; 110(4): 487-92
18. Pacini F, Lippi F, Formica N, Elisei R, Anelli S, Ceccarelli C and Pinchera A. Therapeutic doses of iodine-131 revealed undiagnosed metastases in thyroid cancer patients with detectable serum thyroglobulin levels. *J Nucl Med* 1987 Dec; 28(12): 1888-91